as a result of treatment with a compound disclosed in Table VIII at dosages of 1 μM (A), 10 μM (B), and 50 μM (C) and HIF-1 knock out control (D).

Figure 13 depicts the up regulation of phosphoglycerate kinase (PGK) expression in wild type murine embryonic fibroblasts as a result of treatment with ~~compound~~ a compound disclosed in Table VIII at dosages of 1 μM (E), 10 μM (F), and 50 μM (G) vs. wild type control (H) and the lack of up regulation of PGK expression in HIF-1 knock out cells as a result of treatment with compound a compound disclosed in Table VIII at dosages of 1 μM (A), 10 μM (B), and 50 μM (C) and HIF-1 knock out control (D).

Figure 14 depicts the up regulation of vascular endothelia growth factor (VEGF) expression in wild type murine embryonic fibroblasts as a result of treatment with ~~compound~~ a compound disclosed in Table VIII at dosages of 1 μM (E), 10 μM (F), and 50 μM (G) vs. control (H) and the lack of up regulation of VEGF expression in HIF-1 knock out cells treated with a compound disclosed in Table VIII at dosages of 1 μM (A), 10 μM (B), and 50 μM (C) and HIF-1 knock out control (D). Both cell types were treated for 7 hours.

Figure 15 depicts the results of Example 11 wherein 3 groups of animals are treated with *Staphylococcus aureus* antibiotic sensitive Newman strain. The data show the significant reduction in the size of skin lesions (wounds) for animals in Group 1 (solid circles (●)) treated with 10μM of a compound disclosed in Table VIII versus animal given a bolus of DMSO (solid squares (■)). Figure 15, depicts mice infected with Newman strain of *S. aureus* ~~S. aureus~~ followed by treatment with 10 μM of a compound disclosed in Table VIII or DMSO (control) at 2 hours post-infection. The data show the statistically significant reduction in the size of skin lesions (wounds) for animals treated with compound a compound disclosed in Table VIII (solid circles (●)) or DMSO (solid squares (■)).

Figure 16 also depicts the results of Example 11 showing the reduction in the size of skin lesions (wounds) for animals in Group 1 (solid circles (●)) treated with 10μM a compound disclosed in Table VIII versus animals that are untreated (solid triangles (▲)). **Figure 16** depicts mice infected with Newman strain of *S. aureus* ~~S. aureus~~ followed by treatment with 10 μM of a compound disclosed in Table VIII or no treatment at 2 hours post-infection. The data show the reduction in the size of skin lesions (wounds) for animals treated with compound a compound disclosed in Table VIII (solid circles (●)) or untreated (solid triangles (▲)).

factor then activates several biological pathways which are present as a response to and a means for alleviating the body's state of hypoxia. These responses include, *inter alia*, angiogenic, erythropoietic (EPO), glucose metabolism (PGK), matrix alteration, and enhanced capacity of phagocytes to respond to pathogens.

Figure 1 summaries the metabolism of HIF-1α during normal healthy conditions. The HIF α-subunits are unstable under normoxic conditions; cells continually synthesize and degrade these proteins. The short half-life of HIF-1α is the byproduct of a family of O_2- and iron-dependent prolyl hydroxylases (PH1-3), whose action directs HIF α-subunits for degradation by the ubiquitin-proteasome pathway in a process dependent upon interaction with von Hippel–Lindau tumor-suppressor protein (vHL). In **Figure 1**, PHD's ~~PDH's~~ represents the prolyl hydroxylases that act in the presence of an asparaginyl hydroxylase to hydroxylate prolines 402 and 564, as well as asparagines 804. From this point, because the hydroxylated HIF-1α is also prevented from association with p300-CPB because of other factors, ubiquitin ligase begins to metabolize the hydroxylated HIF-1α via the vHL pathway.

In patients where there is a need for stimulating this response, for example, in patients in need of increased tissue oxygen due to peripheral vascular disease (PVD), inhibiting the HIF1 enzymes, for example, Egl nine homolog 1 (HIFPH2), will stimulate the body's own angiogenic response without the consequences of oxygen deficiency. In addition, in diseases of ischemia, *inter alia*, CAD and anemia, stimulation of angiogenic, erythropoietic, and metabolism adaption can provide therapeutic benefits. Up regulation of HIF-1α also provides a method for enhancing immunity, for example, by increasing the capacity of phagocytes.

There is therefore a long felt need for methods for controlling the activity of HIF-1α which can be effectively accomplished by compounds that inhibit the 4-prolyl hydroxylase enzymes that degrade HIF-1α. This inhibition of 4-prolyl hydroxylase enzymes, *inter alia*, HIFPH2 (also referred to herein as EGLN1 or PHD2) and HIFPH3 (also referred to herein as EGLN3 of PHD-3) thereby provide a method for increasing the concentration of HIF-1α in cells and thus providing methods for treating a variety of diseases or disease states.

Disclosed herein are methods for treating one or more diseases, conditions, syndromes, and the like that are affected by the level of hypoxia-inducible transcription factors. Regulation of these factors both during hypoxia and normoxia can provide methods for re-balancing or regulating one or more biological pathways associated with abnormal

conditions, *inter alia*, invasion of the body by pathogens, *inter alia*, bacteria, fungi, viruses, and parasites, abnormal cellular regulation, *i.e.*, cancer ischemia, and the side effects caused by vaccination.

Targeting HIF1 Stabilization in Cells

HIF-1α is targeted for destruction via prolyl hydroxylation, an oxygen-dependent modification that signals for recognition by the E3 ubiquitin ligase complex containing the von Hippel-Lindau tumor suppressor (VHL). Three prolyl hydroxylases formerly referred to in the literature as EGLN1, EGLN2, and EGLN3 (also known ~~know~~ as , have been identified in mammals, among which, EGLN1 (also known as HIFPH2 or PHD2), and EGLN3 (also known as HIFPH3 or PHD3), are hypoxia-inducible at their mRNA levels in a HIF-1α dependent manner. HIF-1α levels are controlled by these prolyl-4-hydroxylases by hydroxylating the HIF-1α proline residues Pro-402 and Pro-564 in humans (Ivan, M. *et al.*, (2001) "HIFα targeted for VHL-mediated destruction by proline hydroxylation: implications for O_2 sensing." *Science* **292**, 464-468; Jaakkola, P. *et al.*, (2001) "Targeting of HIF-1α to the von Hippel-Lindau ubiquitylation complex by O_2-regulated prolyl hydroxylation." *Science* **292**, 468-472; and Masson, N. *et al.*, (2001) "Independent function of two destruction domains in hypoxia-inducible factor-α chains activated by prolyl hydroxylation." *EMBO J.* **20**, 5197-5206). Under hypoxia conditions, EGLN1 and EGLN3 activity is suppressed.

Stimulated by a build up of the cellular concentration of HIF-1α is the production of Phosphoglycerate Kinase (PGK) and Vascular Endothelial Growth Factor (VEGF). It has been shown that stimulation of VEGF induces the formation of functional neo-vessels in the mouse cornea and enhanced blood flow in a dog model of coronary artery disease. The HIF-1α prolyl hydroxylase inhibitors of the present disclosure provide enhancement in the expression of multiple hypoxia inducible genes including VEGF, GAPDH and erythropoietin (EPO). Additionally, the HIF-1α prolyl hydroxylase inhibitors of the present disclosure provide enhanced the accumulation of HIF1-α in the cytoplasm and nucleus. Transgenic mice expressing a constitutively active HIF-1α in the skin have increased dermal vascularity and had a 13-fold increase in VEGF levels

Wounds

Chronic, non-healing wounds are a major cause of prolonged morbidity in the aged human population. This is especially the case in bedridden or diabetic patients who develop severe, non-healing skin ulcers. In many of these cases, the delay in healing is a result of

nitrogen mustard, trimethylene thiophosphoramide, carmustine, busulfan, chlorambucil, belustine, uracil mustard, chlomaphazin, and dacarbazine. The disclosure encompasses antimetabolites as chemotherapeutic agents. Examples of these types of agents include cytosine arabinoside, fluorouracil, methotrexate, mercaptopurine, azathioprime, and procarbazine. An additional category of chemotherapeutic cancer agents that may be used in the methods and compositions disclosed herein include antibiotics. Examples include without limitation doxorubicin, bleomycin, dactinomycin, daunorubicin, mithramycin, mitomycin, mytomycin C, and daunomycin. There are numerous liposomal formulations commercially available for these compounds. The present disclosure further encompasses other chemotherapeutic cancer agents including without limitation anti-tumor antibodies, dacarbazine, azacytidine, amsacrine, melphalan, ifosfamide and mitoxantrone.

The disclosed HIF-1α prolyl hydroxylase inhibitors herein can be administered in combination with other anti-tumor agents, including cytotoxic/antineoplastic agents and anti-angiogenic agents. Cytotoxic/anti-neoplastic agents are defined as agents which attack and kill cancer cells. Some cytotoxic/anti-neoplastic agents are alkylating agents, which alkylate the genetic material in tumor cells, e.g., cis-platin, cyclophosphamide, nitrogen mustard, trimethylene thiophosphoramide, carmustine, busulfan, chlorambucil, belustine, uracil mustard, chlomaphazin, and dacabazine. Other cytotoxic/anti-neoplastic agents are antimetabolites for tumor cells, e.g., cytosine arabinoside, fluorouracil, methotrexate, mercaptopuirine, azathioprime, and procarbazine. Other cytotoxic/anti-neoplastic agents are antibiotics, e.g., doxorubicin, bleomycin, dactinomycin, daunorubicin, mithramycin, mitomycin, mytomycin C, and daunomycin. There are numerous liposomal formulations commercially available for these compounds. Still other cytotoxic/anti-neoplastic agents are mitotic inhibitors (vinca alkaloids). These include vincristine, vinblastine and etoposide. Miscellaneous cytotoxic/anti-neoplastic agents include Taxol™ (paclitaxel) ~~taxol~~ and its derivatives, L-asparaginase, anti-tumor antibodies, dacarbazine, azacytidine, amsacrine, melphalan, VM-26, ifosfamide, mitoxantrone, and vindesine.

Anti-angiogenic agents are well known to those of skill in the art. Suitable anti-angiogenic agents for use in the disclosed methods and compositions include anti-VEGF antibodies, including humanized and chimeric antibodies, anti-VEGF aptamers and antisense oligonucleotides. Other known inhibitors of angiogenesis include angiostatin, endostatin, interferons, interleukin 1 (including α and β) interleukin 12, retinoic acid, and tissue inhibitors of metalloproteinase-1 and -2. (TIMP-1 and -2). Small molecules,

prostaglandin J2; proteasome inhibitors; protein A-based immune modulator; protein kinase C inhibitor; protein kinase C inhibitors, microalgal; protein tyrosine phosphatase inhibitors; purine nucleoside phosphorylase inhibitors; purpurins; pyrazoloacridine; pyridoxylated hemoglobin polyoxyethylene conjugate; raf antagonists; raltitrexed; ramosetron; ras farnesyl protein transferase inhibitors; ras inhibitors; ras-GAP inhibitor; retelliptine demethylated; rhenium Re 186 etidronate; rhizoxin; ribozymes; RII retinamide; rogletimide; rohitukine; romurtide; roquinimex; rubiginone B1; ruboxyl; safingol; saintopin; SarCNU; sarcophytol A; sargramostim; Sdi 1 mimetics; semustine; senescence derived inhibitor 1; sense oligonucleotides; signal transduction inhibitors; signal transduction modulators; single chain antigen binding protein; sizofiran; sobuzoxane; sodium borocaptate; sodium phenylacetate; solverol; somatomedin binding protein; sonermin; sparfosic acid; spicamycin D; spiromustine; splenopentin; spongistatin 1; squalamine; stem cell inhibitor; stem-cell division inhibitors; stipiamide; stromelysin inhibitors; sulfinosine; superactive vasoactive intestinal peptide antagonist; suradista; suramin; swainsonine; synthetic glycosaminoglycans; tallimustine; tamoxifen methiodide; tauromustine; tazarotene; tecogalan sodium; tegafur; tellurapyrylium; telomerase inhibitors; temoporfin; temozolomide; teniposide; tetrachlorodecaoxide; tetrazomine; thaliblastine; thiocoraline; thrombopoietin; thrombopoietin mimetic; thymalfasin; thymopoietin receptor agonist; thymotrinan; thyroid stimulating hormone; tin ethyl etiopurpurin; tirapazamine; titanocene bichloride; topsentin; toremifene; totipotent stem cell factor; translation inhibitors; tretinoin; triacetyluridine; triciribine; trimetrexate; triptorelin; tropisetron; turosteride; tyrosine kinase inhibitors; tyrphostins; UBC inhibitors; ubenimex; urogenital sinus-derived growth inhibitory factor; urokinase receptor antagonists; vapreotide; variolin B; vector system, erythrocyte gene therapy; velaresol; veramine; verdins; verteporfin; vinorelbine; vinxaltine; vitaxin; vorozole; zanoterone; zeniplatin; zilascorb; and zinostatin stimalamer. In one embodiment, the anti-cancer drug is 5-fluorouracil, Taxol™ (paclitaxel) ~~taxol~~, or leucovorin.

Methods Related to Treatment of Conditions Involving Microorganisms

Disclosed is a method for prophylactically treating a human or a mammal against infection by a microorganism, comprising administering to a human or mammal an effective amount of one or more of the disclosed HIF-1α prolyl hydroxylase inhibitors.

Further disclosed is a method for decreasing the virulence of a microorganism when a human or a mammal is infected with a microorganism, comprising administering to a

Two samples of cells from the human monocyte cell line U937 were pre-treated with 10 μM of a compound disclosed in Table VIII. One sample was pre-incubated for 1 hour and the other sample pre-incubated for 2 hours, both at 37 °C under an atmosphere of 5% CO_2. *S. aureus* (virulent Newman strain) was then added to the cells at an MOI of approximately 1-2 (1-2 bacteria for every 1 cell). Aliquots of cells were removed from each sample at 30, 60, 90, and 120 minutes post-infection, the U937 cells were immediately lysed with Triton™, and total of remaining bacteria remaining were enumerated on THB agar plates.

As depicted in **Figure 4**, U937 monocyte cells pre-treated with 10 μM of a compound disclosed in Table VIII for 1 hour (black bars) had almost no colony forming units present 120 minutes post-infection, whereas the cells pre-treated two hours prior to infection had approximately 15% colony forming units present as compared to cells that were untreated. In addition, **Figure 4** indicates that within 1 hour after the U937 monocyte cells had bee exposed to *S. aureus* (Newman strain), the number of colony forming units present was significantly reduced relative to cells receiving no HIF-1α inhibitor.

EXAMPLE 8

Two samples of cells from the human monocyte cell line U937 were pre-treated with 10 μM of a compound disclosed in Table VIII for 1 hour at 37 °C under an atmosphere of 5% CO_2. *S. aureus* (Newman strain) was added to one sample and to the other was added methicillin-resistant *S. aureus* (MRSA). Both bacteria were added at an MOI of approximately 2-3 (2-3 bacteria for every 1 cell). Aliquots of cells were removed from each sample at 30, 60, 90, and 120 minutes post-infection. The U937 cells were immediately lysed with Triton™, and total of remaining bacteria remaining were enumerated on THB agar plates.

As depicted in **Figure 5**, at120 minutes post-infection, the MRSA infected cells had only 25% of the average percentage of colony forming units present when compared to control as represented by the black bars. Also depicted in **Figure 5**, at 60 minutes post-infection, the Newman strain of *S. aureus* had only approximately 12% of the average percentage of colony forming units present when compared to control, and almost no colony forming units present at120 minutes post-infection as represented by the hatched bars.

EXAMPLE 9

Two samples of cells from the human monocyte cell line U937 treated with 10 μM a compound disclosed in Table VIII were infected with either *S. aureus* (Newman strain) and

Figure 9 depicts the average percent of colony forming units present at 120 minutes post-infection vs DMSO (control) when HaCaT cells are pre-treated for 1 hour according to the examples above with 800 μM mimosine, 10 μM of compound disclosed in Table VIII or 1 μg mL vancomycin followed by inoculation with *S. aureus* (Newman strain, hatched bars) and methicillin-resistant *S. aureus* (MRSA, black bars). **Figure 10** depicts the average percent of colony forming units present at 30, 60, 90, and 120 minutes post-infection for Newman strain of *S. aureus* (hatched bars) and MRSA (black bars) when HaCaT cells are pre-treated for 1 hour according to the examples above with 10 μM of a compound disclosed in Table VIII.

Figure 11 depicts the up regulation of phosphoglycerate kinase (PGK) expression in wild type murine embryonic fibroblasts as a result of treatment with a compound disclosed in Table VIII ~~compound a compound disclosed in Table VIII~~ at dosages of 1 μM (E), 10 μM (F), and 50 μM (G) vs. wild type control (H) and the lack of up regulation of PGK expression in HIF-1 knock out cells as a result of treatment with a compound disclosed in Table VIII at dosages of 1 μM (A), 10 μM (B), and 50 μM (C) and HIF-1 knock out control (D). Both cell types were treated for 7 hours.

Figure 12 depicts the up regulation of phosphoglycerate kinase (PGK) expression in wild type murine embryonic fibroblasts as a result of treatment with a compound disclosed in Table VIII at dosages of 1 μM (E), 10 μM (F), vs. wild type control (G) and the lack of up regulation of PGK expression in HIF-1 knock out cells as a result of treatment with a compound disclosed in Table VIII at dosages of 1 μM (A), 10 μM (B), and 50 μM (C) and HIF-1 knock out control (D).

Figure 13 depicts the up regulation of phosphoglycerate kinase (PGK) expression in wild type murine embryonic fibroblasts as a result of treatment with a compound disclosed in Table VIII at dosages of 1 μM (E), 10 μM (F), and 50 μM (G) vs. wild type control (H) and the lack of up regulation of PGK expression in HIF-1 knock out cells as a result of treatment with a compound disclosed in Table VIII at dosages of 1 μM (A), 10 μM (B), and 50 μM (C) and HIF-1 knock out control (D).

Vascular Endothelial Growth Factor (VEGF) is dependent upon the presence of HIF-1 in cells. **Figure 14** depicts the up regulation of vascular endothelia growth factor (VEGF) expression in wild type murine embryonic fibroblasts as a result of treatment with a compound disclosed in Table VIII at dosages of 1 μM (E), 10 μM (F), and 50 μM (G) vs. control (H) and the lack of up regulation of VEGF expression in HIF-1 knock out cells

treated with ~~compound~~ a compound disclosed in Table VIII at dosages of 1 μM (A), 10 μM (B), and 50 μM (C) and HIF-1 knock out control (D). Both cell types were treated for 7 hours. As seen in **Figure 14**, VEGF is increased when dosed at 10 μM (F) and 50 μM (G). In HIF-1 knock out cells, there is no increase in PGK up regulation when HIF-1 knock out cells are dosed at 1 μM (A), 10 μM (B), and 50 μM (C) when compared to wild type control (H) and HIF-1 knock out control (D).

Wound Healing

EXAMPLE 11

Twenty-four (24) mice were divided into three groups. Group 2 animals were administered bacterial inoculum (*Staphylococcus aureus* antibiotic sensitive Newman strain [ATCC #25904]) by subcutaneous injection on Day 0 and received 10 μM of a compound disclosed in Table VIII for 6 days starting at 2 hours post-infection (Days 0-5). Group 1 received subcutaneous injections of DMSO. Group 3 served as a control group and received no treatment. Lesion size was monitored daily during the study. Only open wounds were considered lesions; bumps and white patches without an open wound were not measured for lesion size. On Day 7, the final lesion size was measured and mice were sacrificed for determination of bacterial load in skin and kidney. Day 7 post-infection, mice were sacrificed after final lesion size measurement and the lesioned skin tissue and both kidneys were collected. Skin and kidneys were homogenized in phosphate buffered saline, serially diluted, and plated on Todd-Hewitt agar plates to enumerate colony forming units of bacteria.

Figure 15 shows the significant reduction in the size of skin lesions (wounds) for animals in Group 1 (solid circles (●)) treated with 10μM of a compound disclosed in Table VIII versus animal treated with DMSO (solid squares (■)). As depicted in **Figure 15**, mice infected with Newman strain of S. aureus followed by treatment with 10 μM of a compound disclosed in Table VIII or DMSO (control) at 2 hours post-infection. The data show the statistically significant reduction in the size of skin lesions (wounds) for animals treated with a compound disclosed in Table VIII (solid circles (●)) or DMSO (solid squares (■)).

Figure 16 shows the significant reduction in the size of skin lesions (wounds) for animals in Group 1 (solid circles (●)) treated with 10μM of a compound disclosed in Table VIII versus untreated animals (solid triangles (▲)). As depicted in **Figure 16**, mice infected with Newman strain of S. aureus followed by treatment with 10 μM of a compound disclosed in Table VIII or no treatment at 2 hours post-infection. The data show the

reduction in the size of skin lesions (wounds) for animals treated with a compound disclosed in Table VIII (solid circles (●)) or untreated (solid triangles (▲)).

EXAMPLE 12

Twenty-four (24) mice were divided into three groups. Group 1 animals were administered bacterial inoculum (*Staphylococcus aureus* antibiotic sensitive Newman strain [ATCC #25904]) by subcutaneous injection on Day 0 and received 10 μM of a compound disclosed in Table VIII for 6 days starting at 2 hours post-infection (Days 0-5). Group 2 received subcutaneous injections of DMSO. Group 3 served as a control group and received no treatment. Lesion size was monitored daily during the study. Only open wounds were considered lesions; bumps and white patches without an open wound were not measured for lesion size. Day 7 post-infection, mice were sacrificed after final lesion size measurement and lesioned skin tissue and both kidneys were collected. Skin and kidneys were homogenized in phosphate buffered saline, serially diluted, and plated on Todd-Hewitt agar plates to enumerate colony forming units of bacteria.

Figure 17 is a plot histogram wherein the number of observed colony forming units per gram of skin tissue is depicted. The straight lines indicate the mean value for each group. The results for the untreated group are plotted under (A), the results for the group treated with DMSO are plotted under (B) and results for the group treated with 10 μM of a compound disclosed in Table VIII are plotted under (C).

Figure 18 is a plot of the observed colony forming units of bacteria found in the kidneys of the animals. The results for the untreated group are plotted under (A), the results for the group treated with DMSO are plotted under (B) and results for the group treated with 10 μM of a compound disclosed in Table VIII are plotted under (C). As can be seen from these data, half of the animals treated with the HIF-1α prolyl hydroxylase inhibitor disclosed in Table VIII had no bacteria in the kidney indicating that the compound disclosed in Table VIII was able to systemically prevent spread of the infection from the wound to the kidney.

EXAMPLE 13

Twenty (20) mice were divided into two groups. Group 1 animals were administered bacterial inoculum (*Streptococcus pyogenes* NZ131 [M49 strain]) by subcutaneous injection on Day 0 and were pretreated with ~~compound~~ a compound disclosed in Table VIII once per day for 4 days, starting 2 hours pre-infection (Days 0-3). ~~Compound~~ ~~a~~ A compound disclosed in Table VIII was formulated in cyclodextran and diluted in

example, tablets, suppositories, pills, capsules, powders, liquids, suspensions, lotions, creams, gels, or the like, preferably in unit dosage form suitable for single administration of a precise dosage. The compositions will include, as noted above, an effective amount of the HIF-1α prolyl hydroxylase inhibitor in combination with a pharmaceutically acceptable carrier and, in addition, can include other medicinal agents, pharmaceutical agents, carriers, adjuvants, diluents, etc.

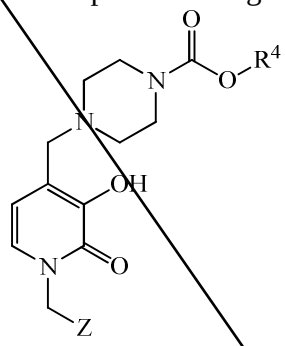
For solid compositions, conventional nontoxic solid carriers include, for example, pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharin, talc, cellulose, glucose, sucrose, magnesium carbonate, and the like. Liquid pharmaceutically administrable compositions can, for example, be prepared by dissolving, dispersing, etc., an active compound as described herein and optional pharmaceutical adjuvants in an excipient, such as, for example, water, saline aqueous dextrose, glycerol, ethanol, and the like, to thereby form a solution or suspension. If desired, the pharmaceutical composition to be administered can also contain minor amounts of nontoxic auxiliary substances such as wetting or emulsifying agents, pH buffering agents and the like, for example, sodium acetate, sorbitan monolaurate, triethanolamine sodium acetate, triethanolamine oleate, etc. Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example see *Remington's Pharmaceutical Sciences*, referenced above.

Parenteral ~~Parental~~ administration, if used, is generally characterized by injection. Injectables can be prepared in conventional forms, either as liquid solutions or suspensions, solid forms suitable for solution or suspension in liquid prior to injection, or as emulsions. A more recently revised approach for parenteral ~~parental~~ administration involves use of a slow release or sustained release system, such that a constant level of dosage is maintained. *See, e.g.*, U.S. Patent No. 3,710,795, which is incorporated by reference herein.

When the HIF-1α prolyl hydroxylase inhibitors are to be delivered into a mammal other than a human, the mammal can be a non-human primate, horse, pig, rabbit, dog, sheep, goat, cow, cat, guinea pig or rodent. The terms human and mammal do not denote a particular age or sex. Thus, adult and newborn subjects, as well as fetuses, whether male or female, are intended to be covered. A patient, subject, human or mammal refers to a subject afflicted with a disease or disorder. The term "patient" includes human and veterinary subjects.

CLAIMS

1. A compound having the formula:



wherein Z is phenyl substituted with from 1 to 5 halogens chosen from fluorine and chlorine;
R^4 is C_1-C_4 linear alkyl or C_3-C_4 branched alkyl;
or a pharmaceutically acceptable salt thereof.

2. The compound according to Claim 1, wherein R^4 is methyl.

3. The compound according to Claim 1, wherein R^4 is ethyl.

4. The compound according to Claim 1, wherein R^4 is *tert*-butyl.

5. The compound according to any of Claims 1 to 4, wherein Z is 4-chlorophenyl.

6. The compound according to any of Claims 1 to 4, wherein Z is chosen from 2-chlorophenyl, 3-chlorophenyl, 2-fluorophenyl, 3-fluorophenyl, or 4-fluorophenyl.

7. The compound according to any of Claims 1 to 4, wherein Z is chosen from 2,3-difluorophenyl, 2,4-difluorophenyl, 2,5-difluorophenyl, 2,6-difluorophenyl, 2,3-dichlorophenyl, 2,4-dichlorophenyl, 2,5-dichlorophenyl, and 2,6-dichlorophenyl.

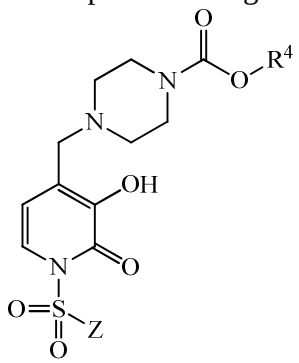
8. The compound *tert*-butyl 4-{[1-(4-chlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate.

9. A compound chosen from:
Methyl 4-{[1-(4-chlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;
Methyl 4-{[1-(3-chlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;
Methyl 4-{[1-(2-chlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;
Ethyl 4-{[1-(4-chlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;
Ethyl 4-{[1-(3-chlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;
Ethyl 4-{[1-(2-chlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;

tert-Butyl 4-{[1-(3-chlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;
tert-Butyl 4-{[1-(2-chlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;
Methyl 4-{[1-(4-fluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;
Methyl 4-{[1-(3-fluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;
Methyl 4-{[1-(2-fluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;
Ethyl 4-{[1-(4-fluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;
Ethyl 4-{[1-(3-fluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;
Ethyl 4-{[1-(2-fluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;
tert-Butyl 4-{[1-(4-fluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;
tert-Butyl 4-{[1-(3-fluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate; and
tert-Butyl 4-{[1-(2-fluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate.

10. A compound according to any one of Claims 1 to 9, wherein the compound is a pharmaceutically acceptable salt of an anion chosen from chloride, bromide, iodide, sulfate, bisulfate, carbonate, bicarbonate, phosphate, hydrogensulfonate, p-toluenesulfonate, methanesulfonate, formate, acetate, propionate, butyrate, pyruvate, lactate, oxalate, malonate, maleate, succinate, tartrate, fumarate, glycolate, or citrate.

11. A compound having the formula:



wherein Z is phenyl substituted with from 1 to 5 halogens chosen from fluorine and chlorine;
R^4 is C_1-C_4 linear alkyl or C_3-C_4 branched alkyl;
or a pharmaceutically acceptable salt thereof.

12. The compound according to Claim 11, wherein R is methyl.

13. The compound according to Claim 11, wherein R is ethyl.

14. The compound according to Claim 11, wherein R is *tert*-butyl.

15. The compound according to any of Claims 11 to 14, wherein Z is 4-chlorophenyl.

16. The compound according to any of Claims 11 to14, wherein Z is chosen from 2-chlorophenyl, 3-chlorophenyl, 2-fluorophenyl, 3-fluorophenyl, or 4-fluorophenyl.

17. The compound according to any of Claims 1 to 14, wherein Z is chosen from 2,3-difluorophenyl, 2,4-difluorophenyl, 2,5-difluorophenyl, 2,6-difluorophenyl, 2,3-dichlorophenyl, 2,4-dichlorophenyl, 2,5-dichlorophenyl, and 2,6-dichlorophenyl.

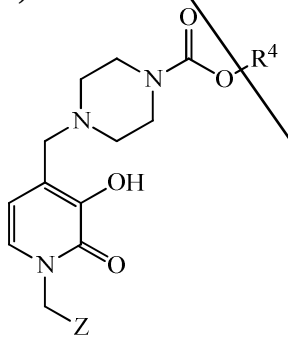
18. The compound *tert*-butyl 4-{[1-(4-chlorophenylsulfonyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate.

19. A compound chosen from:
Methyl 4-{[1-(4-chlorophenylsulfonyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;
Methyl 4-{[1-(3-chlorophenylsulfonyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;
Methyl 4-{[1-(2-chlorophenylsulfonyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;
Ethyl 4-{[1-(4-chlorophenylsulfonyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;
Ethyl 4-{[1-(3-chlorophenylsulfonyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;
Ethyl 4-{[1-(2-chlorophenylsulfonyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;
tert-Butyl 4-{[1-(3-chlorophenylsulfonyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;
tert-Butyl 4-{[1-(2-chlorophenylsulfonyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;
Methyl 4-{[1-(4-fluorophenylsulfonyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;
Methyl 4-{[1-(3-fluorophenylsulfonyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;
Methyl 4-{[1-(2-fluorophenylsulfonyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;
Ethyl 4-{[1-(4-fluorophenylsulfonyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;
Ethyl 4-{[1-(3-fluorophenylsulfonyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;
Ethyl 4-{[1-(2-fluorophenylsulfonyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;
tert-Butyl 4-{[1-(4-fluorophenylsulfonyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;
tert-Butyl 4-{[1-(3-fluorophenylsulfonyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate; and

tert-Butyl 4-{[1-(2-fluorophenylsulfonyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate.

20. A compound according to any one of Claims 11 to 19, wherein the compound is a pharmaceutically acceptable salt of an anion chosen from chloride, bromide, iodide, sulfate, bisulfate, carbonate, bicarbonate, phosphate, hydrogensulfonate, p-toluenesulfonate, methanesulfonate, formate, acetate, propionate, butyrate, pyruvate, lactate, oxalate, malonate, maleate, succinate, tartrate, fumarate, glycolate, or citrate.

21. A composition comprising:
a) one or more compounds having the formula:



wherein Z is phenyl substituted with from 1 to 5 halogens chosen from fluorine and chlorine;
wherein R^4 is C_1-C_4 linear alkyl or C_3-C_4 branched alkyl; or
a pharmaceutically acceptable salt thereof; and
b) one or more pharmaceutically acceptable excipients.

22. The composition according to Claim 21, wherein R^4 is methyl.

23. The composition according to Claim 21, wherein R^4 is ethyl.

24. The composition according to Claim 21, wherein R^4 is *tert*-butyl.

25. The composition according to any one of Claims 21 to 24, wherein Z is 4-chlorophenyl.

26. The composition according to any one of Claims 21 to 24, wherein Z is chosen from 2-chlorophenyl, 3-chlorophenyl, 2-fluorophenyl, 3-fluorophenyl, or 4-fluorophenyl.

27. The composition according to any one of Claims 21 to 24, wherein Z is chosen from 2,3-difluorophenyl, 2,4-difluorophenyl, 2,5-difluorophenyl, 2,6-difluorophenyl, 2,3-dichlorophenyl, 2,4-dichlorophenyl, 2,5-dichlorophenyl, and 2,6-dichlorophenyl.

28. The composition according to Claim 21, comprising *tert*-butyl 4-{[1-(4-chloro-benzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate.

29. The composition according to Claim 21, comprising one or more compounds chosen from:
Methyl 4-{[1-(4-chlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;

Methyl 4-{[1-(3-chlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;
Methyl 4-{[1-(2-chlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;
Ethyl 4-{[1-(4-chlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;
Ethyl 4-{[1-(3-chlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;
Ethyl 4-{[1-(2-chlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;
tert-Butyl 4-{[1-(3-chlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;
tert-Butyl 4-{[1-(2-chlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;
Methyl 4-{[1-(4-fluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;
Methyl 4-{[1-(3-fluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;
Methyl 4-{[1-(2-fluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;
Ethyl 4-{[1-(4-fluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;
Ethyl 4-{[1-(3-fluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;
Ethyl 4-{[1-(2-fluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;
tert-Butyl 4-{[1-(4-fluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;
tert-Butyl 4-{[1-(3-fluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate; or
tert-Butyl 4-{[1-(2-fluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate.

30. The composition according to any one of Claims 21 to 29, wherein the compound is a pharmaceutically acceptable salt of an anion chosen from chloride, bromide, iodide, sulfate, bisulfate, carbonate, bicarbonate, phosphate, hydrogensulfonate, p-toluenesulfonate, methanesulfonate, formate, acetate, propionate, butyrate, pyruvate, lactate, oxalate, malonate, maleate, succinate, tartrate, fumarate, glycolate, or citrate.

31. The composition according to any one of Claims 21 to 30, further comprising one or more chemotherapeutic agents or chemotherapeutic compounds.

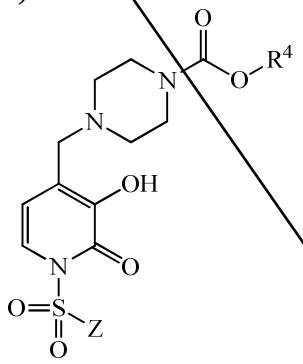
32. The composition according to Claim 31, wherein the chemotherapeutic agent or chemotherapeutic compound is chosen from 5-fluorouracil, taxol, or leucovorin.

33. The composition according to any of Claims 21 to 30, further comprising one or more vaccines.

34. The composition according to Claim 33, wherein the vaccine stimulates antibodies against hepatitis, influenza, measles, rubella, tetanus, polio or rabies.

35. The composition according to any of Claims 21 to 30, wherein the composition further comprises an antimicrobial.

36. A composition comprising:
a) one or more compounds having the formula:



wherein Z is phenyl substituted with from 1 to 5 halogens chosen from fluorine and chlorine;
wherein R^4 is C_1-C_4 linear alkyl or C_3-C_4 branched alkyl; or
a pharmaceutically acceptable salt thereof; and
b) one or more pharmaceutically acceptable excipients.

37. The composition according to Claim 36, wherein R^4 is methyl.

38. The composition according to Claim 36, wherein R^4 is ethyl.

39. The composition according to Claim 36, wherein R^4 is *tert*-butyl.

40. The composition according to any one of Claims 36 to 39, wherein Z is 4-chlorophenyl.

41. The composition according to any one of Claims 36 to 39, wherein Z is chosen from 2-chlorophenyl, 3-chlorophenyl, 2-fluorophenyl, 3-fluorophenyl, or 4-fluorophenyl.

42. The composition according to any one of Claims 36 to 39, wherein Z is chosen from 2,3-difluorophenyl, 2,4-difluorophenyl, 2,5-difluorophenyl, 2,6-difluorophenyl, 2,3-dichlorophenyl, 2,4-dichlorophenyl, 2,5-dichlorophenyl, and 2,6-dichlorophenyl.

43. The composition according to Claim 36, comprising *tert*-butyl 4-{[1-(4-chloro-phenylsulfonyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate.

44. The composition according to Claim 36, comprising one or more compounds chosen from:
Methyl 4-{[1-(4-chlorophenylsulfonyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;
Methyl 4-{[1-(3-chlorophenylsulfonyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;
Methyl 4-{[1-(2-chlorophenylsulfonyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;

Ethyl 4-{[1-(4-chlorophenylsulfonyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;
Ethyl 4-{[1-(3-chlorophenylsulfonyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;
Ethyl 4-{[1-(2-chlorophenylsulfonyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;
tert-Butyl 4-{[1-(3-chlorophenylsulfonyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;
tert-Butyl 4-{[1-(2-chlorophenylsulfonyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;
Methyl 4-{[1-(4-fluorophenylsulfonyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;
Methyl 4-{[1-(3-fluorophenylsulfonyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;
Methyl 4-{[1-(2-fluorophenylsulfonyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;
Ethyl 4-{[1-(4-fluorophenylsulfonyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;
Ethyl 4-{[1-(3-fluorophenylsulfonyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;
Ethyl 4-{[1-(2-fluorophenylsulfonyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;
tert-Butyl 4-{[1-(4-fluorophenylsulfonyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;
tert-Butyl 4-{[1-(3-fluorophenylsulfonyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate; or
tert-Butyl 4-{[1-(2-fluorophenylsulfonyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate.

45. The composition according to any one of Claims 36 to 44, wherein the compound is a pharmaceutically acceptable salt of an anion chosen from chloride, bromide, iodide, sulfate, bisulfate, carbonate, bicarbonate, phosphate, hydrogensulfonate, p-toluenesulfonate, methanesulfonate, formate, acetate, propionate, butyrate, pyruvate, lactate, oxalate, malonate, maleate, succinate, tartrate, fumarate, glycolate, or citrate.

46. The composition according to any one of Claims 36 to 45, further comprising one or more chemotherapeutic agents or chemotherapeutic compounds.

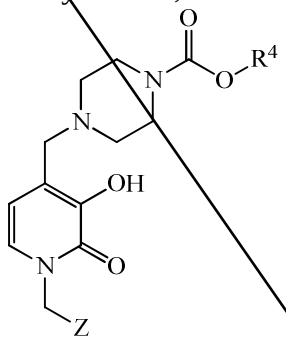
47. The composition according to Claim 46, wherein the chemotherapeutic agent or chemotherapeutic compound is chosen from 5-fluorouracil, taxol, or leucovorin.

48. The composition according to any one of Claims 36 to 45, further comprising one or more vaccines.

49. The composition according to Claim 48, wherein the vaccine stimulates antibodies against hepatitis, influenza, measles, rubella, tetanus, polio or rabies.

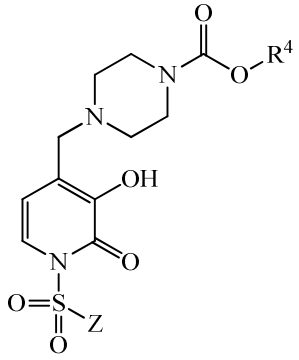
50. The composition according to any one of Claims 36 to 45, wherein the composition further comprises an antimicrobial.

51. The use of a compound for treating a disease or condition wherein the disease or condition is chosen from cancer, a microbial infection, anemia, decreased angiogenesis, sepsis, peripheral artery disease, diabetes, or hypertension, the compound having the formula:



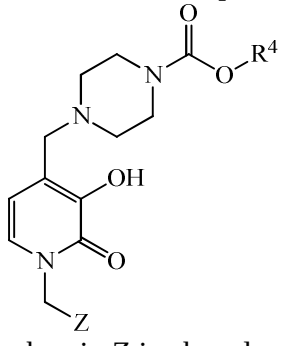
wherein Z is phenyl substituted with from 1 to 5 halogens chosen from fluorine and chlorine;
R^4 is C_1-C_4 linear alkyl or C_3-C_4 branched alkyl;
or a pharmaceutically acceptable salt thereof

52. The use of a compound for treating a disease or condition wherein the disease or condition is chosen from cancer, a microbial infection, anemia, decreased angiogenesis, sepsis, peripheral artery disease, a wound, diabetes, or hypertension, the compound having the formula:



wherein Z is phenyl substituted with from 1 to 5 halogens chosen from fluorine and chlorine;
R^4 is C_1-C_4 linear alkyl or C_3-C_4 branched alkyl;
or a pharmaceutically acceptable salt thereof.

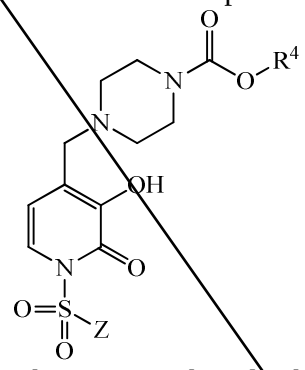
53. The use of a compound for treating a wound, the compound having the formula:



wherein Z is phenyl substituted with from 1 to 5 halogens chosen from fluorine and chlorine;
R^4 is C_1-C_4 linear alkyl or C_3-C_4 branched alkyl;

or a pharmaceutically acceptable salt thereof.

54. The use of a compound for treating a wound, the compound having the formula:



wherein Z is phenyl substituted with from 1 to 5 halogens chosen from fluorine and chlorine;
R^4 is C_1-C_4 linear alkyl or C_3-C_4 branched alkyl;
or a pharmaceutically acceptable salt thereof.

55. The use according to any one of Claims 51 to 54, wherein R^4 is methyl.

56. The use according to any one of Claims 51 to 54, wherein R^4 is ethyl.

57. The use according to any one of Claims 51 to 54, wherein R^4 is *tert*-butyl.

58. The use according to any one of Claims 51 to 54, wherein Z is 4-chlorophenyl.

59. The use according to any one of Claims 51 to 54, wherein Z is chosen from 2-chlorophenyl, 3-chlorophenyl, 2-fluorophenyl, 3-fluorophenyl, or 4-fluorophenyl.

60. The use according to any one of Claims 51 to 54, wherein Z is chosen from 2,3-difluorophenyl, 2,4-difluorophenyl, 2,5-difluorophenyl, 2,6-difluorophenyl, 2,3-dichlorophenyl, 2,4-dichlorophenyl, 2,5-dichlorophenyl, and 2,6-dichlorophenyl.

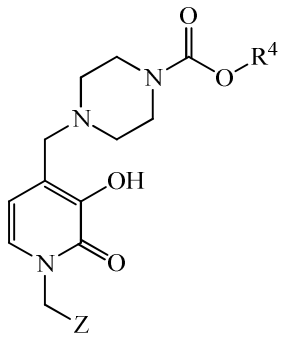
61. The use according to either Claim 51 or 53, comprising *tert*-butyl 4-{[1-(4-chloro-benzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate.

62. The use according to either Claim 51 or 53, wherein the compound is chosen from:
Methyl 4-{[1-(4-chlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;
Methyl 4-{[1-(3-chlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;
Methyl 4-{[1-(2-chlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;
Ethyl 4-{[1-(4-chlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;
Ethyl 4-{[1-(3-chlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;
Ethyl 4-{[1-(2-chlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;

tert-Butyl 4-{[1-(3-chlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;
tert-Butyl 4-{[1-(2-chlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;
Methyl 4-{[1-(4-fluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;
Methyl 4-{[1-(3-fluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;
Methyl 4-{[1-(2-fluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;
Ethyl 4-{[1-(4-fluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;
Ethyl 4-{[1-(3-fluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;
Ethyl 4-{[1-(2-fluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;
tert-Butyl 4-{[1-(4-fluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;
tert-Butyl 4-{[1-(3-fluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate; or
tert-Butyl 4-{[1-(2-fluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate.

63. The use according to any one of Claims 51 to 62, wherein the compound is a pharmaceutically acceptable salt of an anion chosen from chloride, bromide, iodide, sulfate, bisulfate, carbonate, bicarbonate, phosphate, hydrogensulfonate, p-toluenesulfonate, methanesulfonate, formate, acetate, propionate, butyrate, pyruvate, lactate, oxalate, malonate, maleate, succinate, tartrate, fumarate, glycolate, or citrate.

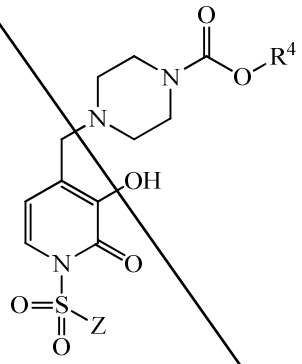
64. The use of a compound for making a medicament for treating a disease or condition wherein the disease or condition is chosen from cancer, a microbial infection, anemia, decreased angiogenesis, sepsis, peripheral artery disease, diabetes, or hypertension, the compound having the formula:



wherein Z is phenyl substituted with from 1 to 5 halogens chosen from fluorine and chlorine;
R^4 is C_1-C_4 linear alkyl or C_3-C_4 branched alkyl;
or a pharmaceutically acceptable salt thereof

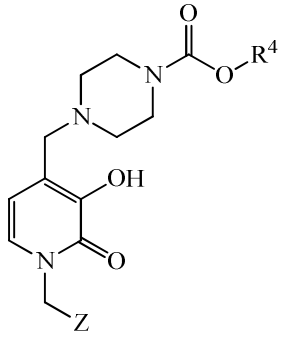
65. The use of a compound for making a medicament for treating a disease or condition wherein the disease or condition is chosen from cancer, a microbial infection, anemia, decreased

angiogenesis, sepsis, peripheral artery disease, diabetes, or hypertension, the compound having the formula:



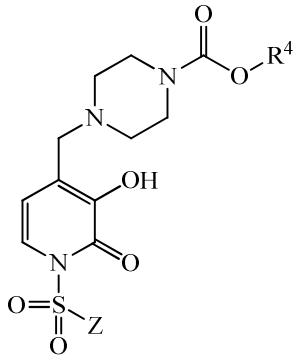
wherein Z is phenyl substituted with from 1 to 5 halogens chosen from fluorine and chlorine;
R^4 is C_1-C_4 linear alkyl or C_3-C_4 branched alkyl;
or a pharmaceutically acceptable salt thereof.

66. The use of a compound for making a medicament for treating a wound, the compound having the formula:



wherein Z is phenyl substituted with from 1 to 5 halogens chosen from fluorine and chlorine;
R^4 is C_1-C_4 linear alkyl or C_3-C_4 branched alkyl;
or a pharmaceutically acceptable salt thereof

67. The use of a compound for making a medicament for treating a wound, the compound having the formula:



wherein Z is phenyl substituted with from 1 to 5 halogens chosen from fluorine and chlorine;
R^4 is C_1-C_4 linear alkyl or C_3-C_4 branched alkyl;
or a pharmaceutically acceptable salt thereof.

68. The use according to any one of Claims 64 to 67, wherein R^4 is methyl.

69. The use according to any one of Claims 64 to 67, wherein R^4 is ethyl.

70. The use according to any one of Claims 64 to 67, wherein R^4 is *tert*-butyl.

71. The use according to any one of Claims 64 to 67, wherein Z is 4-chlorophenyl.

72. The use according to any one of Claims 64 to 67, wherein Z is chosen from 2-chlorophenyl, 3-chlorophenyl, 2-fluorophenyl, 3-fluorophenyl, or 4-fluorophenyl.

73. The use according to any one of Claims 64 to 67, wherein Z is chosen from 2,3-difluorophenyl, 2,4-difluorophenyl, 2,5-difluorophenyl, 2,6-difluorophenyl, 2,3-dichlorophenyl, 2,4-dichlorophenyl, 2,5-dichlorophenyl, and 2,6-dichlorophenyl.

74. The use according to either of Claims 64 or 66, comprising *tert*-butyl 4-{[1-(4-chloro-benzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate.

75. The use according to any one of Claims 64 to 67, wherein the compound is chosen from:
Methyl 4-{[1-(4-chlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;
Methyl 4-{[1-(3-chlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;
Methyl 4-{[1-(2-chlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;
Ethyl 4-{[1-(4-chlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;
Ethyl 4-{[1-(3-chlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;
Ethyl 4-{[1-(2-chlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;
tert-Butyl 4-{[1-(3-chlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;
tert-Butyl 4-{[1-(2-chlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;
Methyl 4-{[1-(4-fluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;
Methyl 4-{[1-(3-fluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;
Methyl 4-{[1-(2-fluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;
Ethyl 4-{[1-(4-fluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;
Ethyl 4-{[1-(3-fluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;
Ethyl 4-{[1-(2-fluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;
tert-Butyl 4-{[1-(4-fluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;

tert-Butyl 4-{[1-(3-fluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate; or

tert-Butyl 4-{[1-(2-fluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate.

76. The use according to any one of Claims 64 to 75, wherein the compound is a pharmaceutically acceptable salt of an anion chosen from chloride, bromide, iodide, sulfate, bisulfate, carbonate, bicarbonate, phosphate, hydrogensulfonate, p-toluenesulfonate, methanesulfonate, formate, acetate, propionate, butyrate, pyruvate, lactate, oxalate, malonate, maleate, succinate, tartrate, fumarate, glycolate, or citrate.

77. The use according to any one of Claims 64 to 76, wherein the medicament further comprisies one or more chemotherapeutic agents or chemotherapeutic compounds.

78. The use according to Claim 77, wherein the chemotherapeutic agent or chemotherapeutic compound is chosen from 5-fluorouracil, taxol, or leucovorin.

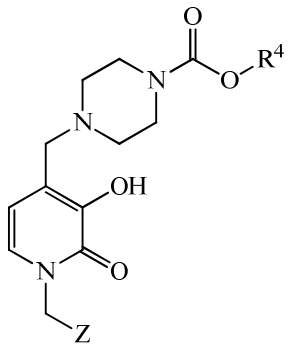
79. The use according to any one of Claims 64 to 76, wherein the medicament further comprises one or more vaccines.

80. The use according to Claim 79, wherein the vaccine stimulates antibodies against hepatitis, influenza, measles, rubella, tetanus, polio or rabies.

81. The use according to any one of Claims 66 or 67, wherein the use further comprises an antimicrobial.

CLAIMS

1. A compound having the formula:



wherein Z is phenyl substituted with from 1 to 5 halogens chosen from fluorine and chlorine;

R^4 is C_1-C_4 linear alkyl or C_3-C_4 branched alkyl;

or a pharmaceutically acceptable salt thereof.

2. The compound according to Claim 1, wherein R^4 is methyl.

3. The compound according to Claim 1, wherein R^4 is ethyl.

4. The compound according to Claim 1, wherein R^4 is *tert*-butyl.

5. The compound according to any of Claims 1 to 4, wherein Z is 4-chlorophenyl.

6. The compound according to any of Claims 1 to 4, wherein Z is chosen from 2-chlorophenyl, 3-chlorophenyl, 2-fluorophenyl, 3-fluorophenyl, or 4-fluorophenyl.

7. The compound according to any of Claims 1 to 4, wherein Z is chosen from 2,3-difluorophenyl, 2,4-difluorophenyl, 2,5-difluorophenyl, 2,6-difluorophenyl, 2,3-dichlorophenyl, 2,4-dichlorophenyl, 2,5-dichlorophenyl, and 2,6-dichlorophenyl.

8. The compound *tert*-butyl 4-{[1-(4-chlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate.

9. A compound chosen from:

Methyl 4-{[1-(4-chlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;

Methyl 4-{[1-(3-chlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;

Methyl 4-{[1-(2-chlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;

Ethyl 4-{[1-(4-chlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;

Ethyl 4-{[1-(3-chlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;

Ethyl 4-{[1-(2-chlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;

tert-Butyl 4-{[1-(3-chlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;

tert-Butyl 4-{[1-(2-chlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;

Methyl 4-{[1-(4-fluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;

Methyl 4-{[1-(3-fluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;

Methyl 4-{[1-(2-fluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;

Ethyl 4-{[1-(4-fluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;

Ethyl 4-{[1-(3-fluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;

Ethyl 4-{[1-(2-fluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;

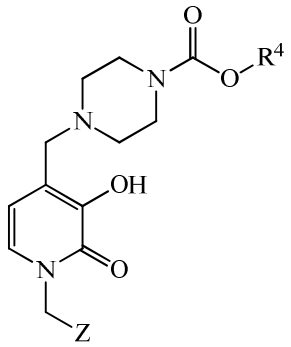
tert-Butyl 4-{[1-(4-fluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;

tert-Butyl 4-{[1-(3-fluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate; and

tert-Butyl 4-{[1-(2-fluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate.

10. A compound according to any one of Claims 1 to 9, wherein the compound is a pharmaceutically acceptable salt of an anion chosen from chloride, bromide, iodide, sulfate, bisulfate, carbonate, bicarbonate, phosphate, hydrogensulfonate, p-toluenesulfonate, methanesulfonate, formate, acetate, propionate, butyrate, pyruvate, lactate, oxalate, malonate, maleate, succinate, tartrate, fumarate, glycolate, or citrate.

11. A compound having the formula:



wherein Z is phenyl substituted with from 1 to 5 halogens chosen from fluorine and chlorine;

R^4 is C_1-C_4 linear alkyl or C_3-C_4 branched alkyl;

or a pharmaceutically acceptable salt thereof.

12. The compound according to Claim 11, wherein R is methyl.

13. The compound according to Claim 11, wherein R is ethyl.

14. The compound according to Claim 11, wherein R is *tert*-butyl.

15. The compound according to any of Claims 11 to 14, wherein Z is 4-chlorophenyl.

16. The compound according to any of Claims 11 to14, wherein Z is chosen from 2-chlorophenyl, 3-chlorophenyl, 2-fluorophenyl, 3-fluorophenyl, or 4-fluorophenyl.

17. The compound according to any of Claims 1 to 14, wherein Z is chosen from 2,3-difluorophenyl, 2,4-difluorophenyl, 2,5-difluorophenyl, 2,6-difluorophenyl, 2,3-dichlorophenyl, 2,4-dichlorophenyl, 2,5-dichlorophenyl, and 2,6-dichlorophenyl.

18. The compound *tert*-butyl 4-{[1-(4-chlorophenylsulfonyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate.

19. A compound chosen from:

Methyl 4-{[1-(4-chlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;

Methyl 4-{[1-(3-chlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;

Methyl 4-{[1-(2-chlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;

Ethyl 4-{[1-(4-chlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;

Ethyl 4-{[1-(3-chlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;

Ethyl 4-{[1-(2-chlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;

tert-Butyl 4-{[1-(3-chlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;

tert-Butyl 4-{[1-(2-chlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;

Methyl 4-{[1-(4-fluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;

Methyl 4-{[1-(3-fluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;

Methyl 4-{[1-(2-fluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;

Ethyl 4-{[1-(4-fluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;

Ethyl 4-{[1-(3-fluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;

Ethyl 4-{[1-(2-fluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;

tert-Butyl 4-{[1-(4-fluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;

tert-Butyl 4-{[1-(3-fluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate; and

tert-Butyl 4-{[1-(2-fluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate.

20. A compound according to any one of Claims 11 to 19, wherein the compound is a pharmaceutically acceptable salt of an anion chosen from chloride, bromide, iodide, sulfate, bisulfate, carbonate, bicarbonate, phosphate, hydrogensulfonate, p-toluenesulfonate, methanesulfonate, formate, acetate, propionate, butyrate, pyruvate, lactate, oxalate, malonate, maleate, succinate, tartrate, fumarate, glycolate, or citrate.

21. A composition comprising:

a) one or more compounds having the formula:

wherein Z is phenyl substituted with from 1 to 5 halogens chosen from fluorine and chlorine;

wherein R^4 is C_1-C_4 linear alkyl or C_3-C_4 branched alkyl; or a pharmaceutically acceptable salt thereof; and

b) one or more pharmaceutically acceptable excipients.

22. The composition according to Claim 21, wherein R^4 is methyl.

23. The composition according to Claim 21, wherein R^4 is ethyl.

24. The composition according to Claim 21, wherein R^4 is *tert*-butyl.

25. The composition according to any one of Claims 21 to 24, wherein Z is 4-chlorophenyl.

26. The composition according to any one of Claims 21 to 24, wherein Z is chosen from 2-chlorophenyl, 3-chlorophenyl, 2-fluorophenyl, 3-fluorophenyl, or 4-fluorophenyl.

27. The composition according to any one of Claims 21 to 24, wherein Z is chosen from 2,3-difluorophenyl, 2,4-difluorophenyl, 2,5-difluorophenyl, 2,6-difluorophenyl, 2,3-dichlorophenyl, 2,4-dichlorophenyl, 2,5-dichlorophenyl, and 2,6-dichlorophenyl.

28. The composition according to Claim 21, comprising *tert*-butyl 4-{[1-(4-chloro-benzyl)-3- hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate.

29. The composition according to Claim 21, comprising one or more compounds chosen from:

Methyl 4-{[1-(4-chlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;

Methyl 4-{[1-(3-chlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;

Methyl 4-{[1-(2-chlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;

Ethyl 4-{[1-(4-chlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;

Ethyl 4-{[1-(3-chlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;

Ethyl 4-{[1-(2-chlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;

tert-Butyl 4-{[1-(3-chlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;

tert-Butyl 4-{[1-(2-chlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;

Methyl 4-{[1-(4-fluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;

Methyl 4-{[1-(3-fluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;

Methyl 4-{[1-(2-fluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;

Ethyl 4-{[1-(4-fluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;

Ethyl 4-{[1-(3-fluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;

Ethyl 4-{[1-(2-fluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;

tert-Butyl 4-{[1-(4-fluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;

tert-Butyl 4-{[1-(3-fluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate; and

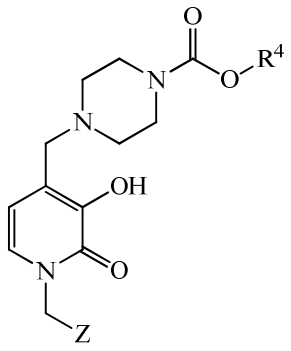
tert-Butyl 4-{[1-(2-fluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate.

30. The composition according to any one of Claims 21 to 29, wherein the compound is a pharmaceutically acceptable salt of an anion chosen from chloride, bromide, iodide, sulfate, bisulfate, carbonate, bicarbonate, phosphate, hydrogensulfonate, p-toluenesulfonate, methanesulfonate, formate, acetate, propionate, butyrate, pyruvate, lactate, oxalate, malonate, maleate, succinate, tartrate, fumarate, glycolate, or citrate.

31. The composition according to any of Claims 21 to 30, wherein the composition further comprises an antimicrobial.

32. A composition comprising:

a) one or more compounds having the formula:



wherein Z is phenyl substituted with from 1 to 5 halogens chosen from fluorine and chlorine;

wherein R^4 is C_1-C_4 linear alkyl or C_3-C_4 branched alkyl; or a pharmaceutically acceptable salt thereof; and

b) one or more pharmaceutically acceptable excipients.

33. The composition according to Claim 32, wherein R^4 is methyl.

34. The composition according to Claim 32, wherein R^4 is ethyl.

35. The composition according to Claim 32, wherein R^4 is *tert*-butyl.

36. The composition according to any one of Claims 32 to 35, wherein Z is 4-chlorophenyl.

37. The composition according to any one of Claims 32 to 35, wherein Z is chosen from 2-chlorophenyl, 3-chlorophenyl, 2-fluorophenyl, 3-fluorophenyl, or 4-fluorophenyl.

38. The composition according to any one of Claims 32 to 35, wherein Z is chosen from 2,3-difluorophenyl, 2,4-difluorophenyl, 2,5-difluorophenyl, 2,6-difluorophenyl, 2,3-dichlorophenyl, 2,4-dichlorophenyl, 2,5-dichlorophenyl, and 2,6-dichlorophenyl.

39. The composition according to Claim 32, comprising *tert*-butyl 4-{[1-(4-chloro-phenylsulfonyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate.

40. The composition according to Claim 32, comprising one or more compounds chosen from:

Methyl 4-{[1-(4-chlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;

Methyl 4-{[1-(3-chlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;

Methyl 4-{[1-(2-chlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;

Ethyl 4-{[1-(4-chlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;

Ethyl 4-{[1-(3-chlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;

Ethyl 4-{[1-(2-chlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;

tert-Butyl 4-{[1-(3-chlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;

tert-Butyl 4-{[1-(2-chlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;

Methyl 4-{[1-(4-fluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;

Methyl 4-{[1-(3-fluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;

Methyl 4-{[1-(2-fluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;

Ethyl 4-{[1-(4-fluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;

Ethyl 4-{[1-(3-fluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;

Ethyl 4-{[1-(2-fluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;

tert-Butyl 4-{[1-(4-fluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;

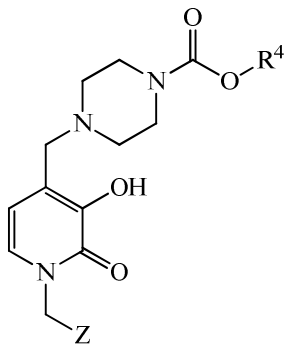
tert-Butyl 4-{[1-(3-fluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate; and

tert-Butyl 4-{[1-(2-fluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate.

41. The composition according to any one of Claims 32 to 40, wherein the compound is a pharmaceutically acceptable salt of an anion chosen from chloride, bromide, iodide, sulfate, bisulfate, carbonate, bicarbonate, phosphate, hydrogensulfonate, p toluenesulfonate, methanesulfonate, formate, acetate, propionate, butyrate, pyruvate, lactate, oxalate, malonate, maleate, succinate, tartrate, fumarate, glycolate, or citrate.

42. The composition according to any one of Claims 32 to 41, wherein the composition further comprises an antimicrobial.

43. The use of a compound for treating a wound, the compound having the formula:

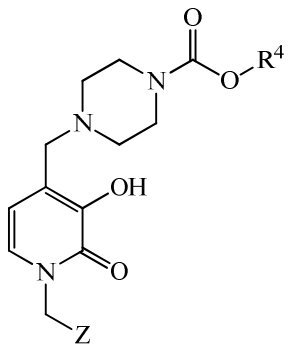


wherein Z is phenyl substituted with from 1 to 5 halogens chosen from fluorine and chlorine;

R^4 is C_1-C_4 linear alkyl or C_3-C_4 branched alkyl;

or a pharmaceutically acceptable salt thereof.

44. The use of a compound for treating a wound, the compound having the formula:



wherein Z is phenyl substituted with from 1 to 5 halogens chosen from fluorine and chlorine;

R^4 is C_1-C_4 linear alkyl or C_3-C_4 branched alkyl;

or a pharmaceutically acceptable salt thereof.

45. The use according to either of Claim 43 or 44, wherein R^4 is methyl.

46. The use according to either of Claim 43 or 44, wherein R^4 is ethyl.

47. The use according to either of Claim 43 or 44, wherein R^4 is *tert*-butyl.

48. The use according to either of Claim 43 or 44, wherein Z is 4-chlorophenyl.

49. The use according to either of Claim 43 or 44, wherein Z is chosen from 2- chlorophenyl, 3-chlorophenyl, 2-fluorophenyl, 3-fluorophenyl, or 4-fluorophenyl.

50. The use according to either of Claim 43 or 44, wherein Z is chosen from 2,3-difluorophenyl, 2,4-difluorophenyl, 2,5-difluorophenyl, 2,6-difluorophenyl, 2,3-dichlorophenyl, 2,4-dichlorophenyl, 2,5-dichlorophenyl, and 2,6-dichlorophenyl.

51. The use according to Claim 43, comprising tert-butyl 4-{[1-(4-chloro-benzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate.

52. The use according to Claim 43, wherein the compound is chosen from:

Methyl 4-{[1-(4-chlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;

Methyl 4-{[1-(3-chlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;

Methyl 4-{[1-(2-chlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;

Ethyl 4-{[1-(4-chlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;

Ethyl 4-{[1-(3-chlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;

Ethyl 4-{[1-(2-chlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;

tert-Butyl 4-{[1-(3-chlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;

tert-Butyl 4-{[1-(2-chlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;

Methyl 4-{[1-(4-fluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;

Methyl 4-{[1-(3-fluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;

Methyl 4-{[1-(2-fluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;

Ethyl 4-{[1-(4-fluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;

Ethyl 4-{[1-(3-fluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;

Ethyl 4-{[1-(2-fluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;

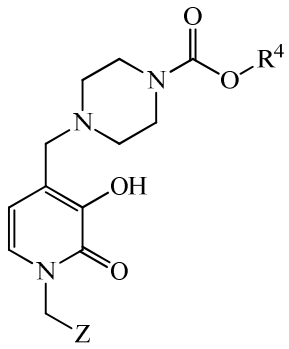
tert-Butyl 4-{[1-(4-fluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;

tert-Butyl 4-{[1-(3-fluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate; and

tert-Butyl 4-{[1-(2-fluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate.

53. The use according to any one of Claims 43 to 52, wherein the compound is a pharmaceutically acceptable salt of an anion chosen from chloride, bromide, iodide, sulfate, bisulfate, carbonate, bicarbonate, phosphate, hydrogensulfonate, p-toluenesulfonate, methanesulfonate, formate, acetate, propionate, butyrate, pyruvate, lactate, oxalate, malonate, maleate, succinate, tartrate, fumarate, glycolate, or citrate.

54. The use of a compound for making a medicament for treating a wound, the compound having the formula:

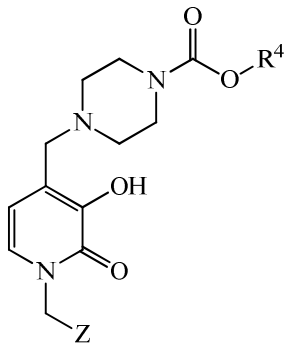


wherein Z is phenyl substituted with from 1 to 5 halogens chosen from fluorine and chlorine;

R^4 is C_1-C_4 linear alkyl or C_3-C_4 branched alkyl;

or a pharmaceutically acceptable salt thereof

55. The use of a compound for making a medicament for treating a wound, the compound having the formula:



wherein Z is phenyl substituted with from 1 to 5 halogens chosen from fluorine and chlorine;

R^4 is C_1-C_4 linear alkyl or C_3-C_4 branched alkyl;

or a pharmaceutically acceptable salt thereof.

56. The use according to either of Claim 54 or 55, wherein R^4 is methyl.

57. The use according to either of Claim 54 or 55, wherein R^4 is ethyl.

58. The use according to either of Claim 54 or 55, wherein R^4 is *tert*-butyl.

59. The use according to either of Claim 54 or 55, wherein Z is 4-chlorophenyl.

60. The use according to either of Claim 54 or 55, wherein Z is chosen from 2- chlorophenyl, 3-chlorophenyl, 2-fluorophenyl, 3-fluorophenyl, or 4-fluorophenyl.

61. The use according to either of Claim 54 or 55, wherein Z is chosen from 2,3-difluorophenyl, 2,4-difluorophenyl, 2,5-difluorophenyl, 2,6-difluorophenyl, 2,3-dichlorophenyl, 2,4-dichlorophenyl, 2,5-dichlorophenyl, and 2,6-dichlorophenyl.

62. The use according to Claim 54, comprising *tert*-butyl 4-{[1-(4-chloro-benzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate.

63. The use according to either of Claim 54 or 55, wherein the compound is chosen from:

Methyl 4-{[1-(4-chlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;

Methyl 4-{[1-(3-chlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;

Methyl 4-{[1-(2-chlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;

Ethyl 4-{[1-(4-chlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;

Ethyl 4-{[1-(3-chlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;

Ethyl 4-{[1-(2-chlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;

tert-Butyl 4-{[1-(3-chlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;

tert-Butyl 4-{[1-(2-chlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;

Methyl 4-{[1-(4-fluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;

Methyl 4-{[1-(3-fluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;

Methyl 4-{[1-(2-fluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;

Ethyl 4-{[1-(4-fluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;

Ethyl 4-{[1-(3-fluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;

Ethyl 4-{[1-(2-fluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;

tert-Butyl 4-{[1-(4-fluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate;

tert-Butyl 4-{[1-(3-fluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate; and

tert-Butyl 4-{[1-(2-fluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl]methyl}piperazine-1-carboxylate.

64. The use according to any one of Claims 54 to 63, wherein the compound is a pharmaceutically acceptable salt of an anion chosen from chloride, bromide, iodide, sulfate, bisulfate, carbonate, bicarbonate, phosphate, hydrogensulfonate, p-toluenesulfonate, methanesulfonate, formate, acetate, propionate, butyrate, pyruvate, lactate, oxalate, malonate, maleate, succinate, tartrate, fumarate, glycolate, or citrate