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(54) Title: PHARMACEUTICAL COMPOSITIONS FOR TREATING DISORDERS OF THE SKIN

(57) Abstract: The invention relates to a method of treating a decubitus ulcer in a subject and a method of identifying a compound useful in the treatment of decubitus. In addition, active dressings, ointments and/or lotions having a means for improving healing of the decubitus ulcer are provided.



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PHARMACEUTICAL COMPOSITIONS FOR TREATING DISORDERS OF THE SKIN

CROSS-REFERENCE TO RELATED APPLICATION

5 This application claims the benefit of U.S. Provisional Patent Application No. 60/592,411, filed July 30, 2004, the entirety of which is incorporated by reference.

TECHNICAL FIELD

10 This invention relates to generally to medicine and biotechnology, and more particularly to methods of treating decubitis ulcers and methods of identifying compounds useful in the treatment of a decubitis ulcer.

BACKGROUND

15 Bed sores, which are also known as pressure sores or decubitis ulcers are painful, odorous and potentially life threatening. Furthermore, severe bed sores (such as a stage III or stage IV) are almost always avoidable with proper care and treatment. Nevertheless, treatment of pressure sores in the United States alone is estimated to cost in excess of \$1 billion annually.

20 In layman's terms, a bed sore is an area of the skin and tissue that is broken down due to external and internal factors. Bed sores occur when a patient is in a sitting or lying position for too long without shifting his or her weight. The constant pressure against the skin causes a decreased blood supply to a particular area of the body. Usually these areas consist of skin covering bony prominences. Without a
25 regular blood supply, the area cannot survive and the affected tissue dies.

 Pressure sores or decubitis ulcers are produced when pressure is exerted on the skin, soft tissue, muscle, and bone by the weight of an individual against a surface beneath the individual. These pressures are often in excess of capillary filling pressure, which in a healthy adult may be about 32 mm Hg. In patients with
30 normal sensitivity, mobility, and mental faculty, pressure sores do not occur. Feedback, both conscious and unconscious, causes the individual to change body position prior to inducing irreversible tissue damage. Irreversible tissue damage may occur after as little as 2 hours of uninterrupted pressure.

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Bed sores commonly occur on the coccyx (area above the tail bone), elbows, heels, hips, ankles, shoulders, back, and the back of the head.

Individuals unable to avoid long periods of uninterrupted pressure, particularly over bony prominences, have an increased risk developing pressure sores. This group typically includes the elderly, neurologically impaired subjects, and those who are acutely hospitalized. These individuals cannot protect themselves from the pressure exerted on their bodies unless they consciously change position or have assistance in doing so. Even the most conscientious patient with an extensive support group and adequate financial resources may develop ulceration resulting from a brief lapse in avoidance of the ill effects of pressure.

If untreated, a pressure sore can progress from a small irritated but unbroken skin patch to a potentially life-threatening wound involving extensive tissue death and infection. Treatment of the serious decubitus ulcer may include drying out of the wound, debriding (excising) the dead tissue, and administering systemic antibiotics.

A number of classification systems for the various stages of pressure ulcers are known to a person of ordinary skill in the art. One such system is the National Pressure Ulcer Advisory Panel classification system (Pressure ulcer prevalence, cost and risk assessment: consensus statement--The National Pressure Ulcer Advisory Panel. *Decubitus*, 1989, 2:24-8). This system consists of four ulceration stages; the stages do not imply that all pressure sores follow a standard progression from stage I to stage IV. Likewise wound healing does not follow a standard regression from stage IV, to stage I, to healed wound. Rather, the system is designed to describe the depth of a pressure sore at the specific time of examination.

Stage I represents intact skin with signs of impending ulceration. Initially this would consist of blanchable erythema from reactive hyperemia that should resolve within 24 hours of the relief of pressure. Warmth and induration also may be present. Continued pressure creates erythema that does not blanch with pressure. This may be the first outward sign of tissue destruction. Finally, the skin may appear white from ischemia.

Stage II represents a partial-thickness loss of skin involving epidermis and possibly dermis. This lesion is visualized as an abrasion, blister, or superficial ulceration.

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Stage III represents a full-thickness loss of skin with extension into subcutaneous tissue but not through the underlying fascia. This lesion is visualized as a crater with or without undermining of adjacent tissue.

5 Stage IV represents full-thickness loss of skin and subcutaneous tissue and extension into muscle, bone, tendon, or joint capsule. Osteomyelitis with bone destruction, dislocations, or pathologic fractures may be present. Sinus tracts and severe undermining commonly are present.

10 Patients over 70 years of age presently account for two thirds of the reported pressure sores. The prevalence rate in nursing homes has been estimated to be 17-28%, and subjects hospitalized with acute illness have an incidence rate of 3-11%. Among patients who are neurologically impaired, pressure sores occur with an annual incidence of 5-8%, and a lifetime risk estimated to be 25-85%. Currently, pressure sores are listed as the direct cause of death in 7-8% of all paraplegics.

15 Disturbingly, even with current medical and surgical therapies, patients who achieve a healed wound have recurrence rates of as high as 90%. Moreover, studies of the direct treatment costs, in the hospital setting, for the treatment of each pressure ulcer range from \$3.55 to \$80 per day (Alterescu V. (1989) The financial costs of inpatient pressure ulcers to an acute care facility, *Decubitus* 2(3):14-23; and Colwell *et al.* (1993) A comparison of the efficacy and cost effectiveness of two
20 methods of managing pressure ulcers, *Decubitus* 6(4):28-36).

Therefore, a need exists in the art for a method of treating a decubitis ulcer.

DISCLOSURE OF THE INVENTION

25 The present invention relates to compositions and methods for the treatment of a decubitis ulcer.

The invention also relates to a method of manufacturing a pharmaceutical or medicament having beneficial properties for the treatment of decubitis ulcers.

30 The invention relates to a method of treating a decubitis ulcer in a subject by administering an effective amount of a compound to a subject having the decubitis ulcer.

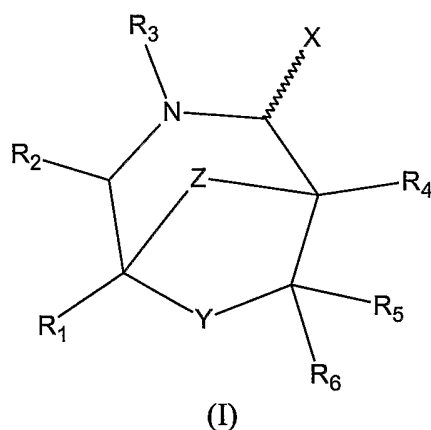
In another exemplary embodiment, a decubitis ulcer is treated in a subject by applying a dressing comprising an effective amount of a compound that improves healing of the decubitis ulcer to the decubitis ulcer on the subject.

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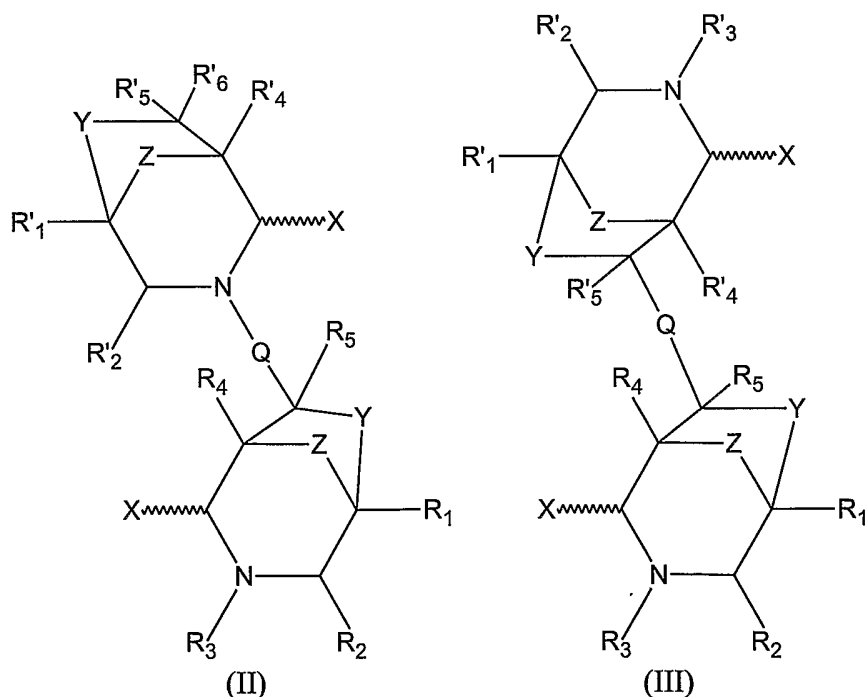
In another exemplary embodiment, the invention provides a method of treating a decubitis ulcer in a subject by applying a dressing to a decubitis ulcer on a subject, wherein the dressing comprises a means for improving healing of the decubitis ulcer.

- 5 In yet another exemplary embodiment, the invention provides a method of treating a decubitis ulcer in a subject by applying an ointment or lotion to a decubitis ulcer on a subject, wherein the ointment or lotion comprises a means for improving healing of the decubitis ulcer.

In another exemplary embodiment, the compound of the invention comprises
 10 an 1,3,3,4,5,6,7-heptamethyl-6-azabicyclo[3.2.1]octane derivative of the general structure (I):



and/or a dimer of the general structure (II) or (III):



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wherein R_1 and R'_1 may be the same or different, and are selected from H, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, cycloalkyl, aryl, heterocycle, aryl C_{1-8} alkyl, heterocycle C_{1-8} alkyl, DD'NC C_{1-8} alkyl, DD'N-aryl, FmocND'-aryl, BocND'-aryl, CbzND'-aryl, DO-aryl, D(O)C-aryl, DO(O)C-aryl, DD'N(O)C-aryl, FmocND'-C C_{1-8} alkyl, BocND'-C C_{1-8} alkyl, CbzND'-C C_{1-8} alkyl, FmocND'-C C_{1-8} aryl, BocND'-C C_{1-8} aryl, and CbzND'-C C_{1-8} aryl;

wherein R_2 and R'_2 may be the same or different, and are selected from H, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, cycloalkyl, aryl, aryl C_{1-8} alkyl, heterocycle C_{1-8} alkyl, amino C_{1-8} alkyl, aminoaryl, C_{1-8} alkyloxyaryl, hydroxyaryl, hydroxy C_{1-8} alkyl, carboxy C_{1-8} alkyl, methyloxycarbonyl C_{1-8} aryl, carboxyaryl, carboalkyloxyaryl, and alkylcarbamoylaryl and -(amino acid side chains), or

wherein R_1 and R_2 , taken together, and R'_1 and R'_2 , taken together, are C_{1-4} alkyl, C_{2-4} alkenyl, cycloalkyl or benzofused cycloalkyl, to form a bridge of 3, 4, 5, and/or 6 terms;

wherein R_3 and R'_3 may be the same or different, and are selected from H, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, cycloalkyl, aryl, aryl C_{1-8} alkyl, heterocycle C_{1-8} alkyl, DD'NC C_{1-8} alkyl, DD'N-aryl, DO-C C_{1-8} alkyl, DO(O)C-C C_{1-8} alkyl, DC(O)O-C C_{1-8} alkyl, DC(O)N(D)C C_{1-8} alkyl, DO-aryl, D(O)C-aryl, DO(O)C-aryl, DO(O)O-aryl, DC(O)N(D)-aryl, -CH(amino acid side-chain)CO₂, -CH(amino acid side-chain)C(O)ND, -CH(CO₂D)-amino acid side chain, CH(CONDD')-amino acid side chain, Fmoc, Boc, and Cbz;

wherein R_4 , R'_4 , R_5 , and R'_5 , may be the same or different, and are selected from H, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, cycloalkyl, aryl, heterocycle, aryl C_{1-8} alkyl, and heterocycle C_{1-8} alkyl;

wherein R_6 , and R'_6 , may be the same or different, and are selected from H, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, cycloalkyl, aryl, heterocycle, aryl C_{1-8} alkyl, heterocycle C_{1-8} alkyl, -C(O)D, -C(O)OD, -C(O)NDD', CH₂OD, CH₂NDD', -C(O)NH-CH(amino acid side chain)C(O)OD, CH₂ND-Fmoc, CH₂ND-Boc, CH₂ND-Cbz;

wherein X, and X', may be the same or different, and are O or S, when X or X' is double bonded to the backbone, and H, when X or X' is joined to the backbone by a single bond;

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wherein Y, Y', Z and Z', may be the same or different, and are selected from O, S, SO, SO₂, and ND;

wherein Q is selected from C=O, CH₂, CONHCH(amino acid side chain)-CO, COND(CH₂)_nCO, C(O)O(CH₂)_nCO, CH₂OC(O)(CH₂)_nCO, and
5 CH₂NDC(O)(CH₂)_nCO, wherein n is an integer between 2 and 6; and

wherein the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and the heterocyclic groups are possibly substituted; and

wherein D, and D', may be the same or different, and are selected from H, C₁₋₈alkyl, C₂₋₈alkenyl, C₂₋₈alkynyl, cycloalkyl, aryl, heterocycle, arylC₁₋₈alkyl;
10 protecting group, -C(O)CH-amino acid side chain)-NHT, -NH-CH(amino acid side chain)COOT, and -CH(amino acid side chain)COOT, where T is H or a C₁₋₈alkyl.

In another exemplary embodiment, a compound that improves healing of and/or treatment of a decubitis ulcer is selected from the group consisting of compounds 1, 2, 5, 7-10, 12, 13, 17, 19-21, 32, 34-36, 38, 40, 44, 58, 60, 64-66, 70,
15 75-79, 83, 87, 91, 95, 99, 101, 103, 138, 145, 152, 154, 163, 164, 168, 172, 174, 176, 178, 184, 186, 192, 322, 324 of Tables 1-3 herein and combinations thereof. In another exemplary embodiment the compound is selected from the group consisting of compounds 91, 325, 9, 50, 13, 144, 42, 25 of Tables 1-3 herein and combinations thereof. In a further exemplary embodiment, the compound is selected from the
20 group consisting of compounds 5, 13, 46, 60, 126, 128, 129, 131, 134, 144, 191 of Tables 1-3 herein and combinations thereof. In a further exemplary embodiment, the compound is selected from the group consisting of compounds 70, 50, 192, 200, 282 and combinations thereof. Some exemplary compounds of the invention are listed in Tables 1-3.

25 In another exemplary embodiment, the invention provides a dressing comprising at least one compound of the invention, wherein the dressing comprises a substance selected from the group consisting of a hydrocolloid, a hydrogel, an alginate, an aquaphor gauze, a paraffin gauze, and combinations thereof.

In another exemplary embodiment, the invention provides administering an
30 antimicrobial agent selected from the group consisting of silver sulphadiazine, cerium nitrate-silver sulphadiazine, mafenide, silver nitrate, nitrofurazone, chlorhexidine, povidone iodine, norfloxacin, mupirocin, gentamicin, bacitracin and combinations thereof in combination with a compound of the invention.

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In another exemplary embodiment, the invention provides one or more compounds that inhibit Smad3 function, for example, a peptide mimetic based on residues 235-331 of cJun, the N-L region of Smad3, and/or the C-terminal region of Smad3 (e.g., the phosphorylation region) (see, International Patent Application
5 PCT/US00/13725 and U.S. Patent Publication 2003-0139366 A1).

BEST MODE(S) FOR CARRYING OUT THE INVENTION

A stage I lesion with signs of impending breakdown may require no dressing, whereas a stage II ulcer confined to the epidermis or dermis may require a
10 dressing, such as a hydrocolloid occlusive dressing (DuoDerm), which maintains a moist environment to facilitate reepithelialization. Current treatment consists of pressure relief, surgical, enzymatic or mechanical debridement, moist wound care, and control of the bacterial load. Topical applications of antimicrobials and platelet-derived growth factor (PDGF) may also be used in the invention (see, Steed, D. L.
15 (1995) Clinical evaluation of recombinant human platelet-derived growth factor for the treatment of lower extremity diabetic ulcers. Diabetic Ulcer Study Group, *J Vasc Surg.* Jan;21(1):71-81). More advanced ulcers are often treated with a regime including wet-to-dry dressings incorporating isotonic sodium chloride solution or dilute Dakins solution (sodium hypochlorite), Silvadene, Sulfamylon, hydrogels
20 (Carrington gel), xerogels (Sorbsan), and vacuum-assisted closure (VAC) sponges. Daily whirlpool use also may serve to irrigate and mechanically debride the wound. While, stage I and some stage II ulcers typically heal on their own, stage III and stage IV ulcers almost always require surgery. Few compounds are known to increase or facilitate healing, particularly of stage II, III and/or IV ulcers. The
25 present invention provides compounds, methods of identifying compounds and methods of using such compounds to treat more advanced decubitus ulcers, such as stage II, III and/or IV ulcers, either with or without surgical closure of the ulcer.

Debridement includes the removal of devitalized and contaminated tissue from wounds, thereby exposing healthier tissue and facilitating wound healing (see,
30 Bowler *et al.* (2001) *Clin. Microbiol. Rev.*, 14(2):244-269). Debridement can be achieved by any of the numerous methods known in the art (for a general review see, Bowler *et al.*). While debridement is used to remove devitalized tissue, which

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helps healthy tissue regenerate, further treatments that promote or stimulate reepithelialization are desired in the art.

It is particularly desirable to discover an enhancing agent and/or a synergistic effect between two or more drugs. Coadministration of several drugs, or
5 combination therapy, is a common medical technique and is often necessary to achieve desired therapeutic objectives. For example, a heart failure patient may be treated with a diuretic in conjunction with a vasodilator and/or a cardiac glucoside, so that the patient will have adequate cardiac output, but be free from edema.

The enhancement of one or more drugs by coadministration of another drug
10 can provide advantages over the administration of either drug individually. For example, many drugs produce undesirable dosage dependent side effects. Therefore, using a combination of drugs provides a method of reducing the dosage, and the side effects, of any one drug. Furthermore, combinational therapies may provide better outcomes by affecting multiple pathways involved in a patient's or subject's medical
15 condition. Therefore, it is desirable to identify compounds having additive and/or synergistic effects.

As used herein, the phrases "*coadministration*," "*in combination with*," "*the combination of*" or similar phrases referring to two or more drugs or compounds means that the compounds are present in the subject being treated at the same time.
20 The compounds may be administered at the same time or sequentially in any order at different points in time. However, the compounds should be administered sufficiently closely in time so as to provide the desired enhancement of treatment effect. Suitable dosing intervals and the order of administration with such compounds will be readily apparent to those skilled in the art, in light of the present
25 disclosure.

As used herein, "*therapeutically-effective amount*" or "*effective amount*" means that amount necessary to achieve an improvement in wound healing; in particular a decubitis ulcer. Methods of determining therapeutically-effective amounts are well known to a practitioner of ordinary skill in the medical arts. For
30 example, an effective amount may be between 1 μ g and 600 μ g/g of an ointment or lotion.

As used herein, "*Treating*" or "*Treatment*" does not mean a complete cure. It means that the symptoms of the underlying wound are reduced, and/or that one or

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more of the underlying cellular, physiological, or biochemical causes or mechanisms causing the symptoms are reduced. It is understood that reduced, as used in this context, means relative to the state of the untreated wound, including the molecular state of the wound, not just the physiological state of the wound.

5 As used herein, "*C_{1-n}alkyl*, *C₂₋₈ alkenyl* and *C₂₋₈ alkynyl*," wherein "n" is 4 or 8, mean linear or branched alkyl radicals, having only single bonds, at least one double bond, or at least one triple bond, respectively. Examples of alkyl groups include, but are not limited to, methyl, ethyl, propyl, isopropyl, butyl, pentyl, hexyl, heptyl, and octyl. Examples of alkenyl groups, include, but are not limited to,
10 ethenyl, propenyl, 1-butenyl, cis-2-butenyl, trans-2-butenyl, 2-methyl-1-propenyl, 1-pentenyl, cis-2-pentenyl, trans-2-pentenyl, and 2-methyl-2-butenyl. Examples of alkynyl groups include, but are not limited to, ethynyl, propynyl; 1-butyne, 2-butyne, 1-pentyne, and 3-methyl-1-butyne.

 As used herein, "*cycloalkyl*" means carbon atom containing ring structure,
15 generally having from 3 to 8 members, and preferably from 5 to 6 members. Examples of cycloalkyl-groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, norbornyl, camphanyl, adamantanyl.

 As used herein, "*aryl*" means a group containing one or more unsaturated
20 rings, each ring having from 5 to 8 members, preferably 5 or 6 members. Examples of aryl groups include, but are not limited to, phenyl, biphenyl and naphthyl.

 As used herein, "*heterocycle*" means a saturated or aromatic heterocycles containing one or more heteroatoms, and preferably one or more N atoms. Examples of heterocycles include, but are not limited to, pyridine, imidazole, pyrrole, indole,
25 triazoles, pyrrolidine, and piperidine.

 As used herein, "*arylalkyl*" means a group having an alkyl and an aryl substituent as defined herein. As an example, arylalkyl includes, but is not limited to, ethylphenyl, isobutylphenyl, benzyl, ethylbenzyl, propylbenzyl, isopropylbenzyl, butylbenzyl, isobutylbenzyl, cyclohexylbenzyl, styrenyl and biphenyl.

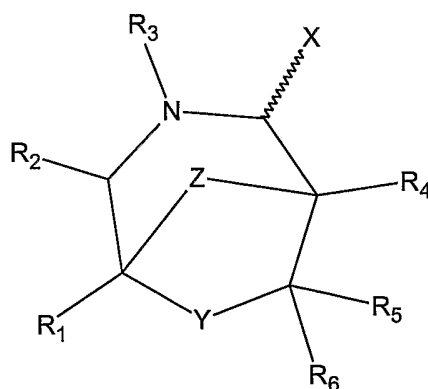
30 The groups fluorenylmethoxycarbonyl, Butoxycarbonyl, Benzyloxycarbonyl, benzyl, phenyl and acetyl are indicated using the common terms Fmoc, Boc, Cbz, Bn, Ph and Ac, respectively.

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The alkyl, alkenyl, alkynyl, cycloalkyl, aryl and heterocyclic groups may be substituted with one or more moieties, and preferably one or two moieties chosen from the group consisting of halogen, cyano, nitro, amino, hydroxy, carboxylic acid, carbonyl and C₁₋₆alkyl. The term “halogen” relates to fluorine, chlorine, bromine and iodine.

The term "pharmaceutically acceptable" refers to compounds and compositions which may be administered to mammals without undue toxicity. Pharmaceutically acceptable salts of an active compound herein may be used, either as an alternative to any compound described herein or in combination with any compound described herein, and are specifically included within the description of any compound, regardless of whether an acceptable and/or pharmaceutically acceptable salt is expressly described. Hence, for the sake of brevity, compound number 91 may be described without reference to an acceptable and/or pharmaceutically acceptable salt thereof, however, it is to be understood that salts of compound 91 have been described. Exemplary pharmaceutically acceptable salts include, but are not limited to, mineral acid salts such as hydrochlorides, hydrobromides, phosphates, sulfates; as well as the salts of organic acids such as acetates, propionates, malonates, benzoates, and the like. Other lists of suitable salts are known in the art and may be found in Remington's Pharmaceutical Sciences, 18th ed., Mack Publishing Company, Easton, Pa., 1985.

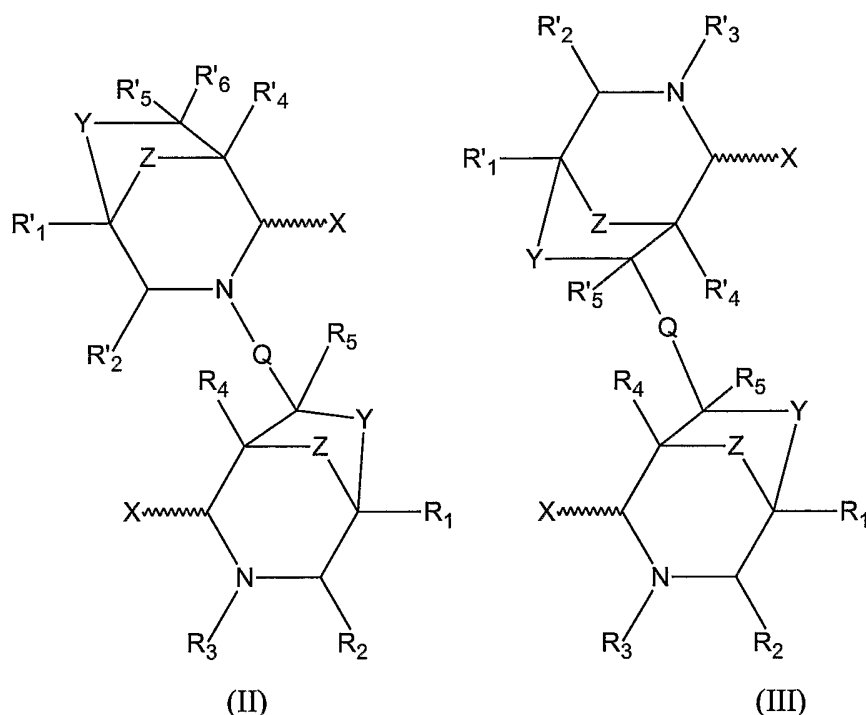
Compounds of the invention include: an 1,3,3,4,5,6,7-heptamethyl-6-azabicyclo[3.2.1]octane derivative of the general structure (I):



(I)

25 and/or a dimer of the general structure (II) or (III):

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wherein R₁ and R'₁ may be the same or different, and are selected from H, C₁₋₈alkyl, C₂₋₈alkenyl, C₂₋₈alkynyl, cycloalkyl, aryl, heterocycle, arylC₁₋₈alkyl, heterocycleC₁₋₈alkyl, DD'NC₁₋₈alkyl, DD'N-aryl, FmocND'-aryl, BocND'-aryl, CbzND'-aryl, DO-aryl, D(O)C-aryl, DO(O)C-aryl, DD'N(O)C-aryl, FmocND'-C₁₋₈alkyl, BocND'-C₁₋₈alkyl, CbzND'-C₁₋₈alkyl, FmocND'-C₁₋₈aryl, BocND'-C₁₋₈aryl, and CbzND'-C₁₋₈aryl;

wherein R₂ and R'₂ may be the same or different, and are selected from H, C₁₋₈alkyl, C₂₋₈alkenyl, C₂₋₈alkynyl, cycloalkyl, aryl, arylC₁₋₈alkyl, heterocycleC₁₋₈alkyl, aminoC₁₋₈alkyl, aminoaryl, C₁₋₈alkyloxyaryl, hydroxyaryl, hydroxyC₁₋₈alkyl, carboxyC₁₋₈alkyl, methyloxycarbonylC₁₋₈aryl, carboxyaryl, carboalkyloxyaryl, and alkylcarbamoylearyl and -(amino acid side chains), or

wherein R₁ and R₂, taken together, and R'₁ and R'₂, taken together, are C₁₋₄alkyl, C₂₋₄alkenyl, cycloalkyl or benzofused cycloalkyl, to form a bridge of 3, 4, 5, and/or 6 terms;

wherein R₃ and R'₃ may be the same or different, and are selected from H, C₁₋₈alkyl, C₂₋₈alkenyl, C₂₋₈alkynyl, cycloalkyl, aryl, arylC₁₋₈alkyl, heterocycleC₁₋₈alkyl, DD'NC₁₋₈alkyl, DD'N-aryl, DO-C₁₋₈alkyl, DO(O)C-C₁₋₈alkyl, DC(O)O-C₁₋₈alkyl, DC(O)N(D)C₁₋₈alkyl, DO-aryl, D(O)C-aryl, DO(O)C-aryl, DO(O)O-aryl, DC(O)N(D)-aryl, -CH(amino acid side-chain)CO₂, -CH(amino acid side-

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chain)C(O)ND, -CH(CO₂D)-amino acid side chain, CH(CONDD')-amino acid side chain, Fmoc, Boc, and Cbz;

wherein R₄, R'₄, R₅, and R'₅, may be the same or different, and are selected from H, C₁₋₈alkyl, C₂₋₈alkenyl, C₂₋₈alkynyl, cycloalkyl, aryl, heterocycle, arylC₁₋₈alkyl, and heterocycleC₁₋₈alkyl;

wherein R₆, and R'₆, may be the same or different, and are selected from H, C₁₋₈alkyl, C₂₋₈alkenyl, C₂₋₈alkynyl, cycloalkyl, aryl, heterocycle, arylC₁₋₈alkyl, heterocycleC₁₋₈alkyl, -C(O)D, -C(O)OD, -C(O)NDD', CH₂OD, CH₂NDD', -C(O)NH-CH(amino acid side chain)C(O)OD, CH₂ND-Fmoc, CH₂ND-Boc, CH₂ND-Cbz;

wherein X, and X', may be the same or different, and are O or S, when X or X' is double bonded to the backbone, and H, when X or X' is a joined to the backbone by a single bond;

wherein Y, Y', Z and Z', may be the same or different, and are selected from O, S, SO, SO₂, and ND;

wherein Q is selected from C=O, CH₂, CONHCH(amino acid side chain)-CO, COND(CH₂)_nCO, C(O)O(CH₂)_nCO, CH₂OC(O)(CH₂)_nCO, and CH₂NDC(O)(CH₂)_nCO, wherein n is an integer between 2 and 6; and

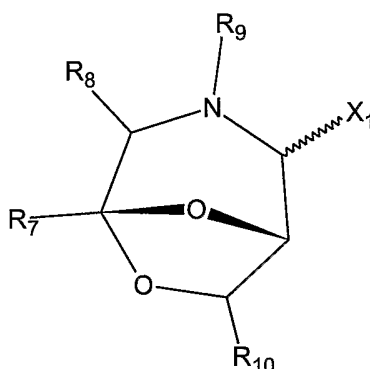
wherein the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and the heterocyclic groups are possibly substituted; and

wherein D, and D', may be the same or different, and are selected from H, C₁₋₈alkyl, C₂₋₈alkenyl, C₂₋₈alkynyl, cycloalkyl, aryl, heterocycle, arylC₁₋₈alkyl; protecting group, -C(O)CH-amino acid side chain)-NHT, -NH-CH(amino acid side chain)COOT, and -CH(amino acid side chain)COOT, where T is H or a C₁₋₈alkyl.

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Exemplary compounds illustrated in Table 1 are derivatives of (1R,5S)-6,8-dioxa-3-azabicyclo[3.2.1]octane, having the general structure shown below:



Compound	X ₁	R ₇	R ₈	R ₉	R ₁₀
1	O	H	H	PhCH ₂	(R)-CO ₂ CH ₃
2	O	H	H	PhCH ₂	(S)-CO ₂ CH ₃
5	O	H	(S)-CH ₃	PhCH ₂	(R)-CO ₂ CH ₃
7	O	H	(R)-CH ₃	PhCH ₂	(R)-CO ₂ CH ₃
8	O	H	(R)-CH ₃	PhCH ₂	(S)-CO ₂ CH ₃
9	O	H	(R)-CH ₂ Ph	PhCH ₂	(S)-CO ₂ CH ₃
10	O	H	(R)-CH ₂ Ph	PhCH ₂	(R)-CO ₂ CH ₃
12	O	H	(S)-CH ₂ Ph	PhCH ₂	(R)-CO ₂ CH ₃
13	O	H	(S)-CH ₂ OBn	PhCH ₂	(R)-CO ₂ CH ₃
17	O	H	(S)-CH ₃ OH	PhCH ₂	(R)-CO ₂ CH ₃
19	O	H	(R)-CH ₃ OH	PhCH ₂	(R)-CO ₂ CH ₃
20	O	H	(R)-CH ₃ OH	PhCH ₂	(S)-CO ₂ CH ₃
21	O	H	=CH ₂	PhCH ₂	(R)-CO ₂ CH ₃
25	S	H	H	PhCH ₂	(R)-CONH(CH ₂) ₂ NH ₂
32	H	H	H	H	(R)-CO ₂ H
34	H	H	H	H	(R)-CO ₂ CH ₃
36	H	H	H	PhCH ₂	(R)-CO ₂ H
38	H	H	H	Fmoc	(R)-CO ₂ H
40	H	H	H	PhCH ₂	(R)-CO ₂ CH ₃
42	H	H	H	Boc	(R)-CO ₂ CH ₃
44	H	H	H	Fmoc	(R)-CO ₂ CH ₃

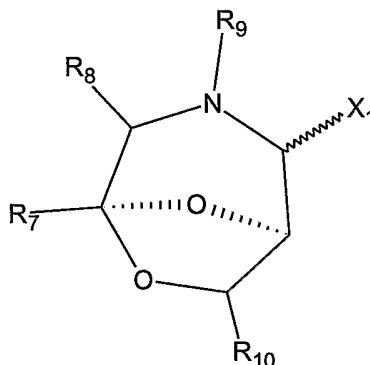
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Compound	X ₁	R ₇	R ₈	R ₉	R ₁₀
46	H	H	H	H	(R)-CONHCH ₃
50	H	H	H	PhCH ₂	(R)-CONHCH ₃
58	H	H	H	H	(R)-CH ₂ OH
60	H	H	H	Fmoc	(S)-CH ₂ OH
64	H	H	H	PhCH ₂	(R)-CH ₂ OH
65	H	H	H	PhCH ₂	(S)-CH ₂ OH
66	H	H	(S)-CH ₂ OBn	PhCH ₂	(R)-CO ₂ CH ₃
70	H	H	(S)-CH ₂ OBn	PhCH ₂	(R)-CH ₂ OH
75	H	H	(S)-COOH	Fmoc	(R)-CO ₂ CH ₃
76	H	H	(S)-COOH	Fmoc	(S)-CO ₂ CH ₃
77	H	H	(R)-COOH	Fmoc	(R)-CO ₂ CH ₃
78	H	H	(R)-COOH	Fmoc	(S)-CO ₂ CH ₃
79	H	H	(S)-CH ₂ OBn	Fmoc	(R)-CO ₂ CH ₃
83	H	H	(S)-CH ₂ OBn	H	(R)-CO ₂ CH ₃
87	H	H	(S)-CH ₂ OH	H	(R)-CO ₂ CH ₃
91	H	H	(S)-CH ₂ OH	Fmoc	(R)-CO ₂ CH ₃
95	H	H	(S)-CH ₂ OH	Fmoc	(R)-CO ₂ CH ₃
99	H	H	(S)-CH ₂ OH	PhCH ₂	(S)-CO ₂ CH ₃
101	H	H	(R)-CH ₂ OH	PhCH ₂	(S)-CO ₂ CH ₃
103	H	H	(S)-CH ₂ OH	Fmoc	(S)-CH ₂ OH
126	H	p-NH ₂ -C ₆ H ₄	H	Ph	(S)-COOCH ₃
128	H	p-NH ₂ -C ₆ H ₄	H	Ph	(S)-CONHCH ₂ CO ₂ CH ₃
129	H	p-NH-(Asp(O ^t Bu)-NH ₂)C ₆ H ₄	H	Ph	(S)-CO ₂ CH ₃
131	H	p-NH-(Asp(O ^t Bu)-NH ₂)C ₆ H ₄	H	Ph	(S)-CONH-Lys(NHBoc)-OMe
134	H	p-NO ₂ -C ₆ H ₄	H	Ph	(S)-COOCH ₃
138	H	Ph	H	PhCH ₂	(R)-CH ₂ OH
144	H	H	(S)-CH ₃	Fmoc	(R)-CO ₂ H
145	H	H	(S)-CH ₃	Fmoc	(S)-CO ₂ H

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Compound	X ₁	R ₇	R ₈	R ₉	R ₁₀
152	H	H	(S)-CH ₃	PhCH ₂	(R)-CO ₂ CH ₃
154	H	H	(R)-CH ₃	PhCH ₂	(R)-CO ₂ CH ₃
163	H	H	(R)-CH ₃	PhCH ₂	(S)-CH ₂ OH
164	H	H	(S)-PhCH ₂	Fmoc	(R)-CH ₂ OH
168	H	H	(S)-PhCH ₂	Fmoc	(R)-CO ₂ CH ₃
172	H	H	(S)-PhCH ₂	PhCH ₂	(R)-CO ₂ CH ₃
174	H	H	(R)-PhCH ₂	PhCH ₂	(R)-CO ₂ CH ₃
176	H	H	(R)-PhCH ₂	H	(R)-CO ₂ CH ₃
178	H	H	(S)-PhCH ₂	H	(R)-CO ₂ CH ₃
184	H	H	(S)-PhCH ₂	PhCH ₂	(R)-CH ₂ OH
186	H	H	(R)-PhCH ₂	PhCH ₂	(R)-CH ₂ OH

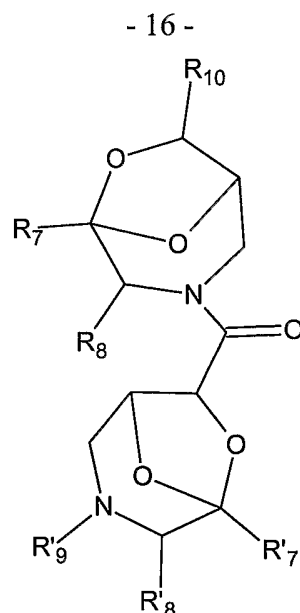
Exemplary compounds illustrated in Table 2 are derivatives of (1S,5R)-6,8-dioxa-3-azabicyclo[3.2.1]octane, having the general structure shown below:



5

Compound	X ₁	R ₇	R ₈	R ₉	R ₁₀
191	O	H	H	PhCH ₂	(R)-CO ₂ CH ₃
192	O	H	(S)-CH ₃	PhCH ₂	(R)-CO ₂ CH ₃
200	O	H	(S)-CH ₂ CH(CH ₃) ₂	PhCH ₂	(R)-CO ₂ CH ₃
282	H	H	(S)-CH ₂ CH(CH ₃) ₂	H	(R)-CO ₂ OH

Additional exemplary compounds illustrated in table 3 are derivatives of either stereoisomer of 6,8-dioxa-3-azabicyclo[3.2.1]octane, having the general structure shown below:



Compound	R ₇	R ₈	R ₉	R' ₇	R' ₈	R ₁₀
322	H	H	H	H	H	CO ₂ CH ₃
324	H	H	PhCH ₂	H	H	CO ₂ CH ₃
325	H	H	PhCH ₂	H	H	CONHCH ₃

Methods of synthesizing the compounds are described, for example, in PCT International Patent Publications WO 04/000324 and WO 01/64686, both by Guarna *et al.* Further compounds of the invention are disclosed in Guarna *et al.* The Guarna *et al.* applications do not disclose the use of the compounds for the treatment of decubitis ulcers.

In particular, the invention provides a method of treating decubitis ulcers in subjects. A subject includes a mammalian subject, for example, a human subject.

Pharmaceutical compositions containing a compound(s) of the invention as the active ingredient(s) can be prepared according to conventional pharmaceutical techniques. *See*, for example, Remington's Pharmaceutical Sciences, 18th Ed. (1990, Mack Publishing Co., Easton, Pa.). Typically, an effective amount of the active ingredient will be admixed with a pharmaceutically acceptable carrier, excipient and/or diluent. The carrier, excipient and/or diluent may take a wide variety of forms depending on the form of preparation desired for administration, for example, enteral (such as, oral), parenteral (such as, intravenous, intramuscular, and subcutaneously) intraperitoneal, transdermal or intrathecal. For example, the

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compounds of the invention may be admixed in Ringer's solution and applied to the wound. The compounds of the invention may also be admixed as a cream or lotion and applied to the wound.

In an exemplary embodiment, a compound(s) of the invention is formulated
5 into an active dressing and/or gel that supplies the active compound(s) to the site of a wound. The active dressing may be composed of a hydrogel, hydrocolloid, Alginate, Aquaphor gauze, Paraffin gauze, gelled foam, or other gel or dressing material known in the art, impregnated with the active compound(s) (for example, *see*, USP 24:NP 19; The United States Pharmacopeia: The National Formulary, USP
10 24:NF 19, United States Pharmacopeial Convention, Inc., Rockville, Md., Jan. 1, 2000; and U.S. Patent 6,599,523. Examples of antimicrobial compounds and/or compositions that may be optionally used in combination with the invention, include, but are not limited to, silver sulphadiazine, cerium nitrate-silver sulphadiazine, mafenide, silver nitrate, nitrofurazone, chlorhexidine, povidone
15 iodine, norfloxacin, mupirocin, gentamicin and/or bacitracin.

International Patent Publication WO 02/38097 describes wound dressings comprising a liquid-permeable top sheet having a wound facing surface and a back surface, and a hydrogel layer on the wound facing surface of the top sheet. The top sheet is adapted to block or restrict passage of liquid from the back surface to the
20 wound facing surface. The hydrogel layer is an insoluble hydrogel adapted to maintain a moist wound healing environment at the wound surface. The hydrogel may contain therapeutic agents such as antimicrobial agents, for sustained release into the wound.

Absorbent sanitary articles for absorbing bodily fluid are also known in the
25 art and may be used with the compounds of the invention, for example, gauze saturated with a salve containing one or more compounds of the invention (Branolind-gauze, PVP-iodide gauze, chlorhexidine gauze and similar). Likewise, laminated collagen films for delayed release of medicaments are known in the art and may be used with the compounds of the invention to produce a therapeutic
30 dressing.

In another exemplary embodiment, the method of the invention includes the optional administration of a protease, including, but not limited to, metalloproteases,

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plasminogen activators/plasminogen system, stratum corneum trypsin-like serine protease, and neuropsin.

Methods and animal models for the study of decubitis ulcers are known in the art and may be used to test the compounds of the invention. For example,
5 methods of inducing pressure ulcers in a rat are described in Bosboom *et al.* (2001) Quantification and localization of damage in rat muscles after controlled loading; a new approach to study the etiology of pressure sores, *Med. Eng. Phys.* 23(3):195-200.

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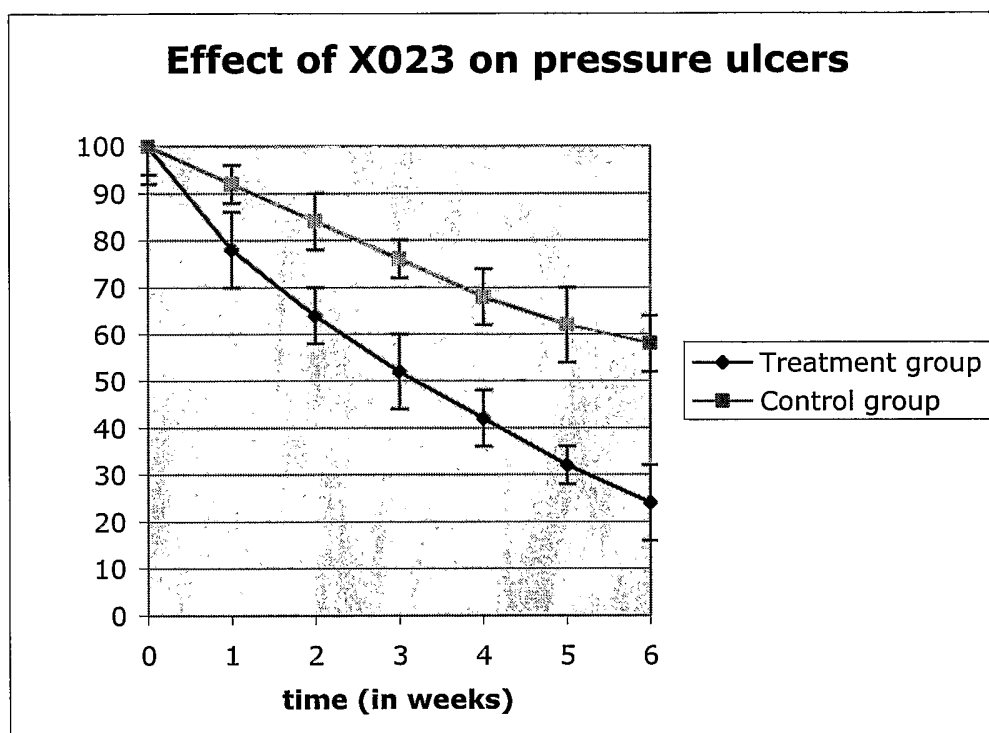
Example I

Pressure ulcers are induced by removing hair from the back of mice, for example, C57bl mice treated with Veet crème, and clamping 2 plates (for example, approximately the size of a dime) onto a skin fold for 4-10 days. After this period the plates are removed, leaving 2 pressure ulcers of approximately similar size.

15

The ulcers in the mice are treated twice a day for 6 weeks. One of the two ulcers on each mouse is treated with saline and the contralateral ulcer is treated with saline containing an effective amount, for example, between about 1mg/ml and 5 mg/ml, of a compound, for example, compound 91 (compound X023 of WO 04/000324), or an acceptable salt thereof. Starting on day 0 and every seven
20 days thereafter, the area of each ulcer is measured and the results are recorded. The results may be plotted as a graph with time on the x-axis and % of original ulcer size on the y-axis, for example, as illustrated below.

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Conclusion: X023 is found to have a significant effect on wound regeneration as compared to the saline control.

In a group of mice paired pressure ulcers of identical size are induced. The left ulcer in each mouse is treated with saline and the right ulcer with saline containing an effective amount, for example, 5 mg/ml of compounds 9, 91, 270, 272, 323 or 325, as described in WO 04/000324. These compounds are found to improve healing of the ulcers relative to saline alone.

10

Example II

In a group of mice paired pressure ulcers of identical size are induced. The left ulcer in each mouse is treated with saline and the right ulcer with saline containing an effective amount, for example, 5 mg/ml of compounds 5, 13, 46, 60, 126, 128, 129, 131, 134, 144, 191, or an acceptable salt thereof. Compounds 5, 13, 46, 60, 126, 128, 129, 131, 134, 144, or 191 were first described in WO 04/000324. These compounds are found to improve healing of the ulcers relative to saline alone.

15

Example III

Mice having paired pressure ulcers are prepared as described in Example I. The left ulcer in each mouse is treated with saline and the right ulcer with saline

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- 20 -

containing an effective amount, for example, 5 mg/ml of compounds 70, 50, 192, 200, or an acceptable salt thereof. Compounds 70, 50, 192, or 200 were first described in WO 04/000324. These compounds are found to improve healing of the ulcers relative to saline alone.

5

Example IV

Mice having paired pressure ulcers are prepared as described in Example I. The left ulcer in each mouse is treated with saline and the right ulcer with saline containing an effective amount, for example, 5 mg/ml, of a combination of two compounds, as described in WO 04/000324, or and acceptable salt thereof. The following combinations of compounds are administered to the mice; compound 91 and 325, 9 and 50, 13 and 144, 42 and 25. These compounds are found to improve healing of the ulcers relative to saline alone.

15

Example V

Mice having paired pressure ulcers are prepared and treated as described in Example I. A library of the compounds described in WO 04/000324, one or more of which may be in the form of an acceptable salt, is prepared and each compound is assayed for improved healing of the ulcers relative to saline alone. One or more compounds are identified as improving the healing of the ulcers.

20

Example VI

Mice having paired pressure ulcers are prepared and treated as described in Example I. A library of the compounds described in WO 04/000324 (including salts thereof) is prepared and the compounds pooled. The pooled compounds are screened for improved healing of the ulcers relative to saline alone. One or more compounds are identified as improving the healing of the ulcers.

25

For example, groups of related compounds may be synthesized either individually or in combination and the group of compounds used to assay for improved healing of the ulcers. For example, compounds 9-12, 13-16, 17-20, 21-22, 27-28, 29-30, 32-33, 34-35, 36-37, 38-39, 40-41, 42-43, 44-45, 46-47, 48-49, 50-51, 52-53, 58-59, 60-61, 62-63, 64-65, 66-69, 70-73, 75-78, 79-82, 83-86, 87-90, 91-98, 99-102, 103-106, 107-110, 111-112, 113-114, 136-143, 144-147, 148-151, 152-155,

30

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156-159, 160-163, 164-171, 172-175, 176-179, 180-183, and 184-187 of Tables 1-3 are examples of related compounds, *see also* WO 04/000324 for the structure of additional compounds, where the related compounds, which includes acceptable salts thereof, may comprise a pool. In addition, related compounds may be
5 synthesized together or in a smaller number of synthesis reactions.

Example VII

Mice having paired ulcers are prepared and treated as described in Example I. Compounds 1, 2, 5, 7-10, 12, 13, 17, 19-21, 32, 34-36, 38, 40, 44, 58, 60, 64-66,
10 70, 75-79, 83, 87, 91, 95, 99, 101, 103, 138, 145, 152, 154, 163, 164, 168, 172, 174, 176, 178, 184, 186, 192, 322, and/or 324 (including salts thereof), as described in WO 04/000324, are tested for the ability to improve healing of the ulcers relative to saline alone. Compounds improving the healing of the ulcers are identified. For example, compound 5 and/or 91 are found to improve wound healing.

15

Example VIII

A combinatorial approach may also be used to identify compounds of the invention. For example, compounds 91-98 may be synthesized and prepared as one pool containing all eight compounds and compounds 5-8, as described in
20 WO 04/000324, prepared as a second pool. Additional pools may be synthesized and prepared by methods known in the art. The pools are then tested for an effect on healing of the ulcers as described in Example I and/or Example XIII. Pools one and/or two are found to improve healing of the ulcers.

In this case, each pool of compounds contains a relatively small number of
25 compounds. Therefore, the compounds may be retested individually and/or in subcombination pools having 2 and/or 3 compounds. Comparison of the results obtained from the individual compounds and one or more pools, either the initially identified pool and/or subcombinations thereof, are used to identify additivity and/or synergism. In the case of 4 compounds contained in the original pool, all of the
30 possible subcombinations and individual compounds will comprise 12 retested groups and provide data regarding individual compound function as well as data regarding additivity and/or synergy.

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Many other approaches for identifying a compound in a library of compounds are known in the art and may be used to identify a compound of the invention. For example, a library of compounds may be produced by the method described in WO 01/64686 and assayed as described herein.

- 5 Compounds 91, from the first pool and compounds 5 and 7 from the second pool are identified as improving healing of ulcers. In addition, it may be found that compounds 5 and 7 are synergistic.

Example IX

- 10 A library and/or combinations of compounds are synthesized by methods known in the art, for example, compounds known to be NGF agonists. For example, a combinatorial library of known NGF agonists is screened for compounds that promote healing of decubitus ulcers. The mouse model described in Example I or an *in vitro* screen, such as described in Example XIII, may be used to screen the library.

15

Example X

- Optionally, a greyhound dog model for decubitus ulcers may be used to study any of the compounds. (*see*, Swaim *et al.* (1993) The greyhound dog as a model for studying pressure ulcers, *Decubitus* 6:32-5, 8-40). For example, one or more
20 compounds identified in a mouse study may be tested for improved healing in the greyhound model.

Example XI

- One or more compounds, such as a compound identified in a mouse study, is
25 tested for improved healing of decubitus ulcers in a human subject (for example, *see*, Wieman *et al.* (1998) Efficacy and Safety of a Topical Gel Formulation of Recombinant Human Platelet-Derived Growth Factor-BB (Becaplermin) in Patients With Chronic Neuropathic Diabetic Ulcers, *Diabetes Care* 21(5):822-827). A compound is formulated as a gel (the active gel) and the compound containing gel is
30 tested (for example, at one or more dosages of about 30, about 50 and about 100 µg/g) and compared to a placebo gel. Each gel is applied for up to 20 weeks in patients with decubitus ulcers. Topical application of the active gel or placebo gel is combined with a standardized regimen of good wound care, which includes initial

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and ongoing sharp debridement of the ulcer, twice-daily moist saline dressing changes, off-loading of pressure from the affected area, and control of infection, if present.

A sufficient number of patients having at least one full thickness (stage III or IV) decubitis ulcer are selected. In the case where more than one ulcer is present, the one that would, in the opinion of the investigator, take the longest time to heal with good wound care practice is designated as the target ulcer. A target ulcer is an ulcer which is identified as having been present for at least 8 weeks prior to being selected, despite previous treatment.

The size of the target ulcer is determined by measuring length multiplied by the width. Initial study visits are scheduled, for example, weekly, and may be decreased after an initial period of time, for example every other week, after the sixth visit.

Moist saline dressings are changed twice daily, for example, once in the morning and once in the evening. Patients are instructed to apply a continuous thin layer of gel to the entire ulcer area once daily, for example, when the dressing is changed in the evening. The amount of study medication to be applied is determined based on the ulcer area. Study medication is administered in conjunction with a standardized regimen of good wound care for 20 weeks or until the target ulcer is completely healed. Complete sharp debridement of ulcers to remove callus, fibrin, and necrotic tissue is performed, for example, by the investigator during clinic visits as necessary.

A compound, for example, as described in any of Examples I-X, is found to improve healing of a decubitis ulcer. Likewise, synergistic activity between two or more compounds may be tested.

Example XII

A library of compounds is screened for biological effect on at least one cell line; for example, PC12 and/or PC3 (*see* WO 04/000324). For example, vaccinia virus-induced growth factor (VGF) production, tropomyosin-related kinase-A, -B, or -C (TrkA, TrkB, or TrkC, preferably TrkA) autophosphorylation, Tissue plasminogen activator (tPA) induction, neuropsinor induction, expression of a reporter construct (*e.g.*, a VGF promoter driving expression of a reporter gene, such

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as LacZ, green fluorescence protein (GFP), CAT, or other reporter genes known in the art (*see*, Possenti *et al.* (1992) Regulatory elements in the promoter region of VGF, a nerve growth factor-inducible gene, *Proc. Natl. Acad. Sci. USA* 89:3815-3819)) and/or nerve growth factor (NGF) displacement may be assayed and the results utilized to identify compounds having a property relating to treatment of a decubitis ulcer. Compounds exhibiting a high biological activity in one or more of the assays described herein are selected for further *in vivo* testing, for example, as described in Example I.

10

Example XIII

A library of compounds is screened for the ability to promote survival of PC12 cells grown in serum free media. PC12 cells are seeded in 96 well plates at a concentration of about 5×10^3 cells per well and cultured in the presence or absence of 5 to 10 μM of the compounds of the library. hrNGF is used as a positive control. After about 60 hours at 37 °C in a humidified, 5% CO₂, atmosphere, 10 μl of 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium (MTT, 0.5 mg/ml in isopropanol) is added to each well and incubated at 37 °C for about 4 hours. 100 μl of 50% dimethylformamide (in 20% SDS, pH 7.4) is added to each well. Colometric readings are determined with a 96 well plate reader at 570 nm. Compounds promoting cell survival are identified.

Optionally, a pool of compounds may be applied to each well, for example, a pool such as described in Example VIII or other pools of compounds. A person of ordinary skill in the art will now recognize that the a large number of compounds or pools may be screened using the method of the invention and individual compounds promoting cell survival, as well as, combinations of compounds (*e.g.*, synergistic combinations) can be identified.

All references, including publications, patents, and patent applications, cited herein are hereby incorporated by reference to the same extent as if each reference were individually and specifically indicated to be incorporated by reference and were set forth in its entirety herein.

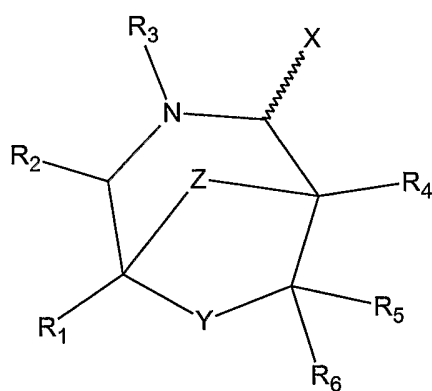
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CLAIMS

What is claimed is:

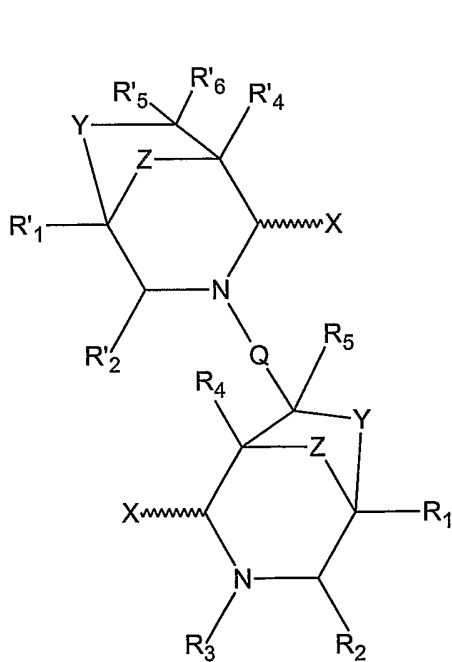
- 5 1. A method of treating a decubitis ulcer in a subject, the method comprising:

 administering an effective amount of a compound to said subject, wherein the compound has the structure of formula (I), (II), (III), or pharmaceutically acceptable salt thereof:

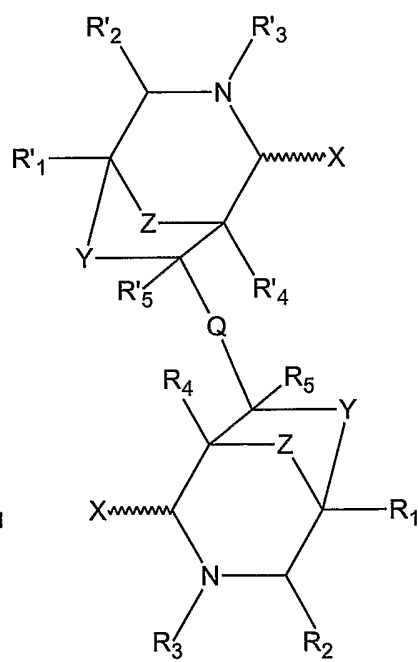
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(I)



(II)



(III)

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wherein the groups fluorenyl[methoxycarbonyl], Butoxycarbonyl, Benzyloxycarbonyl, benzyl, phenyl and acetyl are indicated using the common terms Fmoc, Boc, Cbz, Bn, Ph and Ac, respectively;

wherein R₁ and R'₁ may be the same or different, and are selected from H,
 5 C₁₋₈alkyl, C₂₋₈alkenyl, C₂₋₈alkynyl, cycloalkyl, aryl, heterocycle, arylC₁₋₈alkyl, heterocycleC₁₋₈alkyl, DD'NC₁₋₈alkyl, DD'N-aryl, FmocND'-aryl, BocND'-aryl, CbzND'-aryl, DO-aryl, D(O)C-aryl, DO(O)C-aryl, DD'N(O)C-aryl, FmocND'-C₁₋₈alkyl, BocND'-C₁₋₈alkyl, CbzND'-C₁₋₈alkyl, FmocND'-C₁₋₈aryl, BocND'-C₁₋₈aryl, and CbzND'-C₁₋₈aryl;

10 wherein R₂ and R'₂ may be the same or different, and are selected from H, C₁₋₈alkyl, C₂₋₈alkenyl, C₂₋₈alkynyl, cycloalkyl, aryl, arylC₁₋₈alkyl, heterocycleC₁₋₈alkyl, aminoC₁₋₈alkyl, aminoaryl, C₁₋₈alkyloxyaryl, hydroxyaryl, hydroxyC₁₋₈alkyl, carboxyC₁₋₈alkyl, methyloxycarbonylC₁₋₈aryl, carboxyaryl, carboalkyloxyaryl, and alkylcarbamoylearyl and -(amino acid side chains), or

15 wherein R₁ and R₂, taken together, and R'₁ and R'₂, taken together, are C₁₋₄alkyl, C₂₋₄alkenyl, cycloalkyl or benzofused cycloalkyl, to form a bridge of 3, 4, 5, and/or 6 terms;

wherein R₃ and R'₃ may be the same or different, and are selected from H, C₁₋₈alkyl, C₂₋₈alkenyl, C₂₋₈alkynyl, cycloalkyl, aryl, arylC₁₋₈alkyl, heterocycleC₁₋₈alkyl, DD'NC₁₋₈alkyl, DD'N-aryl, DO-C₁₋₈alkyl, DO(O)C-C₁₋₈alkyl, DC(O)O-C₁₋₈alkyl, DC(O)N(D)C₁₋₈alkyl, DO-aryl, D(O)C-aryl, DO(O)C-aryl, DO(O)O-aryl, DC(O)N(D)-aryl, -CH(amino acid side-chain)CO₂D, -CH(amino acid side-chain)C(O)ND, -CH(CO₂D)-amino acid side chain, CH(CONDD')-amino acid side chain, Fmoc, Boc, or Cbz;

25 wherein R₄, R'₄, R₅, and R'₅, may be the same or different, and are selected from H, C₁₋₈alkyl, C₂₋₈alkenyl, C₂₋₈alkynyl, cycloalkyl, aryl, heterocycle, arylC₁₋₈alkyl, and heterocycleC₁₋₈alkyl;

wherein R₆, and R'₆, may be the same or different, and are selected from H, C₁₋₈alkyl, C₂₋₈alkenyl, C₂₋₈alkynyl, cycloalkyl, aryl, heterocycle, arylC₁₋₈alkyl, heterocycleC₁₋₈alkyl, -C(O)D, -C(O)OD, -C(O)NDD', CH₂OD, CH₂NDD', -C(O)NH-CH(amino acid side chain)C(O)OD, CH₂ND-Fmoc, CH₂ND-Boc, CH₂ND-Cbz;

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wherein X, and X', may be the same or different, and are O or S, when X or X' is double bonded to the backbone, and H, when X or X' is a joined to the backbone by a single bond;

wherein Y, Y', Z and Z', may be the same or different, and are selected from
 5 O, S, SO, SO₂, and ND;

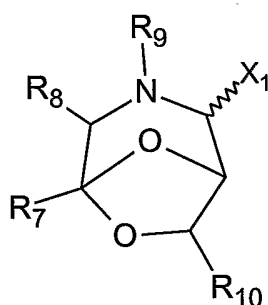
wherein Q is selected from C=O, CH₂, CONHCH(amino acid side chain)-CO, COND(CH₂)_nCO, C(O)O(CH₂)_nCO, CH₂OC(O)(CH₂)_nCO, and CH₂NDC(O)(CH₂)_nCO, wherein n is an integer between 2 and 6;

wherein the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and the heterocyclic
 10 groups are possibly substituted; and

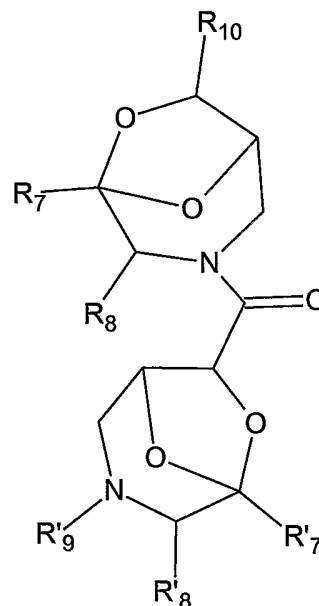
wherein D, and D', may be the same or different, and are selected from H, C₁₋₈alkyl, C₂₋₈alkenyl, C₂₋₈alkynyl, cycloalkyl, aryl, heterocycle, arylC₁₋₈alkyl; protecting group, -C(O)CH-amino acid side chain)-NHT, -NH-CH(amino acid side chain)COOT, and -CH(amino acid side chain)COOT, where T is H or a C₁₋₈alkyl.

15

2. The method according to claim 1, wherein the compound or pharmaceutically acceptable salt is a stereoisomer of the monomer (IV) or dimer (V) having the general structure:



(IV)



(V)

20

wherein X₁ is H or O;

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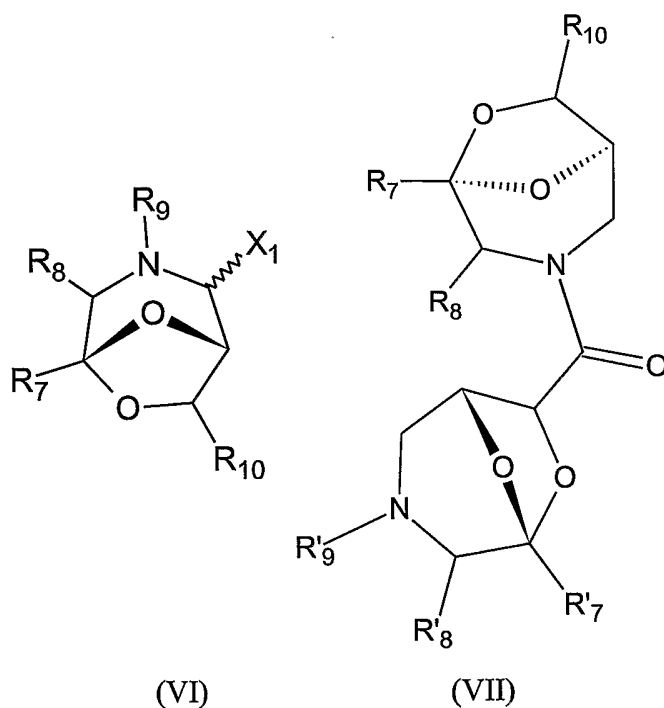
wherein R_7 or R'_7 may be the same or different, and are chosen from H, or phenyl functional groups;

wherein R_8 or R'_8 may be the same or different, and are chosen from H, methyl, methenyl, benzyl, benzyl methyl ether, methoxy, or acetyl functional groups;

wherein R_9 or R'_9 may be the same or different, and are chosen from H, phenyl, benzyl, fluorenyl[methoxycarbonyl] (Fmoc), or butoxycarbonyl (Boc) functional groups; and

wherein R_{10} may be chosen from methyl formate, acetyl, or methoxy functional groups.

3. The method according to claim 1 or claim 2, wherein the compound is a monomer (VI) or dimer (VII) form of the general structure:



15

(VI)

(VII)

wherein X_1 may be H, O or S;

wherein R_7 and R'_7 are H;

wherein R_8 or R'_8 may be the same or different, and are chosen from H, methyl, benzyl, benzyl methyl ether, or methoxy functional groups;

20

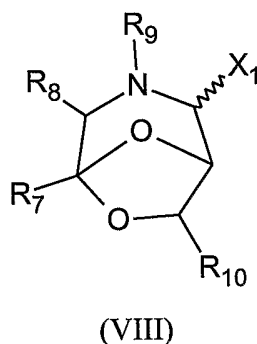
- 29 -

wherein R_9 may be H, fluoreny[methoxycarbonyl] (Fmoc), or butoxycarbonyl (Boc) functional groups; and

wherein R_{10} may be chosen from methyl formate, acetyl, methylformamide, or (2-aminoethyl)formamide functional groups.

5

4. The method according to claim 1 or claim 2, wherein the compound is one of two possible stereoisomers of the general structure (VI):



10

wherein X_1 is H or O;

wherein R_7 may be H, aminocyclohexane, or $p\text{-NH(Asp(O}^t\text{Bu)-NH}_2\text{)C}_6\text{H}_4$ functional groups;

wherein R_8 may be H, alkyl C_{1-4} , or benzyl methyl ether functional groups;

15

wherein R_9 may be H, phenyl, benzyl, benzyl methyl ether, or fluoreny[methoxycarbonyl] (Fmoc), functional groups; and

wherein R_{10} may be methoxy, methyl formate, acetyl, methylformamide, or (2-aminoethyl)formamide functional groups.

20

5. The method according to any one of claims 1-4, comprising applying a dressing to a decubitis ulcer on the subject, wherein the dressing comprises an effective amount of the compound.

25

6. The method according to any one of claims 1-5, wherein administering an effective amount of the compound comprises topically administering the compound.

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7. The method according to any one of claims 1-6, wherein the dressing is selected from the group consisting of a hydrocolloid, a hydrogel, an alginate, an aquaphor gauze, and combinations thereof.

5 8. The method according to any one of claims 1-4, wherein administering an effective amount of the compound comprises parenteral administration of the compound.

10 9. The method according to any one of the preceding claims, wherein the method further comprises administering an antimicrobial agent selected from the group consisting of silver sulphadiazine, cerium nitrate-silver sulphadiazine, mafenide, silver nitrate, nitrofurazone, chlorhexidine, povidone iodine, norfloxacin, mupirocin, gentamicin, bacitracin, and combinations thereof.

15 10. A method of improving healing decubitis ulcer in a subject, the method comprising:
administering to said subject a compound that, *in vitro*, induces vaccinia virus-induced growth factor gene (VGF).

20 11. The method according to claim 11, further comprising administering a compound that induces *in vitro* stimulation of tropomyosin-related kinase-A autophosphorylation.

25 12. A method of improving healing decubitis ulcer in a subject, the method comprising:
administering to said subject a compound that promotes the survival of PC12 cells in an *in vitro* assay.

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13. A method of improving healing decubitis ulcer in a subject, the method comprising:

administering a dressing to a decubitis ulcer on said subject, the dressing comprising a compound that induces vaccinia virus-induced growth factor gene (VGF), tropomyosin-related kinase-A autophosphorylation, or promotes the survival of PC12 cells as identified according to claims 10-12.

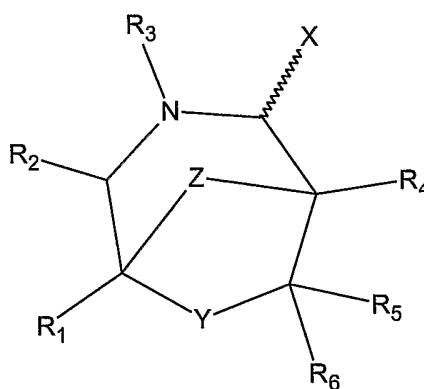
14. A method of treating a decubitis ulcer in a subject, the method comprising:

10 applying a dressing to a decubitis ulcer on said subject, wherein the dressing comprises a means for improving healing of the decubitis ulcer.

15. A method of treating a decubitis ulcer in a subject, the method comprising:

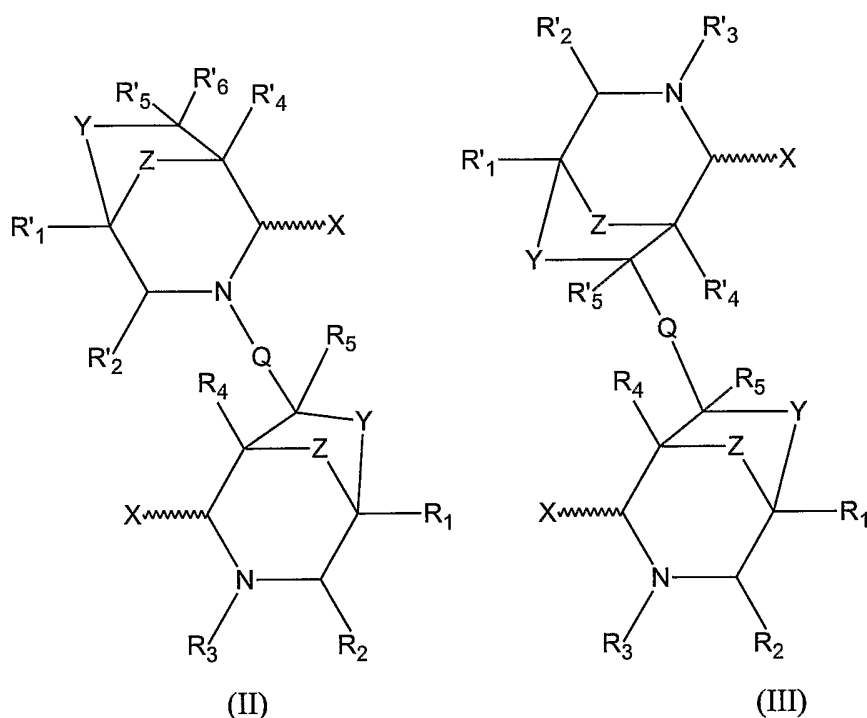
15 applying an ointment or lotion to a decubitis ulcer on a subject, wherein the ointment or lotion comprises a means for treating the decubitis ulcer.

16. A wound dressing comprising a compound having the structure of formula (I), (II), (III), or pharmaceutically acceptable salt thereof:



(I)

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wherein the groups fluorenyl[methoxycarbonyl], Butoxycarbonyl, Benzyloxycarbonyl, benzyl, phenyl and acetyl are indicated using the common
 5 terms Fmoc, Boc, Cbz, Bn, Ph and Ac, respectively;

wherein R₁ and R'₁ may be the same or different, and are selected from H, C₁₋₈alkyl, C₂₋₈alkenyl, C₂₋₈alkynyl, cycloalkyl, aryl, heterocycle, arylC₁₋₈alkyl, heterocycleC₁₋₈alkyl, DD'NC₁₋₈alkyl, DD'N-aryl, FmocND'-aryl, BocND'-aryl, CbzND'-aryl, DO-aryl, D(O)C-aryl, DO(O)C-aryl, DD'N(O)C-aryl, FmocND'-C₁₋₈alkyl, BocND'-C₁₋₈alkyl, CbzND'-C₁₋₈alkyl, FmocND'-C₁₋₈aryl, BocND'-C₁₋₈aryl, and CbzND'-C₁₋₈aryl;

wherein R₂ and R'₂ may be the same or different, and are selected from H, C₁₋₈alkyl, C₂₋₈alkenyl, C₂₋₈alkynyl, cycloalkyl, aryl, arylC₁₋₈alkyl, heterocycleC₁₋₈alkyl, aminoC₁₋₈alkyl, aminoaryl, C₁₋₈alkyloxyaryl, hydroxyaryl, hydroxyC₁₋₈alkyl, carboxyC₁₋₈alkyl, methyloxycarbonylC₁₋₈aryl, carboxyaryl, carboalkyloxyaryl, and alkylcarbamoylearyl and -(amino acid side chains), or
 15

wherein R₁ and R₂, taken together, and R'₁ and R'₂, taken together, are C₁₋₄alkyl, C₂₋₄alkenyl, cycloalkyl or benzofused cycloalkyl, to form a bridge of 3, 4, 5, and/or 6 terms;

20 wherein R₃ and R'₃ may be the same or different, and are selected from H, C₁₋₈alkyl, C₂₋₈alkenyl, C₂₋₈alkynyl, cycloalkyl, aryl, arylC₁₋₈alkyl, heterocycleC₁₋

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8alkyl, DD'NC₁₋₈alkyl, DD'N-aryl, DO-C₁₋₈alkyl, DO(O)C-C₁₋₈alkyl, DC(O)O-C₁₋₈alkyl, DC(O)N(D)C₁₋₈alkyl, DO-aryl, D(O)C-aryl, DO(O)C-aryl, DO(O)O-aryl, DC(O)N(D)-aryl, -CH(amino acid side-chain)CO₂D, -CH(amino acid side-chain)C(O)ND, -CH(CO₂D)-amino acid side chain, CH(CONDD')-amino acid side chain, Fmoc, Boc, or Cbz;

wherein R₄, R'₄, R₅, and R'₅, may be the same or different, and are selected from H, C₁₋₈alkyl, C₂₋₈alkenyl, C₂₋₈alkynyl, cycloalkyl, aryl, heterocycle, arylC₁₋₈alkyl, and heterocycleC₁₋₈alkyl;

wherein R₆, and R'₆, may be the same or different, and are selected from H, C₁₋₈alkyl, C₂₋₈alkenyl, C₂₋₈alkynyl, cycloalkyl, aryl, heterocycle, arylC₁₋₈alkyl, heterocycleC₁₋₈alkyl, -C(O)D, -C(O)OD, -C(O)NDD', CH₂OD, CH₂NDD', -C(O)NH-CH(amino acid side chain)C(O)OD, CH₂ND-Fmoc, CH₂ND-Boc, CH₂ND-Cbz;

wherein X, and X', may be the same or different, and are O or S, when X or X' is double bonded to the backbone, and H, when X or X' is joined to the backbone by a single bond;

wherein Y, Y', Z and Z', may be the same or different, and are selected from O, S, SO, SO₂, and ND;

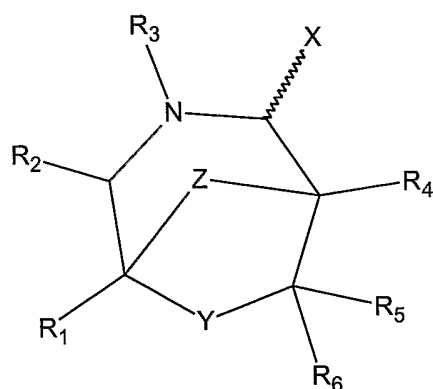
wherein Q is selected from C=O, CH₂, CONHCH(amino acid side chain)-CO, COND(CH₂)_nCO, C(O)O(CH₂)_nCO, CH₂OC(O)(CH₂)_nCO, and CH₂NDC(O)(CH₂)_nCO, wherein n is an integer between 2 and 6;

wherein the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and the heterocyclic groups are possibly substituted; and

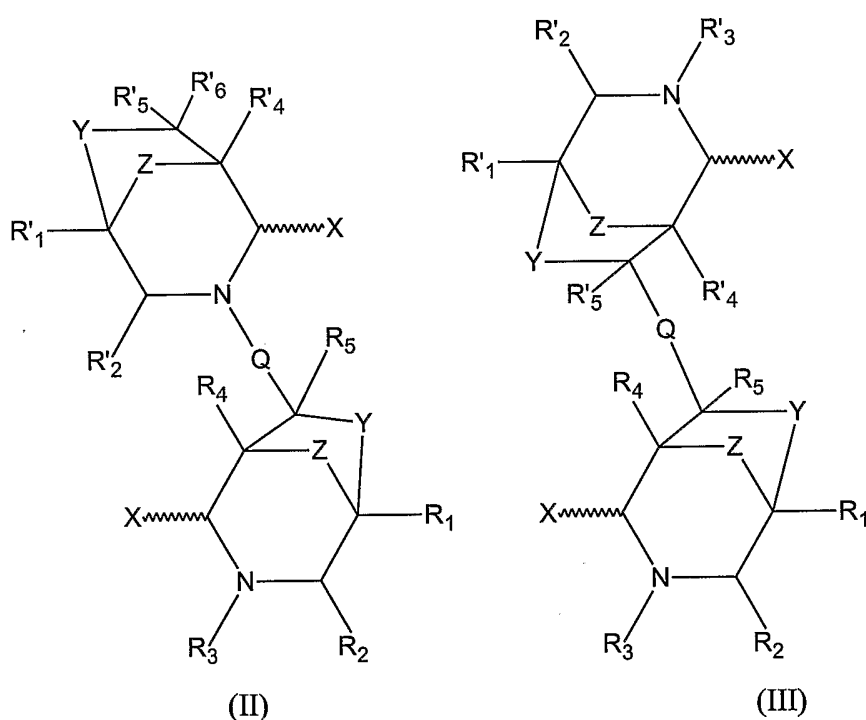
wherein D, and D', may be the same or different, and are selected from H, C₁₋₈alkyl, C₂₋₈alkenyl, C₂₋₈alkynyl, cycloalkyl, aryl, heterocycle, arylC₁₋₈alkyl; protecting group, -C(O)CH-amino acid side chain)-NHT, -NH-CH(amino acid side chain)COOT, and -CH(amino acid side chain)COOT, where T is H or a C₁₋₈alkyl.

17. Use of a compound or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of decubitus ulcers in a subject, wherein the compound has the structure of formula (I), (II), (III), or pharmaceutically acceptable salt thereof:

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(I)



(II)

(III)

5 wherein the groups fluorenyl[methoxycarbonyl], Butoxycarbonyl, Benzyloxycarbonyl, benzyl, phenyl and acetyl are indicated using the common terms Fmoc, Boc, Cbz, Bn, Ph and Ac, respectively;

 wherein R_1 and R'_1 may be the same or different, and are selected from H, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, cycloalkyl, aryl, heterocycle, aryl C_{1-8} alkyl, heterocycle C_{1-8} alkyl, DD'NC $_{1-8}$ alkyl, DD'N-aryl, FmocND'-aryl, BocND'-aryl, CbzND'-aryl, DO-aryl, D(O)C-aryl, DO(O)C-aryl, DD'N(O)C-aryl, FmocND'-C $_{1-8}$ alkyl, BocND'-C $_{1-8}$ alkyl, CbzND'-C $_{1-8}$ alkyl, FmocND'-C $_{1-8}$ aryl, BocND'-C $_{1-8}$ aryl, and CbzND'-C $_{1-8}$ aryl;

 wherein R_2 and R'_2 may be the same or different, and are selected from H, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, cycloalkyl, aryl, aryl C_{1-8} alkyl, heterocycleC $_{1-8}$ alkyl, heterocycleC $_{1-8}$ aryl, and CbzND'-C $_{1-8}$ aryl;

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alkyl, aminoC₁₋₈alkyl, aminoaryl, C₁₋₈alkyloxyaryl, hydroxyaryl, hydroxyC₁₋₈alkyl, carboxyC₁₋₈alkyl, methyloxycarbonylC₁₋₈aryl, carboxyaryl, carboalkyloxyaryl, and alkylcarbamoylearyl and -(amino acid side chains), or

wherein R₁ and R₂, taken together, and R'₁ and R'₂, taken together, are C₁₋₄alkyl, C₂₋₄alkenyl, cycloalkyl or benzofused cycloalkyl, to form a bridge of 3, 4, 5, and/or 6 terms;

wherein R₃ and R'₃ may be the same or different, and are selected from H, C₁₋₈alkyl, C₂₋₈alkenyl, C₂₋₈alkynyl, cycloalkyl, aryl, arylC₁₋₈alkyl, heterocycleC₁₋₈alkyl, DD'NC₁₋₈alkyl, DD'N-aryl, DO-C₁₋₈alkyl, DO(O)C-C₁₋₈alkyl, DC(O)O-C₁₋₈alkyl, DC(O)N(D)C₁₋₈alkyl, DO-aryl, D(O)C-aryl, DO(O)C-aryl, DO(O)O-aryl, DC(O)N(D)-aryl, -CH(amino acid side-chain)CO₂D, -CH(amino acid side-chain)C(O)ND, -CH(CO₂D)-amino acid side chain, CH(CONDD')-amino acid side chain, Fmoc, Boc, or Cbz;

wherein R₄, R'₄, R₅, and R'₅, may be the same or different, and are selected from H, C₁₋₈alkyl, C₂₋₈alkenyl, C₂₋₈alkynyl, cycloalkyl, aryl, heterocycle, arylC₁₋₈alkyl, and heterocycleC₁₋₈alkyl;

wherein R₆, and R'₆, may be the same or different, and are selected from H, C₁₋₈alkyl, C₂₋₈alkenyl, C₂₋₈alkynyl, cycloalkyl, aryl, heterocycle, arylC₁₋₈alkyl, heterocycleC₁₋₈alkyl, -C(O)D, -C(O)OD, -C(O)NDD', CH₂OD, CH₂NDD', -C(O)NH-CH(amino acid side chain)C(O)OD, CH₂ND-Fmoc, CH₂ND-Boc, CH₂ND-Cbz;

wherein X, and X', may be the same or different, and are O or S, when X or X' is double bonded to the backbone, and H, when X or X' is joined to the backbone by a single bond;

wherein Y, Y', Z and Z', may be the same or different, and are selected from O, S, SO, SO₂, and ND;

wherein Q is selected from C=O, CH₂, CONHCH(amino acid side chain)-CO, COND(CH₂)_nCO, C(O)O(CH₂)_nCO, CH₂OC(O)(CH₂)_nCO, and CH₂NDC(O)(CH₂)_nCO, wherein n is an integer between 2 and 6;

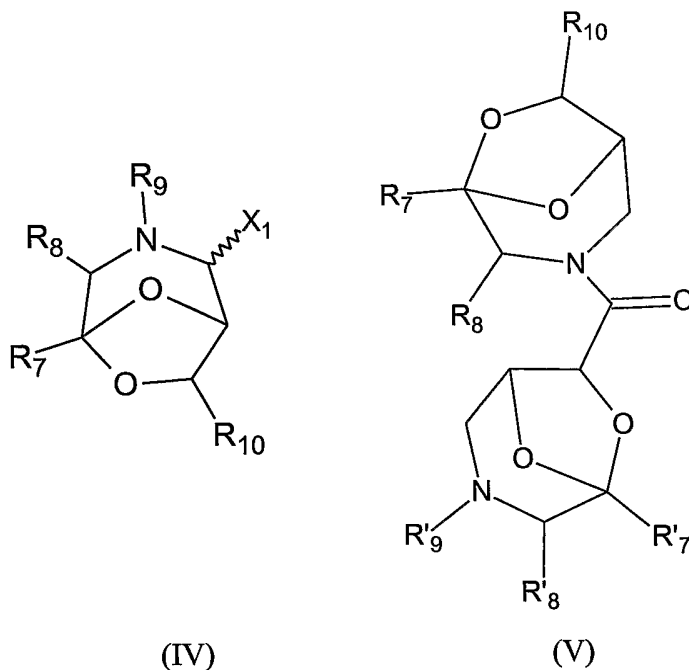
wherein the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and the heterocyclic groups are possibly substituted; and

wherein D, and D', may be the same or different, and are selected from H, C₁₋₈alkyl, C₂₋₈alkenyl, C₂₋₈alkynyl, cycloalkyl, aryl, heterocycle, arylC₁₋₈alkyl;

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protecting group, $-\text{C}(\text{O})\text{CH}(\text{amino acid side chain})-\text{NHT}$, $-\text{NH}-\text{CH}(\text{amino acid side chain})\text{COOT}$, and $-\text{CH}(\text{amino acid side chain})\text{COOT}$, where T is H or a C_{1-8} alkyl.

18. The use of claim 17, wherein the compound or pharmaceutically acceptable salt is a stereoisomer of the monomer (IV) or dimer (V) having the general structure:



10 wherein X_1 is H or O;

wherein R_7 or R'_7 may be the same or different, and are chosen from H, or phenyl functional groups;

wherein R_8 or R'_8 may be the same or different, and are chosen from H, methyl, methenyl, benzyl, benzyl methyl ether, methoxy, or acetyl functional groups;

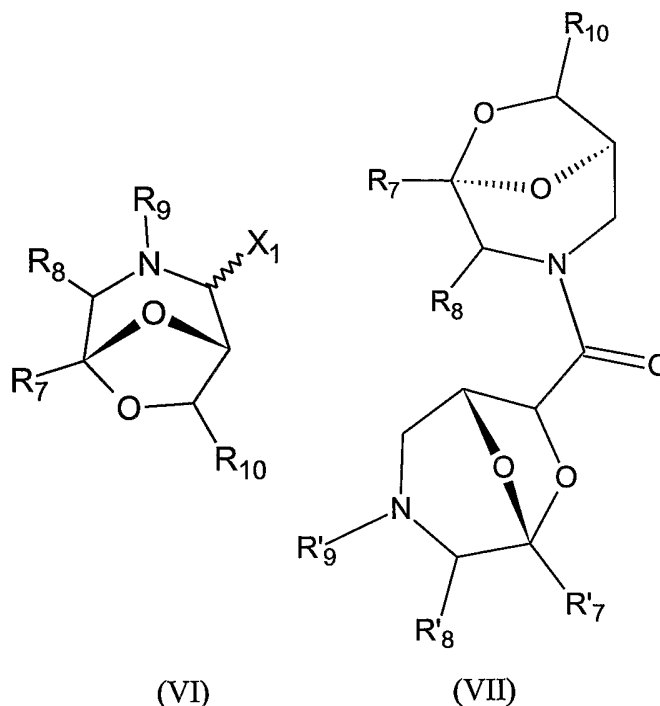
15 wherein R_9 or R'_9 may be the same or different, and are chosen from H, phenyl, benzyl, fluorenyl[methoxycarbonyl] (Fmoc), or butoxycarbonyl (Boc) functional groups; and

wherein R_{10} may be chosen from methyl formate, acetyl, or methoxy functional groups.

20

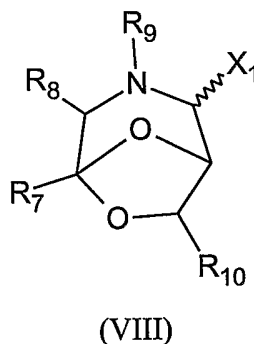
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19. The use of claim 17 or claim 18, wherein the compound is a monomer (VI) or dimer (VII) form of the general structure:



- 5 wherein X_1 may be H, O or S;
 wherein R_7 and R'_7 are H;
 wherein R_8 or R'_8 may be the same or different, and are chosen from H,
 methyl, benzyl, benzyl methyl ether, or methoxy functional groups;
 wherein R_9 may be H, fluorenyl[methoxycarbonyl] (Fmoc), or
 10 butoxycarbonyl (Boc) functional groups; and
 wherein R_{10} may be chosen from methyl formate, acetyl, methylformamide,
 or (2-aminoethyl)formamide functional groups.

20. The use of claim 17 or claim 18, wherein the compound is one of two
 15 possible stereoisomers of the general structure (VI):



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wherein X_1 is H or O;

wherein R_7 may be H, aminocyclohexane, or $p\text{-NH(Asp(O}^t\text{Bu)-NH}_2\text{)C}_6\text{H}_4$ functional groups;

5 wherein R_8 may be H, alkyl C_{1-4} , or benzyl methyl ether functional groups;

wherein R_9 may be H, phenyl, benzyl, benzyl methyl ether, or fluorenyl[methoxycarbonyl] (Fmoc), functional groups; and

wherein R_{10} may be methoxy, methyl formate, acetyl, methylformamide, or (2-aminoethyl)formamide functional groups.

10

21. The use of any one of claim 17-20, wherein the medicament comprises a dressing having an effective amount of the compound.

22. The use of claim 21, wherein the dressing is selected from the group
15 consisting of a hydrocolloid, a hydrogel, an alginate, an aquaphor gauze, and combinations thereof.

23. The use of any one of claim 17-20, wherein the medicament comprises a topically lotion, cream, or ointment.

20

24. The use of any one of claim 17-20, wherein the medicament comprises a parenteral formulation.

25. The use according to any one of claims 17-24, wherein the
25 medicament further comprises an antimicrobial agent selected from the group consisting of silver sulphadiazine, cerium nitrate-silver sulphadiazine, mafenide, silver nitrate, nitrofurazone, chlorhexidine, povidone iodine, norfloxacin, mupirocin, gentamicin, bacitracin, and combinations thereof.