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(54) **METHODS AND COMPOSITIONS TO ENHANCE WHITE BLOOD CELL COUNT**

VERFAHREN UND ZUSAMMENSETZUNGEN ZUR ERHÖHUNG DER ANZAHL WEISSER BLUTZELLEN

PROCEDES ET COMPOSITIONS POUR AMELIORER LA NUMERATION DES GLOBULES BLANCS

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- **BRIDGER G J ET AL: "SYNTHESIS AND STRUCTURE-ACTIVITY RELATIONSHIPS OF PHENYLENEBIS(METHYLENE)-LINKED BIS-TETRAAZAMACROCYCLES THAT INHIBIT HIV REPLICATION. EFFECTS OF MACROCYCLIC RING SIZE AND SUBSTITUENTS ON THE AROMATIC LINKER" JOURNAL OF MEDICINAL CHEMISTRY,US,AMERICAN CHEMICAL SOCIETY. WASHINGTON, vol. 38, no. 2, 20 January 1995 (1995-01-20), pages 366-378, XP000196379 ISSN: 0022-2623**
- **HUNT D W C ET AL: "PHOTOFRIN, BUT NOT BENZOPORPHYRIN DERIVATIVE, STIMULATES HEMATOPOIESIS IN THE MOUSE" IMMUNOPHARMACOLOGY,XX,ELSEVIER SCIENCE PUBLISHERS BV, vol. 26, no. 3, 1 November 1993 (1993-11-01), pages 203-212, XP000567096 ISSN: 0162-3109**

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Description

Technical Field

[0001] The invention is in the field of therapeutics and medicinal chemistry. More particularly, the invention concerns the use of certain cyclic polyamines for the manufacture of a medicament for enhancing white blood cell counts in subjects.

Background Art

[0002] White blood cells play a significant part in maintaining the health and viability of animals, including humans. These white blood cells include neutrophils, macrophage, and basophils/mast cells as well the B and T cells of the immune system. White blood cells are continuously replaced (as are red blood cells and clot forming cells) by the hematopoietic system in response to a number of growth factors, such as colony stimulating factors (CSF) and various cytokines. The nucleotide sequences encoding a number of these growth factors have been cloned and sequenced. Perhaps the most widely known of these is granulocyte colony stimulating factor (G-CSF) which has been approved for use in counteracting the negative effects of chemotherapy. A discussion of the hematopoietic effects of this factor can be found, for example, in U.S. Patent No. 5,582,823.

[0003] While endogenous growth factors are pharmacologically effective, the well known disadvantages of employing proteins and peptides, as opposed to small molecules, as pharmaceuticals underlies the need to add to the repertoire of such growth factors compounds which are themselves small molecules. In another aspect, such small molecules are advantageous over proteins and peptides where production in large quantities are desired.

[0004] A number of cyclic polyamine antiviral agents have been described in a series of U.S. patents and applications over the last several years. These patents include U.S. Patent Nos. 5,021,409; 5,583,131; 5,698,546; and 5,817,807. Copending application Serial No. 09/111,895 filed 8 July 1998 describes additional compounds. These patents describe the structural characteristics of the cyclic polyamine antiviral agents.

[0005] In addition, improved methods for preparation of some of these compounds are described in U.S. Patent Nos. 5,612,478; 5,756,728; 5,801,281; and 5,606,053.

[0006] It has now been found that the cyclic polyamine antiviral agents described in the above-mentioned patents have the effect of enhancing production of white blood cells as well as exhibiting antiviral properties. Thus, these agents are useful where treatment affects the activities within the bone marrow resulting in leukopenia, thus controlling the side-effects of chemotherapy, radiotherapy, enhancing the success of bone marrow transplantation, enhancing wound healing and burn treatment, as well as combating bacterial infections in leukemia.

[0007] Citation of the above documents is not intended as an admission that any of the foregoing is pertinent prior art. All statements as to the date or representation as to the contents of these documents is based on the information available to the applicants and does not constitute any admission as to the correctness of the dates or contents of these documents.

Disclosure of the Invention

[0008] The invention is directed to use of compounds in the manufacture of medicaments for treating animal subjects, in particular, veterinary and human patients, who are defective in white blood cell (WBC) count, or who would benefit from elevation of WBC levels. The use of the invention employs cyclic polyamines including those described in the patents.

[0009] In one aspect, therefore, the invention is directed to use of a compound for the manufacture of a medicament for elevating the white blood cells (WBC) count, in a subject in need of such WBC elevation, which method comprises administering to said subject an amount of a compound of formula (1) or of a pharmaceutical composition thereof effective to elevate WBC levels.

[0010] According to a first aspect of the invention there is provided the use of a compound of the formula

$$Z\text{-linker-}Z' \qquad (1)$$

or pharmaceutically acceptable salt thereof

wherein Z is a cyclic polyamine containing 9-32 ring members of which 3-8 are nitrogen atoms, said nitrogen atoms separated from each other by at least 2 carbon atoms, and wherein said heterocycle may optionally contain additional heteroatoms besides nitrogen and/or may be fused to an additional ring system;

Z' is as defined by Z above, or alternatively is of the formula

$$-N(R)-(CR_2)_n-X$$

wherein each R is independently H or straight, branched or cyclic alkyl (1-6C), n is 1 or 2, and X is an aromatic ring, including heteroaromatic rings, or is a mercaptan;

"linker" represents a bond, alkylene (1-6C) or may comprise aryl, fussed aryl, each optionally containing nitrogen or sulfur atoms and wherein each linker may contain keto groups and/or oxygen atoms;

for preparation of a medicament for use in a method to treat a hematopoietic deficit from chemotherapy or radiation therapy,

aplastic anemia, leukemia, drug-induced anemia, or to enhance the success of transplantation or to en-

hance wound healing, or to ameliorate bacterial inflammation.

[0011] In additional aspects, the invention is directed to pharmaceutical compositions containing the compound of formula (1) for use in effecting WBC count elevation in animal subject.

[0012] The compounds of formula (1) are of the formula:

$$Z\text{-linker-}Z' \qquad (1)$$

wherein Z is a cyclic polyamine containing 9-32 ring members of which 3-8 are nitrogen atoms;

said nitrogen atoms separated from each other by at least 2 carbon atoms,

wherein said heterocycle may optionally contain additional heteroatoms besides nitrogen and/or may be fused to an additional ring system.

[0013] Z' may be embodied in a form as defined by Z above, or alternatively may be of the formula

$$-N(R)-(CR_2)_n-X$$

wherein each R is independently H or straight, branched or cyclic alkyl (1-6C), n is 1 or 2, and

X is an aromatic ring, including heteroaromatic rings, or is a mercaptan;

"linker" represents a bond, alkylene (1-6C) or may comprise aryl, fused aryl, oxygen atoms contained in an alkylene chain, or may contain keto groups or nitrogen or sulfur atoms.

[0014] The preferred forms of the compounds of the invention are discussed below.

Brief Description of the Drawings

[0015]

Figure 1 is a graph showing the response of individual human patients to intravenous administration of a compound of the invention.

Figure 2 is a graph showing the response in elevation of WBC counts observed in HIV-infected patients who received AMD-3100 by continuous infusion for up to 10 consecutive days.

Modes of Carrying Out the Invention

[0016] The compounds useful in the invention are of the general formula set forth as formula (1) above. Certain embodiments are preferred; included among these are the compounds set forth in the above-incorporated U.S. patents.

[0017] In general, preferred embodiments of Z and Z' are cyclic polyamine moieties having from 9-24C that include 3-5 nitrogen atoms. Particularly preferred are 1,5,9,13-tetraazacyclohexadecane; 1,5,8,11,14-pentaazacyclohexadecane; 1,4,8,11-tetraazacylotetradecane; 1,5,9-triazacylcododecane; 1,4,7,10-tetraazacyclododecane; and the like, including such cyclic polyamines which are fused to an additional aromatic or heteroaromatic rings and/or containing a heteroatom other than nitrogen incorporated in the ring. Embodiments wherein the cyclic polyamine contains a fused additional cyclic system or one or more additional heteroatoms are described in U.S. Patent No. 5,698,546 . Also preferred are

3,7,11,17-tetraazabicyclo(13.3.1)heptadeca-1(17), 13,15-triene;

4,7,10,17-tetraazabicyclo(13.3.1)heptadeca-1(17), 13,15-triene;

1,4,7,10-tetraazacyclotetradecane; 1,4,7-triazacyclotetradecane; and

4,7,10-triazabicyclo(13.3.1)heptadeca-1(17),13, 15-triene.

[0018] When Z' is other than a cyclic polyamine as defined in Z, its preferred embodiments are set forth in U. S. Patent No. 5,817,807.

[0019] Preferred forms of the linker moiety include those wherein the linker is a bond, or wherein the linker includes an aromatic moiety flanked by alkylene, preferably methylene moieties. Preferred linking groups include the methylene bracketed forms of 1,3-phenylene, 2,6-pyridine, 3,5-pyridine, 2,5-thiophene, 4,4'-(2,2'-bipyrimidine); 2,9-(1,10-phenanthroline) and the like. A particularly preferred linker is 1,4-phenylene-bis-(methylene).

[0020] Particularly preferred embodiments of the compound of the formula (1) include 2,2'-bicyclam; 6,6'-bicyclam; the embodiments set forth in U.S. Patent No. 5,583,131, and in particular 1,1'-[1,4-phenylene-bis (methylene)]-bis-1,4,8,11-tetraazacyclotetradecane, set forth in U.S. Patent No. 5,021,409, and designated herein AMD3100.

[0021] Other preferred embodiments include

N-[1,4,8,11-tetraazacyclotetradecanyl-1,4-phenylenebis(methylene)]-2-aminomethyl)pyridine;

7,7'-[1,4-phenylenebis(methylene)]bis-4,7,10,17-tetraazabicyclo-[13.3.1] heptadeca-1(17),13,15-triene;

7,7'-[1,4-phenylenebis(methylene)]bis-3,7,11,17-tetraazabicyclo[13.3.1] heptadeca-1(17),13,15-triene;

1,1'-[1,3-phenylenebis(methylene)]-bis-1,4,8,11-tetra-azacyclotetradecane;

1,1'-[1,4-phenylenebis(methylene)]-bis-1,4,8,11-tetra-azacyclotetradecane;

1,1'-[1,4-phenylene-bis-(methylene)]-bis-1,4,7,10-tetraazacyclotetradecane;

1,1'-[1,3-phenylene-bis-(methylene)]-bis-1,4,7,10-tetraazacyclotetradecane;

11,11'-(1,2-propanediyl)bis-1,4,8,11-tetraazacyclotetradecane;
N-[4-(1,4,7-triazacyclotetra-decane)-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine;
N-[7-(4,7,10-triazabicyclo[13.3.1]heptadeca-1(17),13,15-triene)-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine;
N-[7-(4,7,10,17-tetraazabicyclo[13.3.1]heptadeca-1(17),13,15-triene)-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine; and
N-[4-[4,7,10,17-tetraazabicyclo[13.3.1]heptadeca-1(17),13,15-triene]-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine.

[0022] Methods to synthesize the compounds useful in the present invention are set forth in the U.S. patents and application.

[0023] The compounds of the invention may be prepared in the form of prodrugs, i.e., protected forms which release the compounds of the invention after administration to the subject. Typically, the protecting groups are hydrolyzed in body fluids such as in the bloodstream thus releasing the active compound or are oxidized or reduced *in vivo* to release the active compound. A discussion of prodrugs is found in Smith and Williams Introduction to the Principles of Drug Design, Smith, H.J.; Wright, 2nd ed., London (1988).

[0024] The compounds of the invention, as they are polyamines, may be administered prepared in the forms of their acid addition salts or metal complexes thereof. Suitable acid addition salts include salts of inorganic acids that are biocompatible, including HCl, HBr, sulfuric, phosphoric and the like, as well as organic acids such as acetic, propionic, butyric and the like, as well as acids containing more than one carboxyl group, such as oxalic, glutaric, adipic and the like. Typically, at physiological pH, the compounds of the invention will be in the forms of the acid addition salts. Particularly preferred are the hydrobromides. In addition, when prepared as purified forms, the compounds may also be crystallized as the hydrates.

[0025] The compounds of the invention may be administered as sole active ingredients, as mixtures of various compounds of formula (1), and/or in admixture with additional active ingredients that are therapeutically or nutritionally useful, such as antibiotics, vitamins, herbal extracts, antiinflammatories, glucose, antipyretics, analgesics, and the like.

[0026] The compounds of the invention may be formulated for administration to animal subject using commonly understood formulation techniques well known in the art. Formulations which are suitable for particular modes of administration and for compounds of the type represented by those of formula (1) may be found in Remington's Pharmaceutical Sciences, latest addition, Mack Publishing Company, Easton, PA.

[0027] Preferably, the compounds are administered by injection, most preferably by intravenous injection, but also by subcutaneous or intraperitoneal injection, and the like. Additional parenteral routes of administration include intramuscular and intraarticular injection. For intravenous or parenteral administration, the compounds are formulated in suitable liquid form with excipients as required. The compositions may contain liposomes or other suitable carriers. For injection intravenously, the solution is made isotonic using standard preparations such as Hank's solution.

[0028] Besides injection, other routes of administration may also be used. The compounds may be formulated into tablets, capsules, syrups, powders, or other suitable forms for administration orally. By using suitable excipients, these compounds may also be administered through the mucosa using suppositories or intranasal sprays. Transdermal administration can also be effected by using suitable penetrants and controlling the rate of release.

[0029] The formulation and route of administration chosen will be tailored to the individual subject, the nature of the condition to be treated in the subject, and generally, the judgment of the attending practitioner.

[0030] Suitable dosage ranges for the compounds of formula (1) vary according to these considerations, but in general, the compounds are administered in the range of about 0.1 μg/kg-5 mg/kg of body weight; preferably the range is about 1 μg/kg-300 μg/kg of body weight; more preferably about 10 μg/kg-100 μg/kg of body weight. For a typical 70-kg human subject, thus, the dosage range is from about 0.7 μg-350 mg; preferably about 700 μg-21 mg; most preferably about 700 μg-7 mg. Dosages may be higher when the compounds are administered orally or transdermally as compared to, for example, i.v. administration.

[0031] The compounds may be administered as a single bolus dose, a dose over time, as in i.v. or transdermal administration, or in multiple dosages.

[0032] Subjects that will respond favorably to the method of the invention include medical and veterinary subjects generally, including human patients. Among other subjects for whom the methods of the invention is useful are cats, dogs, large animals, avians such as chickens, and the like. In general, any subject who has a WBC deficiency or, more generally, who would profit from the elevation of white blood cell count is appropriate for administration of the invention method.

[0033] Typical conditions which are ameliorated or otherwise benefited by the method of the invention include hematopoietic disorders, such as aplastic anemia, leukemias, drug-induced anemias, and hematopoietic deficits from chemotherapy or radiation therapy. The method of the invention is also useful in enhancing the success of transplantation during and following immunosuppressive treatments as well as in effecting more efficient wound healing and treatment of bacterial inflammation. The method of the present invention is further useful for treating subjects who are immunocompromised or whose immune system is otherwise im-

paired. Typical conditions which are ameliorated or otherwise benefited by the method of the present invention, include those subjects who are infected with a retrovirus and more specifically who are infected with human immunodeficiency virus (HIV). The method of the invention thus targets a broad spectrum of conditions characterized by a deficiency in white blood cell count, or which would benefit from elevation of said WBC count.

[0034] Having now generally described the invention, the same will be more readily understood through reference to the following examples which are provided by way of illustration, and are not intended to be limiting of the present invention, unless specified.

Example 1

Clinical Elevation of WBC Levels - Healthy Volunteers

[0035] Eleven human patients having initial white blood cell counts of 4,000-6,500 cells/mm^3 were used in the study. An intravenous dosing solution of AMD3100 (i.e., 1,1'-[1,4-phenylene-bis(methylene)]-bis-1,4,8,11-tetraazacyclotetradecane) were prepared from a stock solution which is a 1 mg/ml 1:10 dilution of a concentrate in 0.9% saline (normal saline) under sterile conditions. Aliquots from this stock solution were added to 50-ml bags of 0.9% saline for intravenous injection in amounts to achieve the desired dosage levels (10 μg/kg-80 μg/kg).

[0036] The subjects described in this example already contained an indwelling peripheral intravenous catheter. The prescribed amount of AMD3100 was administered over 15 minutes by intravenous fusion in a single dose. Blood samples were obtained prior to the dose, and at various times up to 24 hours after dose administration.

[0037] Eleven human subjects received intravenous administration of AMD-3100 at doses 10, 20, 40, and 80 μg/kg. Five subjects also received a single subcutaneous injection of AMD-3100 at doses of 40 and 80 μg/kg. The effect of AMD3100 given intravenously in these 11 human subject is shown in Figure 1. Three patients were administered dosages of 10 μg/kg (open circles); 3 patients were administered dosages of 20 μg/kg (solid circles); 3 patients were administered 40 μg/kg (open triangles); and 2 patients were administered 80 μg/kg (closed triangles).

[0038] As shown in Figure 1, all of the patients at all levels of administration showed a marked increase in white blood cell count over the succeeding 5-10 hours after administration which WBC count tapered off after about 24 hours, although not, in any case, returning to the original level. Generally, the levels of WBC correlate with the concentration levels of the compound in the bloodstream. For example, one patient who received 80 μg/kg experienced an enhancement of white blood cell count from 6,000 cells/mm^3 to a peak value of 19,000 cells/mm^3. Even the patient showing the least response, who was given 20 μg/kg, experienced an increase from about 6,300 cells/mm^3 to about 9,000 cells/mm^3.

[0039] Thus, it appears that AMD3100 is consistently able to enhance WBC count in human patients.

[0040] While not intending to be bound by any theory, the ability to enhance WBC count across various species and the use of various compounds of formula (1) is believed due to the similarity of action of this compound in its antiviral applications and a possible mechanism for enhancing WBC count. The compounds of the invention are believed to exert their antiviral effects by inhibiting the binding of the second receptor for the HIV virus, CXCR-4, and thus to inhibit entry of the virus into the cell. These particular receptors appear homologous throughout a wide range of species, including mouse, rat, cat and man.

Example 2

Clinical Elevation of WBC Levels - HIV-Infected Patients

[0041] Elevations in WBC counts have also been observed in HIV-infected patients who received AMD-3100 by continuous infusion for up to 10 consecutive days (Figure 2). Eight patients received AMD-3100 at infusion dose rates of 2.5 μg/kg/hr (patients 1-4) and 5.0 μg/kg/hr (patients 5-8). Elevations relative to the baseline were noted in samples taken on days 2, 6, and 11 (immediately prior to end of infusion) of the infusion period. Elevations in WBC count ratios (Day 11 samples) ranged from 1.4 to 2.8 times the baseline. WBC counts returned to baseline 7 days after discontinuation of the infusion. Thus, it appears that AMD3100 is consistently able to enhance WBC count following single dose or with continuous infusion in human patients.

[0042] While not intending to be bound by any theory, the ability to enhance WBC count across various species and the use of various compounds of formula (1) is believed due to the similarity of action of this compound in its antiviral applications and a possible mechanism for enhancing WBC count. The compounds of the invention are believed to exert their antiviral effects by inhibiting the binding of the second receptor for the HIV virus, CXCR-4, and thus to inhibit entry of the virus into the cell. These particular receptors appear homologous throughout a wide range of species, including mouse, rat, cat and man.

Claims

1. The use of a compound of the formula

$$\text{Z-linker-Z'} \qquad (1)$$

or pharmaceutically acceptable salt thereof

wherein Z is a cyclic polyamine containing 9-32 ring members of which 3-8 are nitrogen atoms,

said nitrogen atoms separated from each other by at least 2 carbon atoms, and wherein said heterocycle may optionally contain additional heteroatoms besides nitrogen and/or may be fused to an additional ring system;

Z' is as defined by Z above, or alternatively is of the formula

$$-N(R)-(CR_2)_n-X$$

wherein each R is independently H or straight, branched or cyclic alkyl (1-6C), n is 1 or 2, and X is an aromatic ring, including heteroaromatic rings, or is a mercaptan;

"linker" represents a bond, alkylene (1-6C) or may comprise aryl, fussed aryl, each optionally containing nitrogen or sulfur atoms and wherein each linker may contain keto groups and/or oxygen atoms;

for preparation of a medicament for use in a method to treat a hematopoietic deficit from chemotherapy or radiation therapy,

aplastic anemia, leukemia, drug-induced anemia, or to enhance the success of transplantation or to enhance wound healing, or to ameliorate bacterial inflammation.

2. The use as claimed in claim 1, wherein Z and Z' are both cyclic polyamines.

3. The use as claimed in claim 1 or 2 wherein Z and Z' are identical.

4. The use as claimed in any one of the preceding claims, wherein Z contains 10-24 members and contains 4 nitrogen atoms.

5. The use as claimed in claim 12, wherein Z and Z' are both 1,4,8,11-tetraazocyclotetradecane.

6. The use as claimed in any one of the preceding claims, wherein the linker comprises an aromatic ring bracketed by two methylene moieties.

7. The use as claimed in claim 6, wherein the linker is 1,4-phenylene-bis-methylene.

8. The use as claimed in claim 7, wherein the compound of formula (1) is 1,1'-[1,4-phenylene-bis-(methylene)-bis-1,4,8,11-tetraazacyclotetradecane (AMD3100).

9. The use as claimed in claim 1, wherein the compound of formula (1) is

N-[1,4,8,11-tetraazacyclotetradecanyl-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine;
7,7'[1,4-phenylenebis(methylene)]bis-4,7,10,17-tetraazabicyclo-[13,3.1] heptadeca-1(17),13,15-triene;
7,7'-[1,4-phenylenebis(methylene)]bis-3,7,11,17-tetraazabicyclo-[13,3.1] heptadeca- 1(17),13,15-triene;
1,1'-[1,3-phenylenebis(methylene)]-bis-1,4,8,11-tetraazacyclotetradecane;
1,1'-[1,4-phenylenebis(methylene)]-bis-1,4,8,11-tetraazacyclotetradecane;
1,1'-[1,4-phenylenebis(methylene)]-bis-1,4,7,10-tetraazacyclotetradecane;
1,1'-[1,3-phenylenebis(methylene)]-bis-1,4,7,10-tetraazacyclotetradecane;
11,11'-(1,2-propanediyl)bis-1,4,8,11-tetraazacyclotetradecane;
N-[4-(1,4,7-triazacyclotetra-decane)-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine;
N-[7-(4,7,10-triazabicyclo[13.3.1]heptadeca-1(17),13,15-triene)-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine;
N-[7-(4,7,10,17-tetraazabicyclo[13.3.1]heptadeca-1(17),13,15-triene)-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine; or
N-[4-[4,7,10,17-tetraazabicyclo[13.3.1]heptadeca-1(17),13,15-triene)-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine;

10. The use as claimed in any one of the preceding claims, wherein formula (1) is in the form of its acid addition salt.

11. The use as claimed in claim 10, wherein the acid addition salt is the hydrobromide.

Patentansprüche

1. Verwendung einer Verbindung der Formel

$$Z\text{-Linker-}Z' \qquad (1)$$

oder ein pharmazeutisch verträgliches Salz davon

worin Z für ein cyclisches Polyamin enthaltend 9 - 32 Ringglieder steht, von denen 3 - 8 Stickstoffatome darstellen, wobei die genannten Stickstoffatome durch mindestens 2 Kohlenstoffatome voneinander getrennt sind und worin genannter Heterocyclus außer Stickstoff zusätzliche Heteroatome optional enthalten kann und/oder an ein zusätzliches Ringsystem kondensiert sein kann;

Z' wie durch Z vorstehend definiert ist oder als Alternative die Formel

$$-N-(R)-(CR_2)_n-X$$

darstellt,

worin jedes R unabhängig H oder ein unverzweigtes, verzweigtes oder cyclisches Alkyl (1 - 6 C) darstellt, n für 1 oder 2 steht und X für einen aromatischen Ring, einschließlich heteroaromatischer Ringe, steht oder ein Mercaptan darstellt;

"Linker" eine Bindung, Alkylen (1 - 6 C), darstellt oder aus Aryl, kondensiertem Aryl, bestehen kann, wobei jedes optional Stickstoff- oder Schwefelatome enthält und worin jeder Linker Ketogruppen und/oder Sauerstoffatome enthalten kann;

zur Herstellung eines Medikamentes zur Verwendung in einem Verfahren zur Behandlung eines hämatopoietischen Defizits durch Chemotherapie oder Strahlentherapie,

aplastische Anämie, Leukämie, arzneimittelinduzierte Anämie oder zur Verbesserung des Transplantationserfolgs oder zur Verbesserung der Wundheilung oder zur Besserung bakterieller Entzündungen.

2. Verwendung nach Anspruch 1, worin Z und Z' beide cyclische Polyamine darstellen.

3. Verwendung nach Anspruch 1 oder 2, worin Z und Z' identisch sind.

4. Verwendung nach einem der vorangehenden Ansprüche, worin Z 10 - 24 Glieder und 4 Stickstoffatome enthält.

5. Verwendung nach Anspruch 12, worin Z und Z' beide 1,4,8,11-Tetraazocyclotetradecan darstellen.

6. Verwendung nach einem der vorangehenden Ansprüche, worin der Linker einen aromatischen Ring umfasst, der durch zwei Methylenanteile eingeklammert ist.

7. Verwendung nach Anspruch 6, worin der Linker 1,4-Phenylen-bis-methylen darstellt.

8. Verwendung nach Anspruch 7, worin die Verbindung der Formel (1) 1,1'-[1,4-Phenylen-bis-(methylen)-bis-1,4,8,11-tetraazacyclotetradecan (AMD3100) darstellt.

9. Verwendung nach Anspruch 1, worin die Verbindung der Formel (1) Folgendes darstellt:

N-[1,4,8,11-Tetraazacyclotetradecanyl-1,4-phenylenbis(methylen)]-2-(aminomethyl)pyridin;
7,7'-[1,4-Phenylenbis(methylen)]bis-4,7,10,17-tetraazabicyclo-[13,3.1]heptadeca-1(17),13,15-trien;
7,7'-[1,4-Phenylenbis(methylen)]bis-3,7,11,17-tetraazabicyclo-[13,3.1]heptadeca-1(17),13,15-trien;
1,1'-[1,3-Phenylenbis(methylen)]-bis-1,4,8,11-tetraazacyclotetradecan;
1,1'-[1,4-Phenylenbis(methylen)]-bis-1,4,8,11-tetraazacyclotetradecan;
1,1'-[1,4-Phenylenbis(methylen)]-bis-1,4,7,10-tetraazacyclotetradecan;
1,1'-[1,3-Phenylenbis(methylen)]-bis-1,4,7,10-tetraazacyclotetradecan;
11,11'-(1,2-Propandiyl)bis-1,4,8,11-tetraazacyclotetradecan;
N-[4-(1,4,7-Triazacyclotetradecan)-1,4-phenylenbis(methylen)]-2-(aminomethyl)pyridin;
N-[7-(4,7,10-Triazabicyclo[13.3.1]heptadeca-1(17),13,15-trien)-1,4-phenylenbis(methylen)]-2-(aminomethyl)pyridin;
N-[7-(4,7,10,17-Tetraazabicyclo[13.3.1]heptadeca-1(17),13,15-trien)-1,4-phenylenbis(methylen)]-2-(aminomethyl)pyridin; oder
N-[4-[4,7,10,17-Tetraazabicyclo[13.3.1]heptadeca-1(17),13,15-trien)-1,4-phenylenbis(methylen)]-2-(aminomethyl)pyridin.

10. Verwendung nach einem der vorangehenden Ansprüche, worin Formel (1) in der Form ihres Säureadditionssalzes vorliegt.

11. Verwendung nach Anspruch 10, worin das Säureadditionssalz das Hydrobromid darstellt.

Revendications

1. Utilisation d'un composé de formule :

$$Z - lieur - Z' \qquad (1)$$

ou d'un sel pharmaceutiquement acceptable de celui-ci

dans laquelle Z est un polyamine cyclique contenant de 9 à 32 éléments annulaires dont 3 à 8 atomes d'azote, lesdits atomes d'azote étant séparés les uns des autres par au moins 2 atomes de carbone, et dans laquelle ledit hétérocycle peut facultativement contenir des hétéroatomes supplémentaires en plus de l'azote et / ou peut être fondu dans un système annulaire supplémentaire ;

Z' est tel que défini par Z ci-dessus, ou en variante correspond à la formule :

$$-N(R)-(CR_2)_n-X$$

dans laquelle chaque R est indépendamment

H ou un alkyle (1-6C) droit, ramifié ou cyclique, n est 1 ou 2, et X est un anneau aromatique, y compris les anneaux hétéroaromatiques ou est un mercaptan ;

« lieur » représente un lien, alkylène (1-6C) ou peut comprendre de l'aryle, de l'aryle fondu, chacun comportant facultativement des atomes d'azote ou de soufre et dans laquelle chaque lieur peut contenir des groupes cétones et / ou des atomes d'oxygène ;

pour la préparation d'un médicament destiné à être utilisé dans un procédé de traitement d'un déficit hématopoïétique de chimiothérapie ou de radiothérapie ;

l'anémie aplasique, la leucémie, l'anémie liée à la prise de médicaments ou pour améliorer le succès d'une transplantation ou pour améliorer le traitement des plaies ou pour améliorer le traitement d'une inflammation bactérienne.

2. Utilisation selon la revendication 1, dans laquelle Z et Z' sont tous deux des polyamines cycliques.

3. Utilisation selon la revendication 1 ou 2, dans laquelle Z et Z' sont identiques.

4. Utilisation selon l'une quelconque des revendications précédentes, dans laquelle Z contient de 10 à 24 éléments et contient 4 atomes d'azote.

5. Utilisation selon la revendication 12, dans laquelle Z et Z' sont tous les deux du 1,4,8,11-tétraazocyclotétradécane.

6. Utilisation selon l'une quelconque des revendications précédentes, dans laquelle le lieur comprend un anneau aromatique entouré par deux segments de méthylène.

7. Utilisation selon la revendication 6, dans laquelle le lieur est du 1,4-phénylène-bis-méthylène.

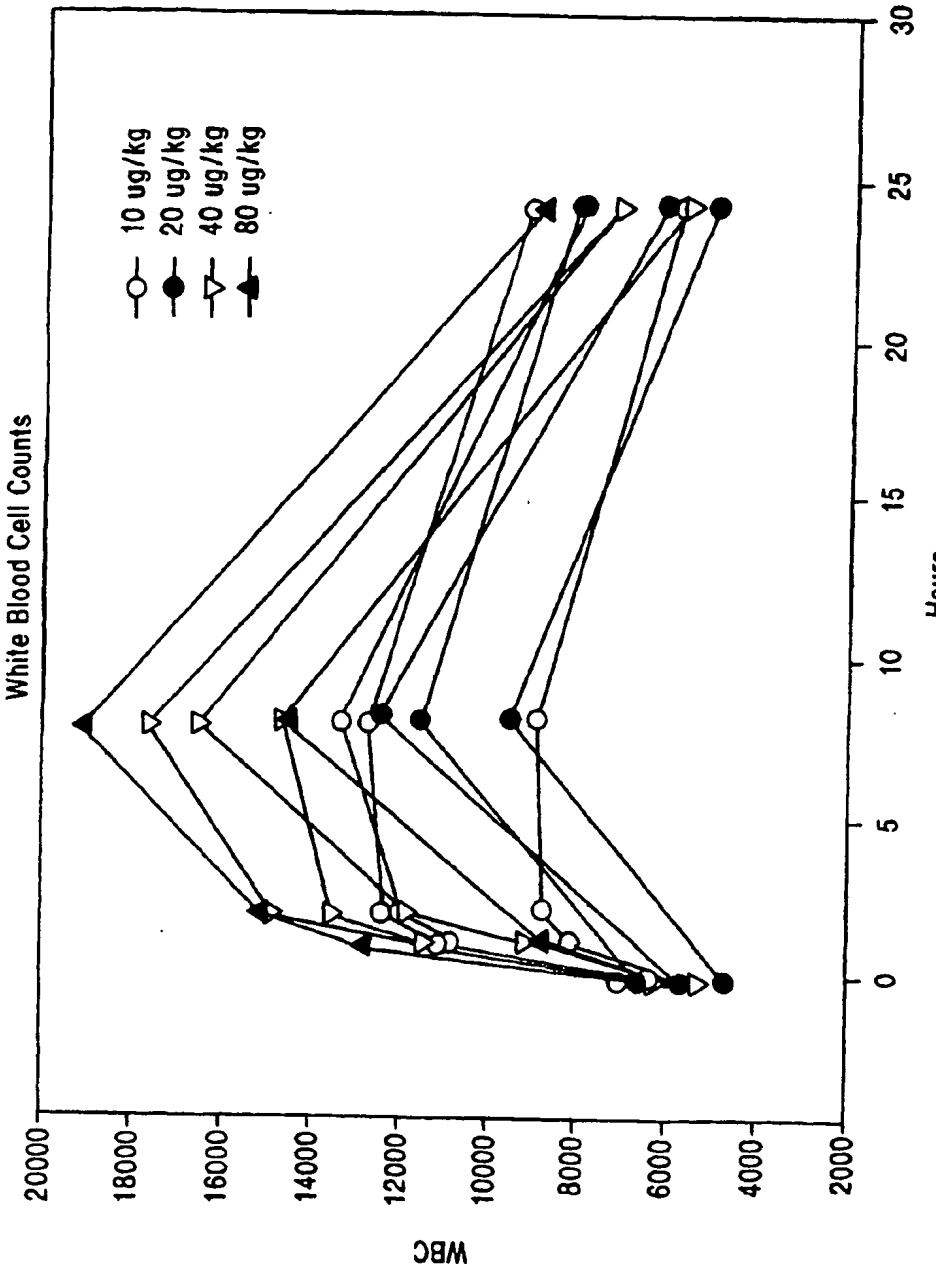
8. Utilisation selon la revendication 7, dans laquelle le composé de formule (1) est du 1,1'-[1,4-phénylène-bis-(méthylène)-bis-1,4,8,11-tétraazacyclotétradécane] (AMD3100).

9. Utilisation selon la revendication 1, dans laquelle le composé de formule (1) est :

de la N-[1,4,8,11-tétraazacyclotétradécanyl-1, 4-phénylènebis(méthylène)]-2-(aminométhyl) pyridine ;
du 7,7'[1,4-phénylènebis(méthylène)]bis-4,7, 10,17-tétraazabicyclo-[13,3,1] heptadéca-1 (17),13, 15-triène ;
du 7,7'[1,4-phénylènebis(méthylène)]bis-3,7, 11,17-tétraazabicyclo-[13,3,1] heptadéca-1 (17),13, 15-triène ;
du 1,1'-[1,3-phénylènebis(méthylène)]-bis-1,4, 8,11-tétraazacyclotétradécane ;
du 1,1'-[1,4-phénylènebis(méthylène)]-bis-1,4, 8,11-tétraazacyclotétradécane ;
du 1,1'-[1,4-phénylènebis(méthylène)]-bis-1,4, 7,10-tétraazacyclotétradécane ;
du 1,1'-[1,3-phénylènebis(méthylène)]-bis-1,4, 7,10-tétraazacyclotétradécane ;
du 11,11'-(1,2-propanediyl)bis-1,4,8,11-tétraazacyclotétradécane ;
du N-[4-(1,4,7-triazacyclotetra-décane)-1,4-phénylènebis(méthylène)]-2-(aminométhyl) pyridine ;
duN-[7-(4,7,10-triazabicyclo[13, 3,1]heptadéca-1(17),13,15-triène)-1,4-phénylènebis(méthylène)]-2-(aminométhyl)pyridine ;
du N-[7-(4,7,10,17-tétraazabicyclo[13, 3,1] heptadéca-1(17),13,15-triène)-1,4-phénylène-bis(méthylène)]-2-(aminométhyl)pyridine; ou
du N-[4-[4,7,10,17-tétraazabicyclo[13, 3,1] heptadéca-1(17),13,15-triène)-1,4-phénylène-bis(méthylène)]-2-(aminométhyl)pyridine.

10. Utilisation selon l'une quelconque des revendications précédentes, dans laquelle la formule (1) est sous la forme de son sel d'addition acide.

11. Utilisation selon la revendication 10, dans laquelle le sel d'addition acide est du bromhydrate.


White Blood Cell Counts
WBC
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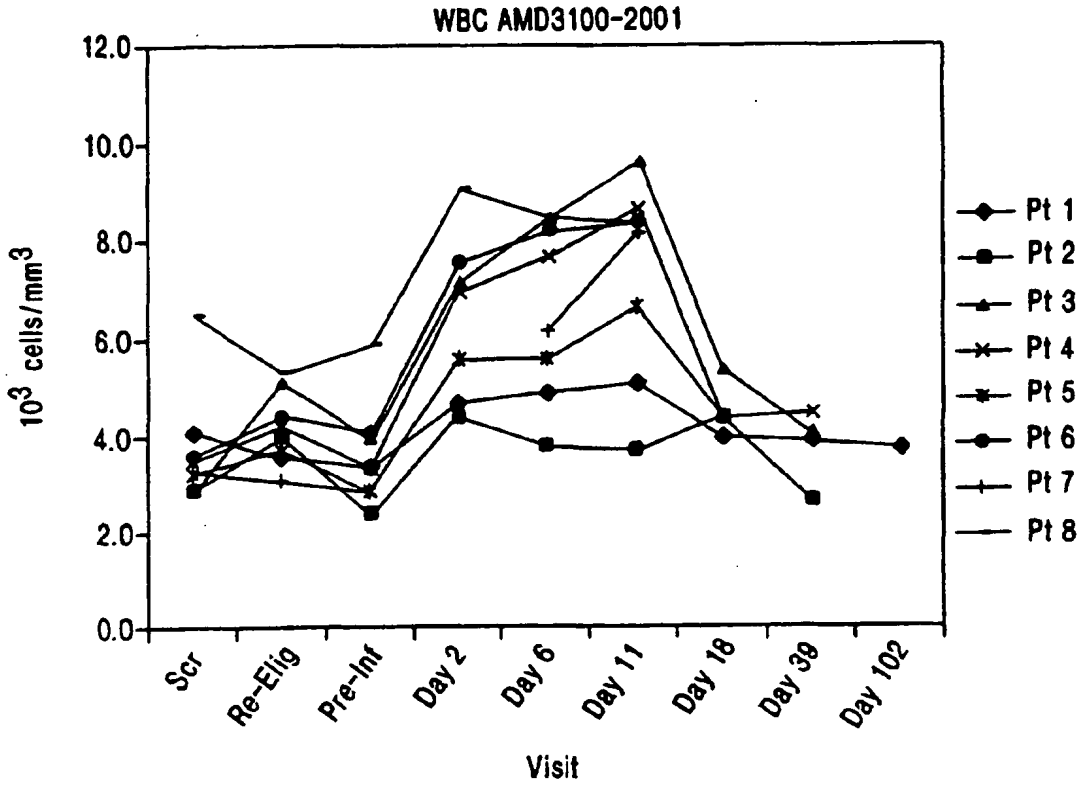
20 ug/kg
40 ug/kg
80 ug/kg
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
5
10
15
20
25
30

FIG. 1


WBC AMD3100-2001
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10.0
8.0
6.0
4.0
2.0
0.0
10^3 cells/mm^3
Scr
Re-Elig
Pre-Inf
Day 2
Day 6
Day 11
Day 18
Day 39
Day 102
Visit
Pt 1
Pt 2
Pt 3
Pt 4
Pt 5
Pt 6
Pt 7
Pt 8

FIG. 2