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NOTICE OF ENTITLEMENT

I,

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being the applicant in respect of this Application state the following:-

The person(s) nominated for the grant of the patent:

The nominated person would be entitled to have assigned to it a patent granted to any one or more of the actual inventors in respect of the invention.

The person(s) nominated for the grant of the patent:

The applicant and nominated person is the basic applicant.

The basic application(s) listed in the declaration made under Article 8 of the PCT is/are the first application(s) made in a Convention country in respect of the invention.

FARMITALIA CARLO ERBA s.r.l.

27th August 1991

GRIFFITH HACK & CO.

Patent Attorneys for and
on behalf of the applicant.

AU9170599

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NEW UREIDO DERIVATIVES OF POLY-4-AMINO-2-CARBOXY-1-METHYL COMPOUNDS

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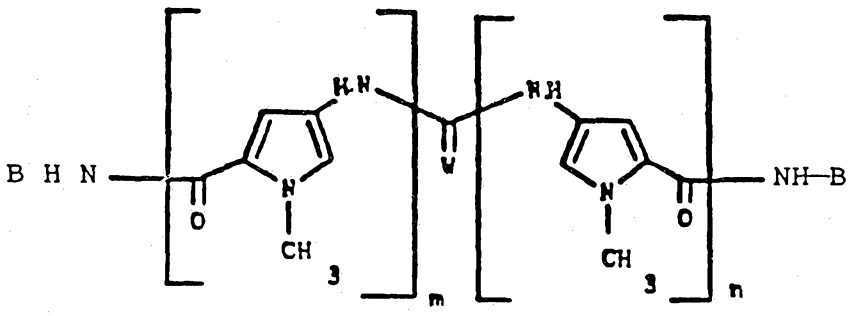
(57) Claim

1. A compound of formula (I):

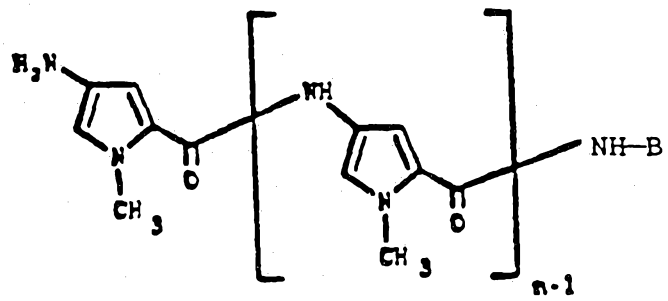


(I)

wherein
each of m and n, being the same, is an integer of 1 to 3;
W is oxygen or sulphur;
each of the B groups, which are the same, is
a) a phenyl or naphthyl group substituted by one or more acid groups;
b) a tetrahydropyranyl, tetrahydrofuranyl or quinoline ring, substituted by one or more acid groups; or
c) a pyranyl or furanyl sugar residue substituted by one or more acid groups;
and the pharmaceutically acceptable salts thereof.

.../2

13. A compound of formula (II):



(II)

wherein n and B are as defined in any one of claims 1 to 3; or a salt thereof.

11. A method of treating a disease state in which TNFα plays a detrimental role, comprising administering to a host suffering from said disease state a therapeutically effective amount of a compound of formula (I) as defined in any one of claims 1 to 7 or a pharmaceutically acceptable salt thereof.

12. A method of neutralizing TNFα activity, comprising administering a therapeutically effective amount of a compound of formula (I) as defined in any one of claims 1 to 7 or a pharmaceutically acceptable salt thereof to a host suffering from AIDS, cachexia, septic shock, graft-versus-host disease, cerebral malaria or rheumatoid arthritis.

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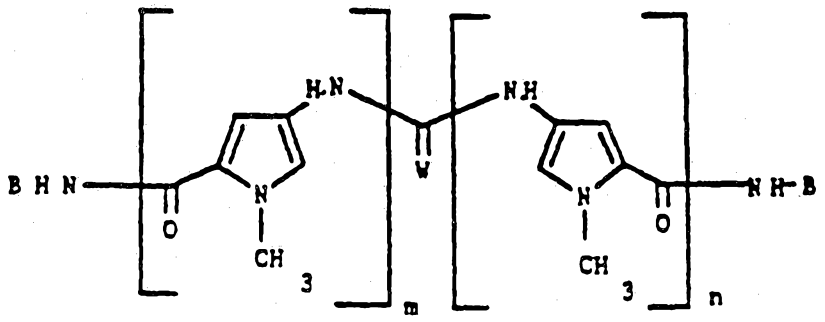


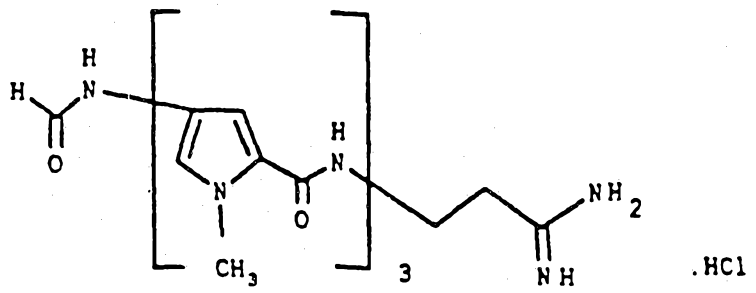
(I)

(57) Abstract

The invention relates to ureido derivatives of substituted pyrroles of formula (I) wherein each of m and n, being the same, is an integer of 1 to 3; W is oxygen of sulphur; each of the B groups, which are the same, is a) a saturated or unsaturated, carbocyclic or condensed carbocylic ring substituted by one or more acid groups; b) a saturated or unsaturated, heteromonocyclic or heterobicyclic ring, containing one or more heteroatoms chosen from nitrogen. oxygen and sulphur, substituted by one or more acid groups; c) a pyranyl or furanyl sugar residue substituted by one or more acid groups; or d) a $-CH_2(CHA)_rCH_2A$ group, wherein each A group, being the same or different, is an acid group and r is 0, 1 or 2; and the pharmaceutically acceptable salts thereof, which are useful as angiogenesis inhibitors.

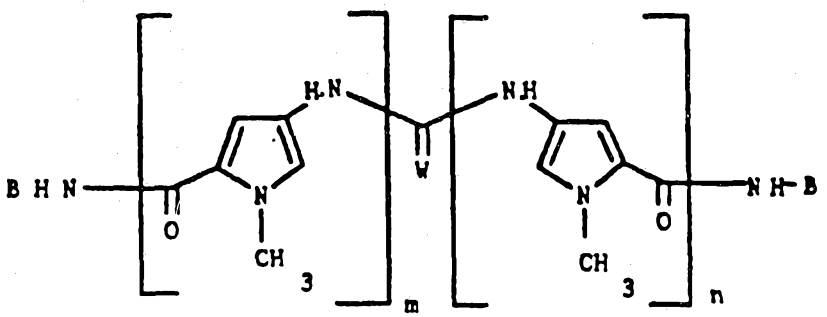
NEW UREIDO DERIVATIVES OF POLY-4-AMINO-2-CARBOXY-1-METHYL COMPOUNDS

The present invention relates to ureido derivatives of substituted pyrroles, to a process for their preparation, to a pharmacological composition containing them, to a method of treating disease states in which TNFα plays a detrimental role, and to intermediate compounds. The pyrrole derivatives of the invention may be regarded as derivatives of Distamycin A which is a known compound having the following formula



Literature referring to Distamycin A includes, for example NATURE 203, 1064 (1964).

The present invention provides ureido derivatives of substituted carboxypyrroles having the following general formula (I)



(I)

wherein

each of m and n, being the same, is an integer of 1 to 3; W is oxygen or sulphur;

each of the B groups, which are the same, is

a) a phenyl or naphthyl group substituted by one or more acid groups;

b) a tetrahydropyranyl, tetrahydrofuranyl or quinoline ring, substituted by one or more acid groups; or

c) a pyranyl or furanyl sugar residue substituted by one or more acid groups;

and the pharmaceutically acceptable salts thereof.

When two or more acid groups are present on a B group they may be the same or different. Examples of acid groups according to the definition of a B group given above for instance may be those chosen from the group including sulfonic, sulfuric, sulfamic, sulfinic, phosphoric, phosphonic, phosphamic or carboxylic acid groups, i.e. SO_3H, SO_4H, SO_3NH_2, SO_2H, PO_4H_2, PO_3O_2, PO_3,NH_3 and CO_2H.

Preferably the B groups are substituted by 1 to 3 of such acid groups.

When B is a sugar residue as defined above under c) it is for example a residue deriving from glucose or ribose.

As already said, the invention includes within its scope also the pharmaceutically acceptable salts of the compounds of formula (I).

Examples of pharmaceutically acceptable salts are either those with inorganic bases, such as sodium, potassium, calcium and aluminium hydroxides, or with organic bases, such as lysine, arginine, N-methyl-glucamine,

triethylamine, triethanolamine, dibenzylamine, methylbenzylamine, di-(2-ethyl-hexyl)-amine, piperidine, N-ethylpiperidine, N,N-diethylaminoethylamine, N-ethylmorpholine, β-phenethylamine, N-benzyl-β-phenethylamine, N-benzyl-N,N-dimethylamine and the other acceptable organic amines.

Preferred compounds according to the present invention are the compounds of formula (I), wherein

each of m and n, being the same, is 2;

W is oxygen;

each of the B groups, which are the same, is a') a phenyl or naphthyl group substituted by 1 to 3 acid groups; b') a tetrahydropyranyl or tetrahydrofuranyl ring substituted by 1 to 3 acid groups; or c') a glucosefuranosyl residue substituted by 1 to 3 acid groups; and the pharmaceutically acceptable salts thereof.

Specific examples of preferred compounds of the invention, are the following (in the nomenclature used, references to "4,2-pyrrolecarbonyl" are to be taken to indicate that the carbonyl group is attached to the 2-position, and an amino group is attached to the 4-position, of the pyrrole ring):

8,8'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino (N-methyl-4,2-pyrrole)carbonylamino))bis(1,3-naphthalendisulfonic acid);

8,8'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis(3,5-naphthalendisulfonic acid);

8,8'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis(2,5-naphthalendisulfonic acid);

8,8'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis(2,4-naphthalendisulfonic acid);

8,8'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis(1,6-naphthalendisulfonic acid);

8,8'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis(2,6-naphthalendisulfonic acid);

8.8'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis(3,6-naphthalendisulfonic acid);

8.8'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis(1,5-naphthalendisulfonic acid);

8,8'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis (1-naphthalensulfonic acid);

8,8'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis (3-naphthalensulfonic acid);

8,8'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino (N-methyl-4,2-pyrrole)carbonylimino))bis(5- naphthalen-sulfonic acid);

8,8'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino (N-methyl-4,2-pyrrole)carbonylimino))bis(1,3,5-naphthalentri-sulfonic acid);

8,8'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino (N-methyl-4,2-pyrrole)carbonylimino))bis(1,4,6-naphthalentri-sulfonic acid);

8,8'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino (N-methyl-4,2-pyrrole)carbonylimino))bis(2,4,6-naphthalentri-sulfonic acid);

8,8'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino (N-methyl-4,2-pyrrole)carbonylimino))bis(1,3,6-naphthalentri-sulfonic acid);

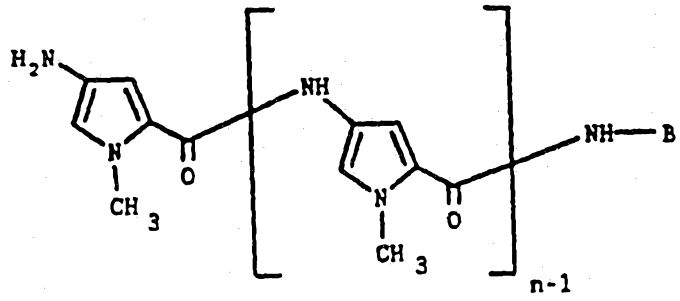
8,8'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino (N-methyl-4,2-pyrrole)carbonylimino))bis(2,3,5-naphthalen-sulfonic acid);

2,2'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino (N-methyl-4,2-pirrole)carbonylimino))bis(2-deoxy-D-glucose-6-sulphate); and

2,2'(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino (N-methyl-4,2-pyrrole)carbonylimino))bis(2-deoxy-D-glucose-6-phosphate);

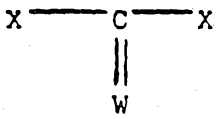
and the pharmaceutically acceptable salts thereof, in particular the sodium and potassium salts.

The compounds of the invention, and the salts thereof, can be prepared by a process comprising reacting a compound of formula (II)



(II)

wherein n and B are as defined above, or a salt thereof, with a compound of formula (III)



(III)

wherein W is as defined above, and each of the X groups, which may be the same or different, is a good leaving group, and if desired, salifying a compound of formula (I) thus obtained; and/or if desired, obtaining a free compound of formula (I) from a salt thereof.

A salt of a compound of formula (II) may be a salt with inorganic bases, for example those mentioned above as to the pharmaceutically acceptable salts of the invention, the sodium and potassium salts being the preferred.

Preferred examples of good leaving groups, according to the meaning of X, are halogen atoms, in particular chlorine, or

other easily displaceable groups such as, imidazolyl, triazolyl, p-nitrophenoxy or trichlorophenoxy.

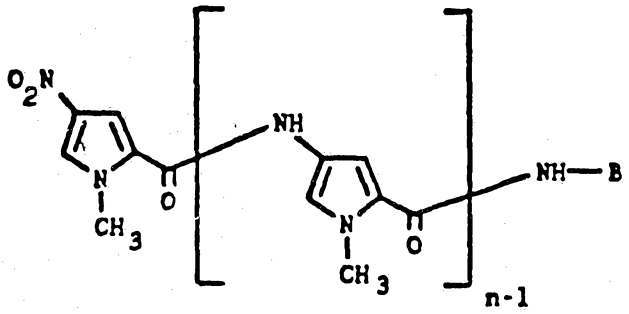
The reaction of a compound of formula (II), or a salt thereof, with a compound of formula (III) is an analogy process and can be carried out according to well known methods; for example according to the conditions described in organic chemistry for this kind of reaction, i.e. for synthesis of urea derivatives. Preferably when in a compound of formula (III) X is an halogen atom, e.g. chlorine, the reaction may be carried out at a molar ratio of compound (II), or a salt thereof: compound (III) from about 1:1 to about 1:4. The reaction is preferably performed in organic solvents such as dimethylsulphoxide, hexamethyl-phosphotriamide, dimethylacetamide or, preferably, dimethyl-formamide, or their aqueous mixtures, or in water/dioxane or water/toluene mixtures, in the presence of either an organic base such as triethylamine or diisopropylethylamine, or an inorganic base such as sodium bicarbonate or sodium acetate. The reaction temperature may vary from about -10°C. to about 50°C. and the reaction time from about 1 to about 12 hours.

The compounds of formula (I) prepared according to the above described procedures may be purified by conventional methods such as by silica gel or alumina column chromatography, and/or by rechrystallization from organic solvents such as lower aliphatic alcohols or dimethylformamide.

Analogously salification of a compound of formula (I) can be carried out by known methods in the art.

The present invention also provides a compound of formula (II) or a salt thereof as defined above. The compounds of formula (II) may be obtained according to known procedures.

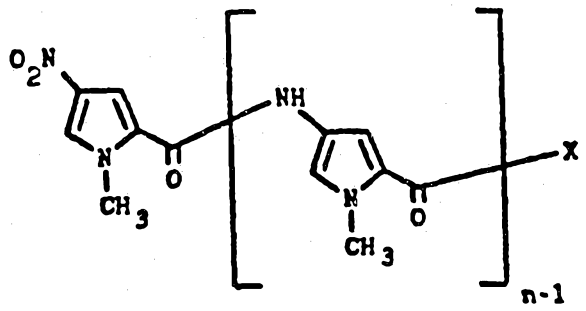
The present invention additionally provides a process for producing a compound of formula (II), or a salt thereof, which comprises reducing the corresponding compound of formula (IV):



(IV)

wherein n and B are as defined above.

The reduction is carried out by methods well known in the art. The compounds of formula (IV) may be obtained by reacting an amine of formula $B\text{-}NH_2$, where B is defined as above, with a compound of formula (V)



(V)

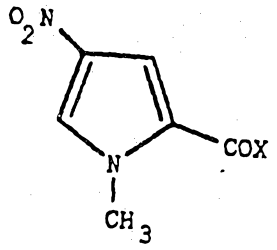
wherein

n and X are as defined above.

AUSTRALIA PATENT OFFICE

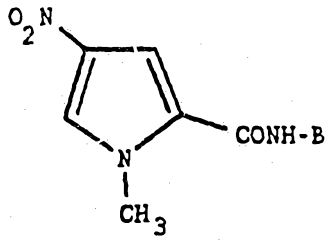
Also the reaction of an amine of formula $B-NH_2$ with a compound of formula (V) is a well known process.

Alternatively a compound of formula (IV) wherein n is 2 or 3 may be obtained by a multi-step-process comprising reacting a compound of formula (VI)



(VI)

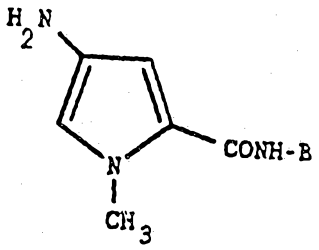
wherein X is as defined above, with an amine of formula $B-NH_2$, in which B is as defined above. The reaction, which may be carried out according to known methods, provides compounds of formula (VII)



(VII)

wherein B is as defined above.

A compound of formula (VII) is reduced according to known methods to provide a compound of formula (VIII)



(VIII)

wherein

B is as defined above, wich in its turn is reacted with a compound of formula (VI), as defined above, thus obtaining a compound of formula (IV), as defined above, wherein n is 2. If a compound of formula (IV), wherein n is 3 is desired, a further reduction and acylation step is required.

The compounds of formula (V) are known compounds and may be obtained for example according to Heterocycles, vol 27,No. 8, 1988, p. 1945-52,

The compounds of formula (VI) and the amine of formula $B\text{-}NH_2$ are known products or may be easily obtained according to known methods.

PHARMACOLOGY

The compounds of the invention have been found to be active as angiogenesis inhibitors.

Angiogenesis inhibitor is meant an agent capable of suppressing the growth of new blood vessels. Therefore the compounds of the present invention are useful in treating several pathological conditions in mammals, including humans, where the growth of new blood vessels is detrimental, for example in chronic inflammation, diabetic retinopathy, psoriasis, rheumatoid arthritis and tumor growth. In particular, in the cancer therapy the compounds of the invention can be administered alone or in association with antitumor agents such as doxorubicin, etoposide, fluorouracil, mephalan, cyclophosphamide, bleomycin, vinblastin or mitomycin. The angiogenesis inhibitor activity of the compounds of the present invention is shown e.g. by the fact that they have been found to be active in the chorioallantoic membrane test, according to the Folkman's method [Nature, 297, 307 (1982)].

Moreover the compounds of the present invention have been found to be endowed with TNF α-neutralizing activity and therefore they can be employed in humans for prophylactic and/or therapeutic use in any disease state in which TNF α is known to play a detrimental role. Typically such disease states are cachexia, septic shock, graft-versus-host disease, AIDS, cerebral malaria, rheumatoid arthritis. The TNF α-inhibiting activity of the compounds according to the present invention is proven, for instance, by the fact that they are active in inhibiting the cytotoxic activity of human TNFα on untreated mouse LM cells.

The compounds of the invention can be administered by the usual routes, for example, parenterally, e.g. by intravenous injection or infusion, intramuscularly, subcutaneously, topically or orally. The dosage depends on the age, weight and conditions of the patient and on the administration route.
For example, a suitable dosage for administration to adult humans may range from about 0.5 to about 300 mg pro dose 1-4 times a day.

The pharmaceutical compositions of the invention may contain a compound of formula (I) as the active substance, in association with one or more pharmaceutically acceptable excipients and/or carrier
The pharmaceutical compositions of the invention are usually prepared following conventional methods and are administered in a pharmaceutically suitable form.
For instance, solutions for intravenous injection or infusion may contain as carrier, for example, sterile water or preferably, they may be in the form of sterile aqueous isotonic saline solutions.
Suspensions or solutions for intramuscular injections may contain, together with the active compound, a pharmaceutically acceptable carrier, e.g. sterile water, olive oil, ethyl oleate, glycols, e.g. propylene glycol, and if desired, a suitable amount of lidocaine hydrochloride.
In the forms for topical application, e.g. creams, lotions or pastes for use in dermatological treatment, the active ingredient may be mixed with conventional oleoginous or emulsifying excipients.
The solid oral forms, e.g. tablets and capsules, may contain, together with the active compound, diluents, e.g. lactose, dextrose, saccharose, cellulose, corn starch and potato starch; lubricants, e.g. silica, talc,stearic acid, magnesium or calcium stearate, and/or polyethylene glycols; binding agents, e.g. starches, arabic gums, gelatin, methylcellulose, carboxy-methyl cellulose, polyvinylpyrrolidone; disaggregating agents,

e.g. a starch, alginic acid, alginates, sodium starch glycolate; effervescing mixtures; dyestuffs; sweeteners; wetting agents, for instance, lecithin, polysorbates, laurylsulphates: and, in general, non-toxic and pharmacologically inactive substances used in pharmaceutical formulations. Said pharmaceutical preparations may be manufactured in a known manner, for example by means of mixing, granulating, tabletting, sugar-coating, or film-coating processes.

Furthermore, according to the invention there is provided a method of treating pathological conditions where the growth of new blood vessels is detrimental,for example chronic inflammation, diabetic retinopathy, psoriasis, rheumatoid arthritis and tumors, in mammals in need thereof, including humans, comprising administering to the said mammals a composition of the invention.

Object of the present invention are also products containing a compound of formula (I), or a pharmaceutically acceptable salt thereof, and a biologically active amount of a different active agent, as a combined preparation for simultaneous, separate or sequential use in the treatment of a disease in which TNFα plays a detrimental role.
The term "combined" method of treatment is meant to include both separate and substantially contemporaneous administration of a composition containing a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutical composition containing a therapeutically effective amount of a different pharmaceutically active agent.

Active agents, that can be formulated with a compound of the invention or alternatively, can be administered in a combined method of treatment depend on the disease state to be cured and are, for instance, gamma globulin, immune globulin and monoclonal antibody products, antibiotics and antimicrobial products. Typically, the antimicrobial agents may include a penicillin in conjunction with an aminoglycoside (e.g. gentamycin, tobramycin). However several well known additional agents, e.g. cephalosporins, can be utilized.

The present invention also provides a method of inhibiting angiogenesis, comprising administering to a host in need thereof a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

The present invention further provides a method of neutralizing TNFα activity, comprising administering a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof to a host suffering from AIDS, cachexia, septic shock, graft-versus-host disease, cerebral malaria or rheumatoid arthritis.

The following examples illustrate but do not limit the invention.



Example 1

8,8'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis(1,5-naphthalendisulfonic acid) tetrasodium salt.

To a solution of 8-(amino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylmino))(1,5-naphthalendisulfonic acid) disodium salt hydrochloride (0.6 g., 1.02 10^{-3} mols) in water (20 ml), sodium acetate (0.328 g., 4 mmols) was added under stirring. The whole was cooled to 0°C with an ice-salt bath, then a solution of phosgene in toluene (1 ml ~ 4 eq.) was added dropwise. The mixture was stirred 1 hr at 0°C.

The solvents were evaporated under vacuum and the residue was taken up with methanol and filtered. The filtrate was evaporated and the residue was chromatographed on a silica gel column with methylene chloride: methanol: 60:40 as eluent, affording 0.16 g. of the title compound.

I.R.(KBr) cm^{-1}: 3440 b, 1660, 1640, 1585, 1180, 1030.

N.M.R. (DMSO-d6): δ 3.84 (3H,s); 3.85 (3H,s); 6.80 (1H,d);
7.07 (2H,m); 7.41 (2H,m); 7.92 (2H,dd);
8.12 (1H,s); 8.27 (1H,dd); 9.07 (1H,dd);
9.90 (1H,bs); 12.27 (1H;bs).

F.A.B.-M.S.: m/z 1209; M^++1; 1231, M^++23; 1128, M-80

U.V. (H_2O) nm: λmax ($E^{1\%}_{1cm}$): 316 (331), 229 (478)

By analogous procedure the following compounds can be obtained:

8,8'-(carbonyl-bis(imino-N-mehyl-4,2-pyrrole-carbonyl-imino (N-methyl-4,2-pyrrole)carbonylimino))bis(3-naphthalensulfonic-acid)disodium salt.

I.R.(KBr)cm^{-1}: 3430 b, 1640, 1585, 1200, 1030

N.M.R.(DMSO-d6): δ 3.84 (6H,s); 6.86 (1H,d); 7.05 (1H,d); 7.24 (1H,d); 7.35 (1H,d); 7.54 (2H,m); 7.70 (1H,dd); 7.90 (2H,m); 8.15 (1H,d); 8.15 (1H,d); 8.95 (1H,bs); 9.94 (1H,bs); 10.03 (1H,bs).

F.A.B. M.S.: m/z 1005, M^++H; 1027, M^++Na

U.V. (H_2O)nm: λ max ($E^{1\%}_{1cm}$): 304 (366), 226 (1002)

8,8'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino (N-methyl-4,2-pyrrole)carbonylimino))bis(1-naphthalensulfonic acid) disodium salt;

8-8'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino (N-methyl-4,2-pyrrole)carbonylimino))bis(5 -naphthalensulfonic acid) disodium salt;

8,8'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino (N-methyl-4,2-pyrrole)carbonylimino))bis(1,3-naphthalendisulfonic acid) tetrasodium salt;

8-8'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis(3,5-naphthalendisulfonic acid) tetrasodium salt;

8,8'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis(2,5-naphthalendisulfonic acid) tetrasodium salt;

8,8'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis(2,4-naphthalendisulfonic acid) tetrasodium salt;

8-8'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis(1,6-naphthalendisulfonic acid) tetrasodium salt;

8,8'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-mehtyl-4,2-pyrrole)carbonylimino))bis(2,6-naphthalendisulfonic acid) tetrasodium salt; and

8-8'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis(3,6-naphthalendisulfonic acid) tetrasodium salt.

Example 2

8,8'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis(1,3,5-naphthalentrisulfonic acid) hexasodium salt.

To a solution of 8-(amino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))(1,3,5-naphthalentrisulfonic acid trisodium salt) hydrochloride (2.19 g, 3 mmols) in water (60 ml) and dioxane (15 ml), sodium acetate (0,984 g, 12 mmols) was added under stirring. The whole was cooled to 8°C with an ice bath, then a 20% solution of phosgene in toluene (3 ml, ~6 mmols), diluted with ml 9 of dioxane, was added dropwise in 1 hr.

The mixture was stirred 2 hrs at ~8°C.

The solvents were evaporated under vacuum and the residue was taken up with methanol.

After filtration of the salts, the filtrate was evaporated and the residue was cromotographed on a silica gel column with methylene chloride: methanol: water 60:40:4 as eluent, affording g 0.82 of the title compound.

I.R.(KBr)cm^{-1}: 3440 b, 1640, 1590, 1190, 1030

N.M.R.(DMSO-d6): δ3.80 (3H,s); 3.83 (3H,s); 6.80 (1H,d);
7.06 (2H,m); 7.40 (1H,d); 7.88 (1H,d);
7.99 (1H,d); 8.02 (1H,bs); 8.57 (1H,d);
9.33 (1H,d); 9.91 (1H,bs); 12.29 (1H,bs).

F.A.B.-M.S: m/z 1411, M^--H; 1389, M^--Na

U.V. (H_2O)nm: λ max ($E^{1\%}_{1cm}$): 311 (266), 233 (551).

By analogous procedure the following compounds can be obtained:

8-8'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino (N-methyl-4,2-pyrrole)carbonylimino))bis(1,4,6-naphthalentrisulonic acid) hexasodium salt;

8,8'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino (N-methyl-4,2-pyrrole)carbonylimino))bis(2,4,6-naphthalentrisulfonic acid) hexasodium salt;

8,8'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino (N-methyl-4,2-pyrrole)carbonylimino))bis(1,3,6-naphthalentrisulfonic acid) hexasodium salt; and

8,8'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino (N-methyl-4,2-pyrrole)carbonylimino))bis(2,3,5-naphthalentrisulfonic acid) hexasodium salt.

7,7'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonylimino))-bis(1,3-naphthalenedisulfonic acid), tetrapotassium salt,

^{1}H-NMR (200 MHz,DMSO): δ 3.86 (s, 3H); 6.98, 7.15 (two-d, J=1.9Hz,2H);
7.87 (m, 2H); 8.00 (d, J=1.7Hz,1H); 8.17 (s, 1H);
8.22 (d, J=1.7 Hz,1H); 8.90 (s, 1H); 10.08 (s, 1H).

7,7'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonylimino)(N-methyl-4,2-pyrrolecarbonylimino(N-methyl-4,2-pyrrole)carbonylimino))-bis-(1,3-naphthalenedisulfonic acid), tetrapotassium salt,

^{1}H-NMR (200 MHz,DMSO): δ 3.84, 3.86, 3.88 (three-s, 9H);
6.80 (d, J=1.7 Hz, 1H); 7.05 (m,2H);
7.20 (d, J=1.6 Hz, 1H); 7.25 (d, J=1.6Hz, 1H);
7.34 (d, J=1.6 Hz, 1H); 7.87 (m, 2H);
7.80 (d, J=1.7 Hz, 1H); 8.16 (s, 1H);
8.21 (d, J=1.7 Hz, 1H); 8.95 (s, 1H);
9.85, 9.99, 10.23 (three-s, 3H).

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Example 3

8-(Amino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole) carbonylimino))(1,3,5-naphthalentrisulfonic acid trisodium salt) hydrochloride.

The compound 8-(nitro-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))(1,3,5-naphthalentrisulfonic acid trisodium salt) (2.17 g = 3 mmols) was dissolved into a mixture of water (120 ml) and 1N HCl (3 ml) and reduced over a Pd catalyst (10% on carbon; mg 900) under H_2 pressure (50 p.s.i.) for 3 hours.

The catalyst was filtered and the resulting solution was concentrated in vacuum to dryness, affording 2,1 g of the title compound.

I.R.(KBr) cm^{-1}: 3440 b, 1640, 1520, 1190, 1030

N.M.R.(DMSO-d6): δ 3.85 (3H,s); 3.90 (3H,s); 7.1 (3H,m); 7.4 (1H,d); 7.95 (2H,m); 8.60 (1H,d); 9.35 (1H,d); 10.1 (4H,bs); 12.3 (1H, bs)

Example 4

8(Nitro-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole) carbonylimino))(1,3,5-naphthalenetrisulfonic acic trisodium salt)

To a solution of 8-(amino(N-methyl-4,2-pyrrole)carbonylimino) (1,3,5-naphthalentrisulfonic acid trisodium salt)hydrochloride (1.824 g, 3 mmols) in water (45 ml) and 1N NaOH (1 ml), sodium acetate (0.492 g, 6 mmols) was added under stirring.

The solution was cooled at 5°C with an ice bath, then a solution of (4-nitro-N methyl-2-pyrrole) carbonyl chloride (0.567 g, 3 mmols) in dioxane (30 ml) was added dropwise in 1 hr. The mixture was stirred 1 hr at 5°C, acidified at pH 4 with 1N HCl and evaporated under vacuum to dryness. The residue was treated with ethyl acetate (300 ml), stirred for 1 hour and filtered, to obtain the title compound (2.1 g).

I.R. (KBr) cm^{-1}: 3440 b, 1650, 1520, 1305, 1195, 1030

N.M.R. (DMSO-d6; 80 M.Hz.) δ : 3.89 (3H,s); 3.99 (3H,s); 7.18 (1H,d); 7.46 (1H,d); 7.70 (1H,d); 8.02 (2H,m); 8.2 (1H,d); 8.63 (1H,d); 9.41 (1H,d); 10.45 (1H,b s); 12.42 (1H,b s).

Example 5

8-(amino(N-methyl-4.2-pyrrole)carbonylimino)(1,3,5-naphthalentrisulfonic acid trisodium salt), hydrochloride.

The solution of 8-(nitro(N methyl-4.2-pyrrole)carbonylimino) (1,3,5-naphthalentrisulfonic acid trisodium salt)(1.803 g = 3 mmols) in water (120 ml) and 1NHCl (3 ml) was reduced over a Pd catalyst (10% on carbon g 800) under H_2 pressure (50 p.s.i.) for 4 h.

The catalyst was filtered and the resulting solution was concentrated in vacuum to dryness, affording 1.8 g of the title compound.

I.R. (KBr) cm^{-1}: 3440 b, 1640, 1520, 1190, 1030

N.M.R. (DMSO-d6): δ 3.9 (3H,s); 7.11 (1H,d); 7.29 (1H,d); 8.04 (2H,m); 8.6 (1H,d); 9.88 (1H,d); 10.04 (3H, b s); 12.39 (1H, b s).

Example 6

8-(nitro(N-methyl-4.2-pyrrole) carbonylimino)(1,3,5-naphthalen-trisulfonic acid trisodium salt).

To a solution of 8-amino, 1,3,5-naphthalentrisulfonic acid trisodium salt (1.347 g = 3 mmols) in water (45 ml), sodium acetate (0.492 g = 6 mM) was added under stirring. The solution was cooled at 5°C with an ice bath, then a solution of (4-nitro-N methyl-2-pyrrole)carbonyl chloride (0.943 = 5 mmols) in dioxane (45 ml) was added dropwise in 1 h. The mixture was stirred 3 h at 5°C, acidified and pH 4 with 1N HCl and evaporated under vacuum to dryness.

The residue was treated with ethylacetate (300 ml), stirred for 1 hour and filtered, to obtain g 1.7 of the title compound.

I.R.(KBr) cm^{-1}: 3440 b, 1650, 1530, 1305, 1200, 1030.

N.M.R.(DMSO-d6): δ 3.96 (3H,s); 7.84 (1H,d); 8.06 (2H,m); 8.15 (1H,d); 8.63 (1H,d); 9.4 (1H,d); 12.55 (1H, bs).

Example 7

7,7'-(carbonyl-bis(imino-N-methyl-4.2-pyrrolecarbonyl-imino (N-methyl-4.2-pyrrole)carbonylimino))bis(1.3-naphthalendisulfonic acid) tetrapotassium salt.

To a solution of 7-(amino-N-methyl-4.2-pyrrolecarbonylimino(N-methyl-4,2-pyrrole)carbonylimino))(1,3-naphthalendisulfonic acid dipotassium salt) hydrochloride (160 mg, 0.24 mmols) in water (15 ml) and dioxane (10 ml), potassium acetate (50 mg, 0.51 mmols) was added under stirring. A 20% solution of phosgene

in toluene (0.5 ml, ≃ 1 mmol), diluted with dioxane (2 ml), was added dropwise in half hr at room temperature. The mixture was stirred 1 hr. at room temperature.

The solvents were evaporated undervacuum, the residue was cromatographed on a silica gel column with methylene chloride:methanol: water 40:60:6 as eluent, affording 90 mg of the title compound.

I.R.(KBr) cm^{-1}: 3450 (b); 1650; 1580; 1530; 1190; 1030

N.M.R.(DMSO-d6): δ 3.84 (3H,s); 3.87 (3H,s); 6.80 (1H,d); 7.05 (1H,d); 7.18 (1H,d); 7.33 (1H,d); 7.86 (2H,m); 8.00 (1H,d); 8.16 (1H,bs); 8.21 (1H,d); 8.95 (1H, bs); 9.86 (1H, bs); 10.21 (1H, bs).

U.V. (H_2O)mm: λ max ($E^{1\%}_{1cm}$): 316.8 (371), 248.95 (444)

F.A.B. M.J.: m/z : 1273 ($M^+ + H$); 1311 ($M^+ + K$)

By analogous procedure the following compounds can be obtained:

7,7'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis(1-naphthalensulfonic acid)disodium salt;

7,7'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino (N-methyl-4,2-pyrrole)carbonylimino))bis(2-naphthalensulfonic acid) disodium salt;

7,7'-(carbonyl-bis(imino-N-methyl-4,2-pyrrole-carbonyl-imino (N-methyl-4,2-pyrrole)carbonylimino))bis(3-naphthalensulfonic acid) disodium salt;

7,7'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino (N-methyl-4,2-pyrrole)carbonylimino))bis(4-naphthalensulfonic acid) disodium salt;

7,7'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino (N-methyl-4,2-pyrrole)carbonylimino))bis(2,3-naphthalen-disulfonic acid) tetrasodium salt;

7,7'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino (N-methyl-4,2-pyrrole)carbonylimino))bis(2,4-naphthalen-disulfonic acid) tetrasodium salt;

7,7'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino (N-methyl-4,2-pyrrole)carbonylimino))bis(1,5-naphthalen-disulfonic acid) tetrasodium salt;

7,7'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino (N-methyl-4,2-pyrrole)carbonylimino))bis(2,5-naphthalen-disulfonic acid) tetrasodium salt;

7,7'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino (N-methyl-4,2-pyrrole)carbonylimino))bis(3,5-naphthalen-disulfonic salt;

7,7'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino (N-methyl-4,2-pyrrole)carbonylimino))bis(1,6-naphthalen-disulfonic acid) tetrasodium salt;

7,7'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino (N-methyl-4,2-pyrrole)carbonylimino))bis(2,6-naphthamen-disulfonic acid) tetrasodium salt;

7,7'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino (N-methyl-4,2-pyrrole)carbonylimino))bis(3,6-naphthalen-disulfonic acid) tetrasodium salt;

7-7'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino (N-methyl-4,2-pyrrole)carbonylimino))bis(1,3,5-naphthalen-trisulfonic acid) hexasodium salt;

7,7'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino (N-methyl-4,2-pyrrole)carbonylimino))bis(1,4,6-naphthalen-trisulfonic acid) hexasodium salt;

7,7'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino (N-methyl-4,2-pyrrole)carbonylimino))bis(1,3,6-naphthalen-trisulfonic acid) hexasodium salt;

7,7'-(carbonyl-bis(imino-N-methyl-4,2-pyrrole-carbonyl-imino (N-methyl-4,2-pyrrole)carbonylimino))bis(2,4,6-naphthalen-trisulfonic acid) hexasodium salt;

7,7'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino (N-methyl-4,2-pyrrole)carbonylimino))bis(2,3,5-naphthalen-trisulfonic acid) hexasodium salt;

2,2'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino (N-methyl-4,2-pyrrole)carbonylimino))bis(2-deoxy-D-glucose-6-sulfate) disodium salt;

2,2'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino (N-methyl-4,2-pyrrole)carbonylimino))bis(2-deoxy-D-glucose-6-phosphate) disodium salt;

5,5'-(carbonyl-bis(imino-N-methyl-4,2-pyrrocarbonyl-imino (N-methyl-4,2-pyrrole)carbonylimino))bis(8-quinolinesulfonic acid) disodium salt;

5,5'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino (N-methyl-4,2-pyrrole)carbonylimino))bis(6-quinolinesulfonic acid) disodium salt;

8,8'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolcarbonyl-imino (N-methyl-4,2-pyrrole)carbonylimino))bis(5,7-quinoline-disulfonic acid) tetrasodium salt; and

5,5'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino (N-methyl-4,2-pyrrole)carbonylimino))bis(6,8-quinoline-disulfonic acid) tetrasodium salt.

Example 8

8,8'-carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino (N-methyl-4,2-pyrrole)carbonylimino))bis(1,3,5-naphthanentrisulfonic acid).

A solution of 8,8'-(carbonyl-bis(imino-N-methyl-4,2-pyrrole-carbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis (1,3,5-naphthalentrisulfonic acid)hexasodium salt (400 mg) in water (10 ml), is chromatographed on an Amberlite 1R-120(H) column (20 ml), with water as eluent.

The solution is evaporated to dryness in vacuum, affording 0,3 g of the title compound.

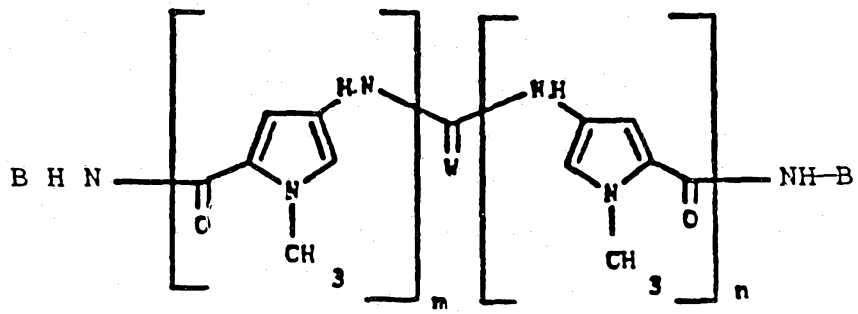
Example 9

Intramuscular injection 40 mg/ml.

A injectable pharmaceutical preparation can be manufactured by dissolving 40 g of 8,8'-(carbonyl-bis(imino-N-methyl-4,2-pyrrole-carbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino)) bis(1,3,5-naphthalentrisulfonic acid)hexasodium salt in water for injection (1000 ml) and sealing ampoules of 1-10 ml.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A compound of formula (I):



(I)

wherein
each of m and n, being the same, is an integer of 1 to 3;
W is oxygen or sulphur;
each of the B groups, which are the same, is
a) a phenyl or naphthyl group substituted by one or more acid groups;
b) a tetrahydropyranyl, tetrahydrofuranyl or quinoline ring, substituted by one or more acid groups; or
c) a pyranyl or furanyl sugar residue substituted by one or more acid groups;
and the pharmaceutically acceptable salts thereof.

2. A compound of formula (I), according to claim 1, wherein each of m and n, being the same, is 2;
W is oxygen;
each of the B groups, which are the same, is a') a phenyl or naphthyl group substituted by 1 to 3 acid groups; b') a tetrahydropyranyl or tetrahydrofuranyl ring substituted by 1 to 3 acid groups; or c') a glucosefuranosyl residue substituted by 1 to 3 acid groups; and the pharmaceutically acceptable salts thereof.

3. A compound of formula (I) according to claim 1 or 2, wherein each of the acid groups is independently chosen from sulfonic, sulfuric, sulfamic, sulfinic, phosphoric, phosphonic, phosphamic and carboxylic acid groups.

4. A compound selected from the group consisting of

8,8'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino (N-methyl-4,2-pyrrole)carbonylamino))bis(1,3-naphthalendisulfonic acid);

8,8'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis(3,5-naphthalendisulfonic acid);

8,8'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis(2,5-naphthalendisulfonic acid);

8,8'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino (N-methyl-4,2-pyrrole)carbonylimino))bis(2,4-naphthalendisulfonic acid);

8,8'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino (N-methyl-4,2-pyrrole)carbonylimino))bis(1,6-naphthalendisulfonic acid);

8,8'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino (N-methyl-4,2-pyrrole)carbonylimino))bis(2,6-naphthalendisulfonic acid);

8,8'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino (N-methyl-4,2-pyrrole)carbonylimino))bis(3,6-naphthalendisulfonic acid);

8,8'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino (N-methyl-4,2-pyrrole)carbonylimino))bis(1,5-naphthalendisulfonic acid);

8,8'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino (N-methyl-4,2-pyrrole)carbonylimino))bis(1-naphthalensulfonic acid);

8,8'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino (N-methyl-4,2-pyrrole)carbonylimino))bis(3-naphthalensulfonic acid);

8,8'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino (N-methyl-4,2-pyrrole)carbonylimino))bis(5-naphthalen-sulfonic acid);

8,8'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino (N-methyl-4,2-pyrrole)carbonylimino))bis(1,3,5-naphthalentri-sulfonic acid);

8,8'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino (N-methyl-4,2-pyrrole)carbonylimino))bis(1,4,6-naphthalentri-sulfonic acid);

8,8'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino (N-methyl-4,2-pyrrole)carbonylimino))bis(2,4,6-naphthalentri-sulfonic acid);

8,8'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino (N-methyl-4,2-pyrrole)carbonylimino))bis(1,3,6-naphthalentri-sulfonic acid);

8,8'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino (N-methyl-4,2-pyrrole)carbonylimino))bis(2,3,5-naphthalen-sulfonic acid);

2,2'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino (N-methyl-4,2-pyrrole)carbonylimino))bis(2-deoxy-D-glucose-6-sulphate);and

2,2'(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino (N-methyl-4,2-pyrrole)carbonylimino))bis(2-deoxy-D-glucose-6-phosphate);

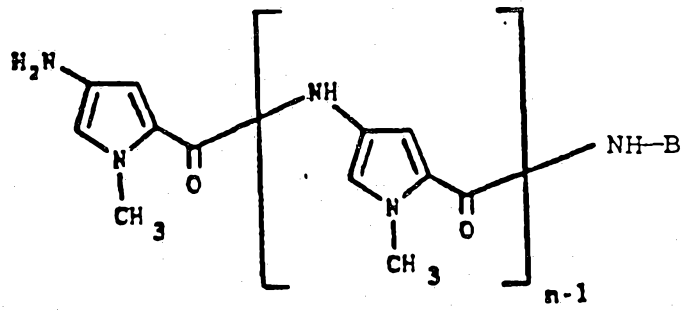
and the pharmaceutically acceptable salts thereof.

5 . A pharmaceutically acceptable salt of a compound of claim 4 , wherein said salt is the sodium or the potassium salt.

6. 7,7'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis(1,3-naphthalendisulfonic acid)tetrapotassium salt.

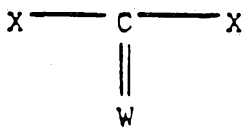
7. A compound of formula (I), or a pharmaceutically acceptable salt thereof, according to claim 1, specifically mentioned herein.

8. A process for the preparation of a compound of formula (I), or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 7, the process comprising reacting a compound of formula (II).



(II)

wherein n and B are as defined in claim 1, or a salt thereof, with a compound of formula (III)



(III)

wherein W is as defined in claim 1, and each of the X groups, which may be the same or different, is a good leaving group, and if desired, salifying a compound of formula (I) thus obtained; and/or if desired, obtaining a free compound of formula (I) from a salt thereof.

9. A pharmaceutical composition containing a pharmaceutically acceptable carrier and/or diluent and, as an active principle, a compound of formula (I) according to any one of claims 1 to 7 or a pharmaceutically acceptable salt thereof.

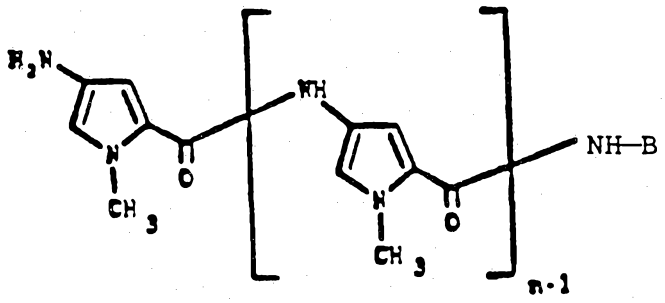
10. A method of inhibiting angiogenesis, comprising administering to a host in need thereof a therapeutically

effective amount of a compound of formula (I) as defined in any one of claims 1 to 7 or a pharmaceutically acceptable salt thereof.

11. A method of treating a disease state in which TNFα plays a detrimental role, comprising administering to a host suffering from said disease state a therapeutically effective amount of a compound of formula (I) as defined in any one of claims 1 to 7 or a pharmaceutically acceptable salt thereof.

12. A method of neutralizing TNFα activity, comprising administering a therapeutically effective amount of a compound of formula (I) as defined in any one of claims 1 to 7 or a pharmaceutically acceptable salt thereof to a host suffering from AIDS, cachexia, septic shock, graft-versus-host disease, cerebral malaria or rheumatoid arthritis.

13. A compound of formula (II):



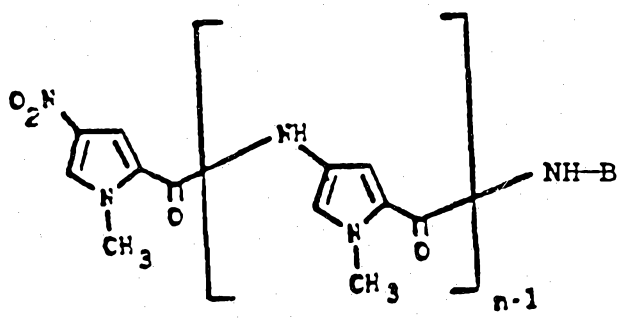
(II)

wherein n and B are as defined in any one of claims 1 to 3; or a salt thereof.

14. A compound selected from the group consisting of:
8-(amino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino)(1,5-naphthalendisulfonic acid disodium salt)hydrochloride;
8-(amino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino)(1,3,5-naphthalentrisulfonic acid trisodium salt)hydrochloride;
8-(amino(N-methyl-4,2-pyrrole)carbonylimino)(1,3,5-naphthalentrisulfonic acid trisodium salt)hydrochloride; and
7-(amino-N-methyl-4,2-pyrrolecarbonylimino(N-methyl-4,2-pyrrole)carbonylimino)(1,3-naphthalendisulfonic acid dipotassium salt)hydrochloride.

15. A process for producing a compound of formula (II) as defined in claim 13, or a salt thereof, which comprises

reducing the corresponding compound of formula (IV):



(IV)

wherein n and B are as defined in claim 13.

DATED THIS 8TH DAY OF SEPTEMBER 1993

FARMITALIA CARLO ERBA Srl

By its Patent Attorneys:

GRIFFITH HACK & CO

Fellows Institute of Patent
Attorneys of Australia.



INTERNATIONAL SEARCH REPORT

International Application No PCT/EP 91/00014

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC5: C 07 D 207/34, A 61 K 31/40

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
IPC5	C 07 D

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category *	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
X	J. Med. Chem., vol. 32, October 1989, J.W. Lown et al: "Novel linked antiviral and antitumor agents related to netropsin and distamycin: synthesis and biological evaluation", pages 2368-2375, see compound 13a	1,6-10
A	--	2-5
X,P	US, A, 4912199 (J.W. LOWN ET AL.) 27 March 1990, see example 2	1,6-10
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* Special categories of cited documents:[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
11th April 1991	29. 05. 91
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	miss T. MORTENSEN

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. [X] OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This International search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. [ ] Claim numbers ....., because they relate to subject matter not required to be searched by this Authority, namely:

2. [X] Claim numbers 1-2, because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

These claims are too broadly formulated to permit a meaningful search. The search has been limited to the compounds considered to be most relevant.

3. [ ] Claim numbers....., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

[ ] The additional search fees were accompanied by applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.PCT/EP 91/00014

SA 43483

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on 28/02/91
The European Patent office is in no way liable for theseparticulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A- 4912199	27/03/90	NONE	

For more details about this annex : see Official Journal of the European patent Office, No. 12/82

EPO FORM P0479