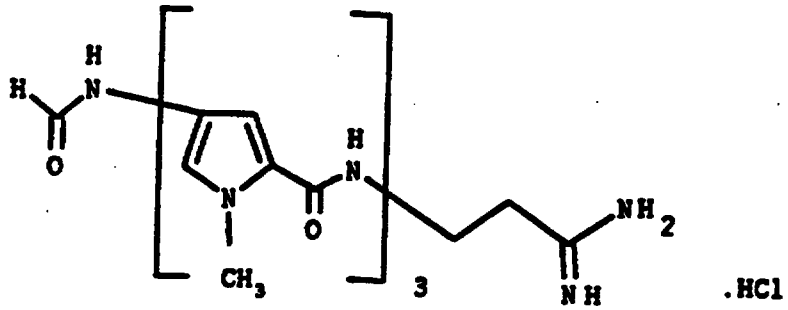
Description

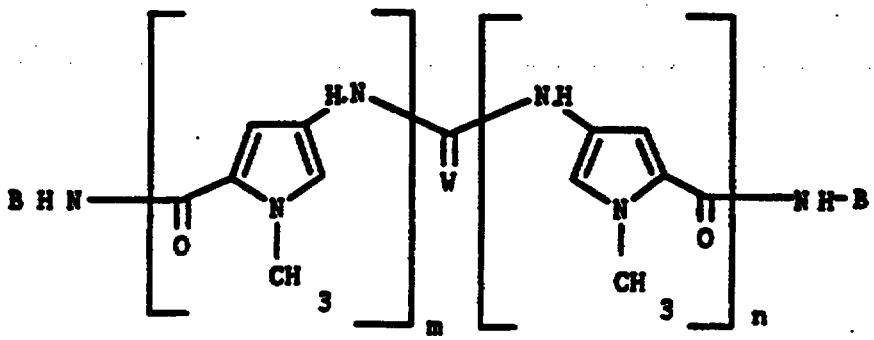
The present invention relates to ureido derivatives of substituted pyrroles, to a process for their preparation and to a pharmacological composition containing them.

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 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 2-deoxy-D-glucose group 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 wherein each of the above acid groups is independently chosen from sulfonic, sulfuric, sulfamic, sulfinic, phosphoric, phosphonic, phosphamic and carboxylic acid groups;

and the pharmaceutically acceptable salts thereof.

When two or more acid groups are present on a B group, as defined above under a), b) and c), they may be the same or different. The acid groups are SO_3H, SO_4H, SO_3NH_2, SO_2H, PO_4H_2, PO_3H_2, PO_3NH_3 or CO_2H groups.

Preferably the B groups, as defined above under a), b) and c), are substituted by 1 to 3 of such acid groups.

When B is a ring as defined above under b) it is for example tetrahydropyranyl or tetrahydrofuranyl.

When B is a group as defined above under d) r is preferably 2.

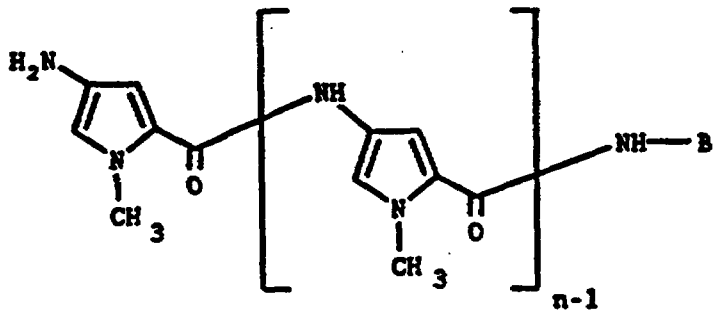
As already said, the invention includes within its scope also the pharmaceutically acceptable salts of the compounds of formula (I).

Examples of pharmaceutically acceptable salts are either those with inorganic bases, such as sodium, potassium, calcium and aluminium hydroxydes, 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 by 1 to 3 acid groups; b') a tetrahydropyranyl or tetrahydrofuranyl ring substituted by 1 to 3 acid groups; or c') a 2-deoxy-D-glucose group substituted by 1 to 3 acid groups; and the pharmaceutically acceptable salts thereof.

Specific examples of preferred compounds of the invention, are the followings:
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-naphthalensulfonic acid);
8,8'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino (N-methyl-4,2-pyrrole)carbonylimino))bis(1,3,5-naphthalentrisulfonic acid);
8,8'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino (N-methyl-4,2-pyrrole)carbonylimino))bis(1,4,6-naphthalentrisulfonic acid);
8,8'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino (N-methyl-4,2-pyrrole)carbonylimino))bis(2,4,6-naphthalentrisulfonic acid);
8,8'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino (N-methyl-4,2-pyrrole)carbonylimino))bis(1,3,6-naphthalentrisulfonic acid);
8,8'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino (N-methyl-4,2-pyrrole)carbonylimino))bis(2,3,5-naphthalensulfonic 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.

The present invention also provides a compound of formula (II), or a salt thereof, with the proviso that B is not a $-CH_2(CHA)_rCH_2A$ group as defined above.

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.

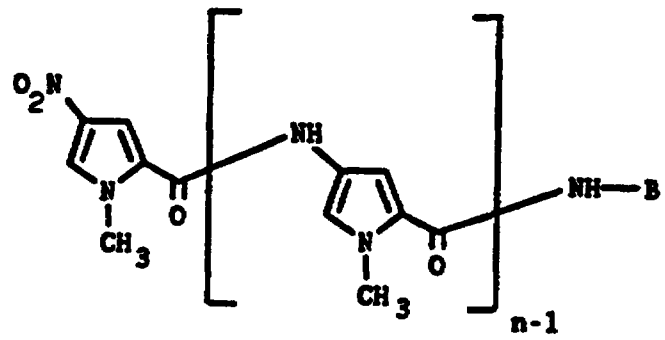
Preferably when in a compound of formula (III) X is an halogen atom, e.g. chlorine, the reaction may be carried out at a molar ratio of compound (II), or a salt thereof: compound (III) from about 1:1 to about 1:4. The reaction is preferably performed in organic solvents such as dimethylsulphoxide, hexamethylphosphotriamide, dimethylacetamide or, preferably, dimethylformamide, 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 compounds of formula (II) may be obtained according to known procedures.

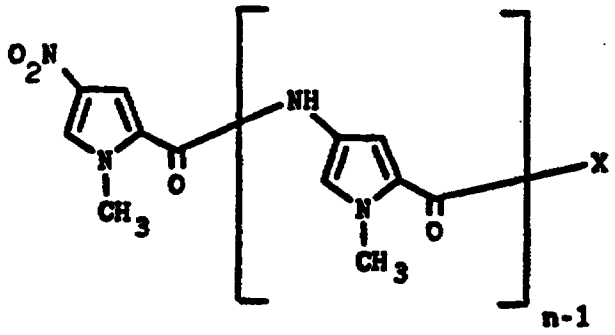
For instance, a compound of formula (II) may be obtained by reduction of a compound of formula (IV)



(IV)

wherein
n and B are as defined above by methods well known in the art.

The compounds of formula (IV) may be obtained by reacting an amine of formula B-NH_2, where B is defined as above, with a compound of formula (V)

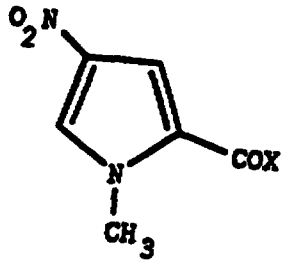


(V)

wherein
n and X are as defined above.

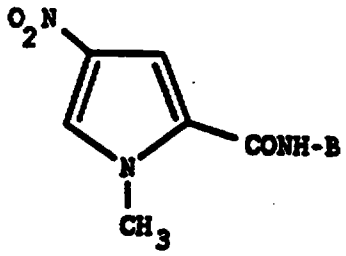
Also the reaction of an amine of formula B-NH_2 with a compound of formula (V) is a well known process.

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)

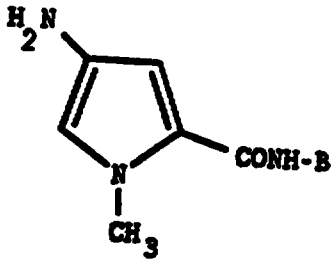
wherein X is as defined above, with an amine of formula B-NH_2, in which B is as defined above. The reaction, which may be carried out according to known methods, provides compounds of formula (VII)



(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-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.

By 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, carboxymethyl 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 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):δ3.84 (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:

$\lambda max\ (E^{1\%}_{1cm})$:

316 (331), 229 (478)
By analogous procedure the following compounds can be obtained:
8,8'-(carbonyl-bis(imino-N-methyl-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:

$\lambda\ max\ (E^{1\%}_{1cm})$:

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:

$$\lambda \text{ max } (E^{1\%}_{1cm}):$$

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.

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):δ3.9 (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-naphthalentrisulfonic 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):δ3.96 (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:

$$\lambda \text{ max } (E^{1\%}_{1cm}):$$

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

7,7'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino (N-methyl-4,2-pyrrole)carbonylimino))bis(2,5-naphthalendisulfonic acid) tetrasodium salt;
7,7'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino (N-methyl-4,2-pyrrole)carbonylimino))bis(3,5-naphthalendisulfonic salt;
7,7'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino (N-methyl-4,2-pyrrole)carbonylimino))bis(1,6-naphthalendisulfonic acid) tetrasodium salt;
7,7'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino (N-methyl-4,2-pyrrole)carbonylimino))bis(2,6-naphthamendisulfonic acid) tetrasodium salt;
7,7'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino (N-methyl-4,2-pyrrole)carbonylimino))bis(3,6-naphthalendisulfonic acid) tetrasodium salt;
7-7'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino (N-methyl-4,2-pyrrole)carbonylimino))bis(1,3,5-naphthalentrisulfonic acid) hexasodium salt;
7,7'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino (N-methyl-4,2-pyrrole)carbonylimino))bis(1,4,6-naphthalentrisulfonic acid) hexasodium salt;
7,7'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino (N-methyl-4,2-pyrrole)carbonylimino))bis(1,3,6-naphthalentrisulfonic 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-naphthalentrisulfonic acid) hexasodium salt;
7,7'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino (N-methyl-4,2-pyrrole)carbonylimino))bis(2,3,5-naphthalentrisulfonic 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-quinolinedisulfonic acid) tetrasodium salt; and
5,5'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino (N-methyl-4,2-pyrrole)carbonylimino))bis(6,8-quinolinedisulfonic 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-pyrrolecarbonyl-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.

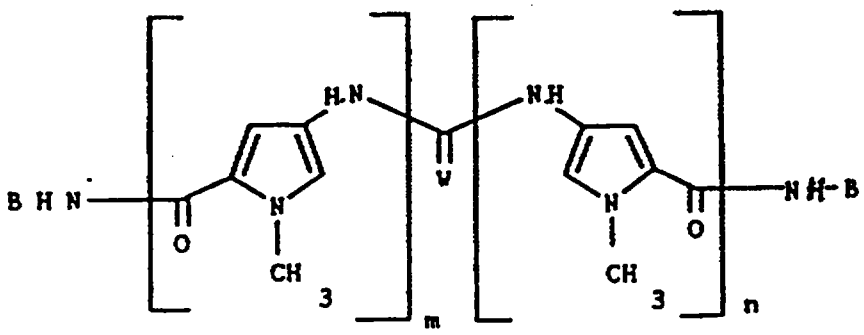
A injectable pharmaceutical preparation can be manufactured by dissolving 40 g of 8,8'-(carbonyl-bis-(imino-N-methyl-4,2-pyrrole-carbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino)) bis(1,3,5-naphthalentrisulfonic acid)hexasodium salt in water for injection (1000 ml) and sealing ampoules of 1-10 ml.

* C L M S *

Claims

Claims for the following Contracting States : AT, BE, CH, LI, DE, DK, FR, GB, IT, NL, SE

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 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 2-deoxy-D-glucose group 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 wherein each of the above acid groups is independently chosen from sulfonic, sulfuric, sulfamic, sulfinic, phosphoric, phosphonic, phosphamic and carboxylic 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 2-deoxy-D-glucose group substituted by 1 to 3 acid groups; and the pharmaceutically acceptable salts thereof.

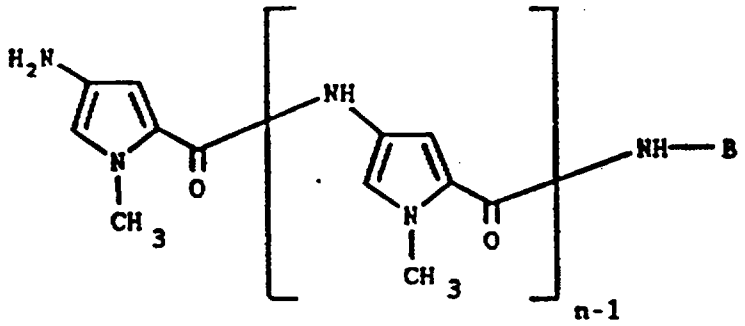
3. A compound selected from the group consisting of 8,8'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylamino))bis(1,3-naphthalendisulfonic acid);
8,8'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis-(3,5-naphthalendisulfonic 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-naphthalendi-sulfonic acid);
8,8'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis-(1,6-naphthalendi-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-napthalentri-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.

4. A pharmaceutically acceptable salt of a compound of claim 3, wherein said salt is the sodium or the potassium salt.

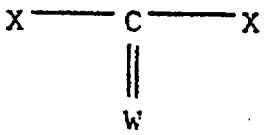
5. 7,7'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis-(1,3-naphthalendisulfonic acid)tetrapotassium salt.

6. 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 5, 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.

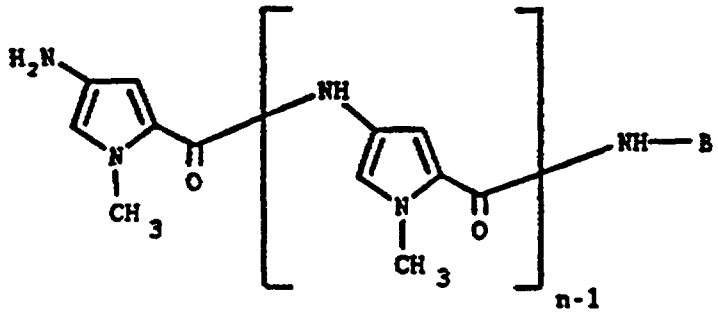
7. A pharmaceutical composition containing a pharmaceutically acceptable carrier and/or diluent and, as an active principle, a compound of formula (I), or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 5.

8. A compound of formula (I), or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 5 for use as an angiogenesis inhibitor.

9. Use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 5 in the preparation of a medicament for use in the treatment of angiogenesis.

10. Use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 5 in the preparation of a medicament for prophylactic and/or therapeutic use in a disease state in which TNFα plays a detrimental role.

11. A compound of formula (II)

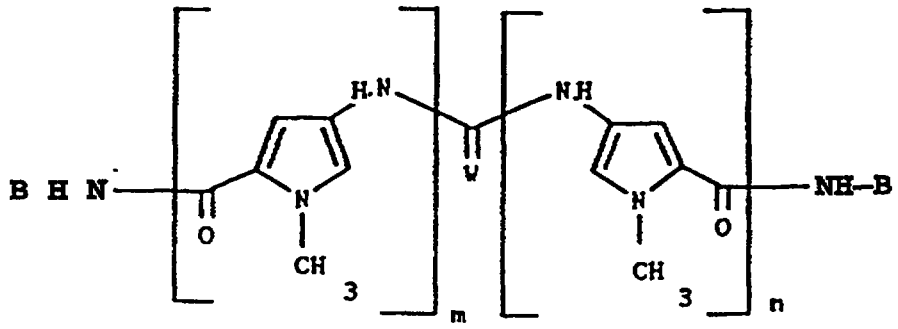


(II)

wherein n and B are as defined in claim 1 or 2, or a salt thereof, with the proviso that B is not a $-CH_2-(CHA)_rCH_2A$ group as defined in claim 1.

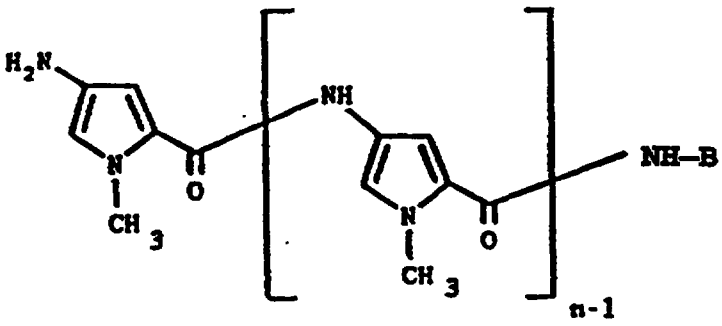
Claims for the following Contracting State : ES

1. A process for the preparation of a compound of formula (I):



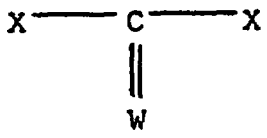
(I)

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 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 2-deoxy-D-glucose group 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 wherein each of the above acid groups is independently chosen from sulfonic, sulfuric, sulfamic, sulfinic, phosphoric, phosphonic, phosphamic and carboxylic acid groups; and the pharmaceutically acceptable salts thereof, which process comprises reaching 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.

2. A process 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 2-deoxy-D-glucose group substituted by 1 to 3 acid groups; and the pharmaceutically acceptable salts thereof.

3. A process according to claim 1 wherein the compound prepared is 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-naphthalendi-sulfonic acid);
8,8'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis-(1,6-naphthalendi-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-napthalentri-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.

4. A process according to claim 3 wherein said salt is the sodium or the potassium salt.

5. A process according to claim 1 wherein the compound prepared is 7,7'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis(1,3-naphthalendisulfonic acid)-tetrapotassium salt.

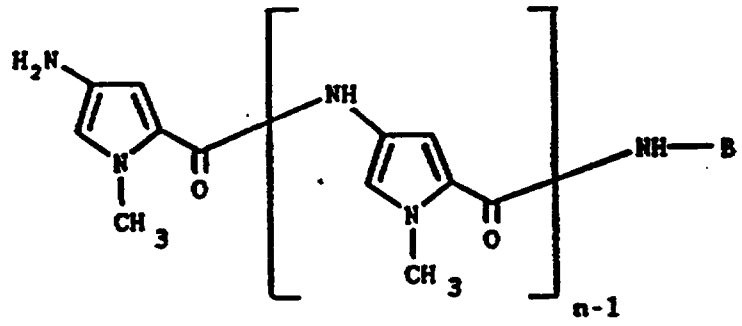
6. A process for preparing a pharmaceutical composition which comprises mixing together a pharmaceutically acceptable carrier and/or diluent and, as an active principle, a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined in any one of claims 1 to 5.

7. Use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined in any one of claims 1 to 5 in the preparation of a medicament for use in the treatment of angiogenesis.

8. Use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined in any one of claims 1 to 5 in the preparation of a medicament for prophylactic and/or therapeutic use in a disease

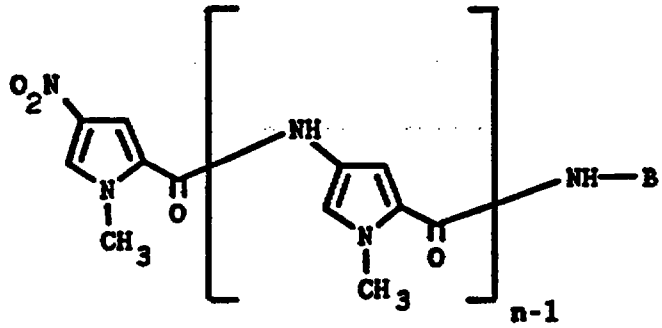
state in which TNFα plays a detrimental role.

9. A process for the preparation of a compound of formula (II)



(II)

wherein n and B are as defined in claim 1 or 2, or a salt thereof, with the proviso that B is not a $-CH_2-(CHA)_rCH_2A$ group as defined in claim 1, which process comprises reducing a compound of formula (IV):

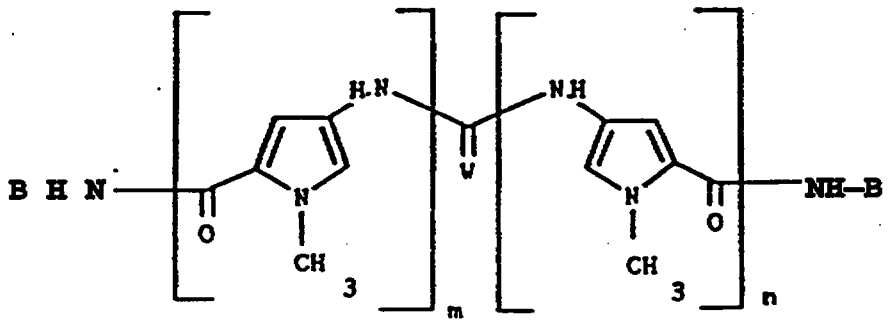


(IV)

wherein n and B are as defined above.

Claims for the following Contracting State : GR

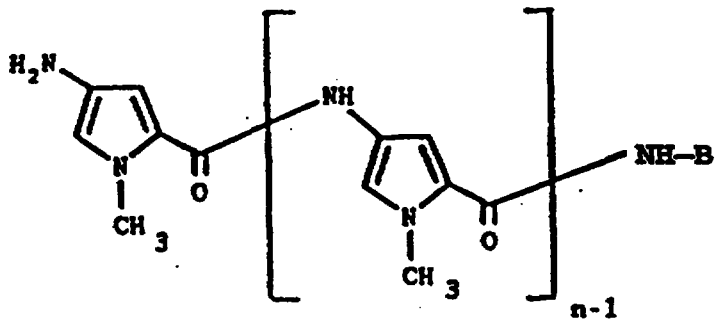
1. A process for the preparation of a compound of formula (I):



(I)

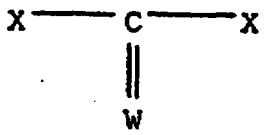
wherein
each of m and n, being the same, is an integer of 1 to 3;
W is oxygen or sulphur;
each of the B groups, which are the same, is
a) a phenyl or naphthyl group substituted by one or more acid groups;
b) a saturated or unsaturated, heteromonocyclic or heterobicyclic ring, containing one or more heteroatoms chosen from nitrogen, oxygen and sulphur, substituted by one or more acid groups;

c) a 2-deoxy-D-glucose group 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 wherein each of the above acid groups is independently chosen from sulfonic, sulfuric, sulfamic, sulfinic, phosphoric, phosphonic, phosphamic and carboxylic acid groups; and the pharmaceutically acceptable salts thereof, which process comprises reaching 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.

2. A process 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 2-deoxy-D-glucose group substituted by 1 to 3 acid groups; and the pharmaceutically acceptable salts thereof.

3. A process according to claim 1 wherein the compound prepared is 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-naphthalendi-sulfonic acid);
8,8'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis-(1,6-naphthalendi-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-napthalentri-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.

4. A process according to claim 3 wherein said salt is the sodium or the potassium salt.

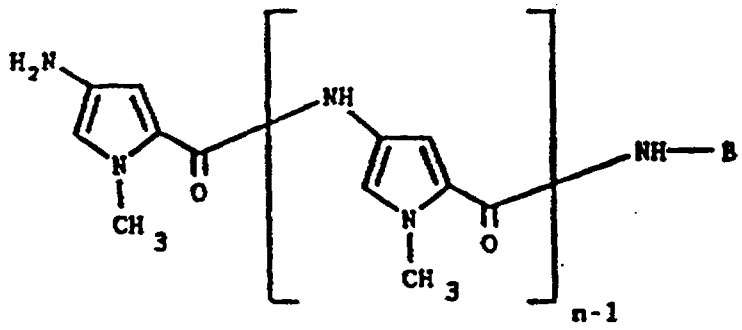
5. A process according to claim 1 wherein the compound prepared is 7,7'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis(1,3-naphthalendisulfonic acid)-tetrapotassium salt.

6. A process for preparing a pharmaceutical composition which comprises mixing together a pharmaceutically acceptable carrier and/or diluent and, as an active principle, a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined in any one of claims 1 to 5.

7. Use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined in any one of claims 1 to 5 in the preparation of a medicament for use in the treatment of angiogenesis.

8. Use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined in any one of claims 1 to 5 in the preparation of a medicament for prophylactic and/or therapeutic use in a disease state in which TNFα plays a detrimental role.

9. A compound of formula (II)

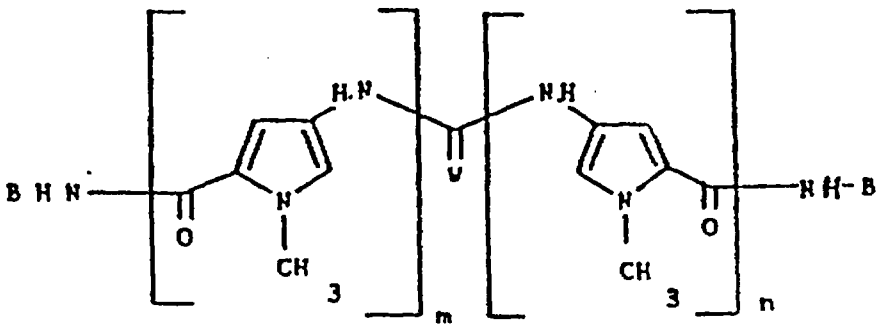


(II)

wherein n and B are as defined in claim 1 or 2, or a salt thereof, with the proviso that B is not a $-CH_2-(CHA)_rCH_2A$ group as defined in claim 1.

Patentansprüche
Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, LI, DE, DK, FR, GB, IT, NL, SE

1. Verbindung der Formel (I)



(I)

in der m und n jeweils gleich sind und eine ganze Zahl von 1 bis 3 bedeuten; W Sauerstoff oder Schwefel bedeutet;

die einzelnen Gruppen B gleich sind und
a) eine durch eine oder mehrere Säuregruppen substituierte Phenyl- oder Naphthylgruppe bedeuten;
b) einen gesättigten oder ungesättigten, heteromonocyclischen oder heterobicyclischen Ring mit einem oder mehreren Heteroatomen, die unter Stickstoff, Sauerstoff und Schwefel ausgewählt sind, der durch eine oder mehrere Säuregruppen substituiert ist, bedeuten;
c) eine 2-Desoxy-D-glucosegruppe, die durch eine oder mehrere Säuregruppen substituiert ist, bedeuten; oder
d) eine $-CH_2(CHA)_rCH_2A$-Gruppe bedeuten, wobei die einzelnen A-Gruppen gleich oder verschieden sind und eine Säuregruppe bedeuten und r den Wert 0, 1 oder 2 hat;
wobei die einzelnen vorstehenden Säuregruppen unabhängig voneinander unter Sulfonsäure-, Schwefelsäure-, Sulfaminsäure-, Sulfinsäure-, Phosphorsäure-, Phosphonsäure-, Amidophosphorsäure- und Carbonsäuregruppen ausgewählt sind;
und pharmazeutisch verträgliche Salze davon.

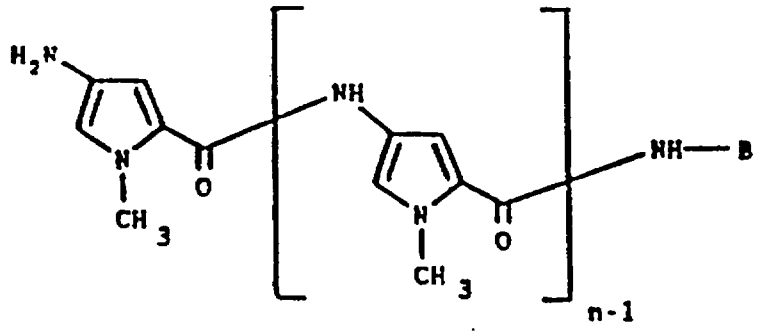
2. Verbindung der Formel (I) nach Anspruch 1, worin m und n, die gleich sind, den Wert 2 haben;
W Sauerstoff bedeutet;
die einzelnen B-Gruppen, die gleich sind, a') eine durch 1 bis 3 Säuregruppen substituierte Phenyl- oder Naphthylgruppe; b') eine durch 1 bis 3 Säuregruppen substituierte Tetrahydropyranyl- oder Tetrahydrofuranylgruppe; oder c') eine durch 1 bis 3 Säuregruppen substituierte 2-Desoxy-D-glucosegruppe bedeuten;
und die pharmazeutisch verträglichen Salze davon.

3. Eine verbindung, ausgewählt aus folgender Gruppe:
8,8'-(Carbonyl-bis-(imino-N-methyl-4,2-pyrrolcarbonylimino-(N-methyl-4,2-pyrrol)-carbonylimino))-bis-(1,3-naphthalindisulfonsäure);
8,8'-(Carbonyl-bis-(imino-N-methyl-4,2-pyrrolcarbonylimino-(N-methyl-4,2-pyrrol)-carbonylimino))-bis-(3,5-naphthalindisulfonsäure);
8,8'-(Carbonyl-bis-(imino-N-methyl-4,2-pyrrolcarbonylimino-(N-methyl-4,2-pyrrol)-carbonylimino))-bis-(2,5-naphthalindisulfonsäure);
8,8'-(Carbonyl-bis-(imino-N-methyl-4,2-pyrrolcarbonylimino-(N-methyl-4,2-pyrrol)-carbonylimino))-bis-(2,4-naphthalindisulfonsäure);
8,8'-(Carbonyl-bis-(imino-N-methyl-4,2-pyrrolcarbonylimino-(N-methyl-4,2-pyrrol)-carbonylimino))-bis-(1,6-naphthalindisulfonsäure);
8,8'-(Carbonyl-bis-(imino-N-methyl-4,2-pyrrolcarbonylimino-(N-methyl-4,2-pyrrol)-carbonylimino))-bis-(2,4,6-naphthalintrisulfonsäure);
8,8'-(Carbonyl-bis-(imino-N-methyl-4,2-pyrrolcarbonylimino-(N-methyl-4,2-pyrrol)-carbonylimino))-bis-(1,3,6-naphthalintrisulfonsäure);
8,8'-(Carbonyl-bis-(imino-N-methyl-4,2-pyrrolcarbonylimino-(N-methyl-4,2-pyrrol)-carbonylimino))-bis-(2,3,5-naphthalintrisulfonsäure);
2,2'-(Carbonyl-bis-(imino-N-methyl-4,2-pyrrolcarbonylimino-(N-methyl-4,2-pyrrol)-carbonylimino))-bis-(2-desoxy-D-glucose-6-sulfat); und
2,2'-(Carbonyl-bis-(imino-N-methyl-4,2-pyrrolcarbonylimino-(N-methyl-4,2-pyrrol)-carbonylimino))-bis-(2-desoxy-D-glucose-6-phosphat);
und die pharmazeutisch verträglichen Salze davon.

4. Pharmazeutisch verträgliches Salz einer Verbindung nach Anspruch 3, wobei es sich bei dem Salz um das Natrium- oder Kaliumsalz handelt.

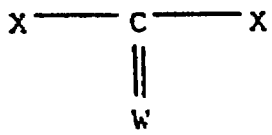
5. 7,7'-(Carbonyl-bis-(imino-N-methyl-4,2-pyrrolcarbonylimino-(N-methyl-4,2-pyrrol)-carbonylimino))-bis-(1,3-naphthalindisulfonsäure)-tetrakaliumsalz.

6. Verfahren zur Herstellung einer Verbindung der Formel (I) oder eines pharmazeutisch verträglichen Salzes davon nach einem der Ansprüche 1 bis 5, umfassend die Umsetzung einer Verbindung der Formel (II)



(II)

in der n und B die in Anspruch 1 definierte Bedeutung haben, oder eines Salzes davon mit einer Verbindung der Formel)III)



(III)

in der W die in Anspruch 1 definierte Bedeutung hat und die einzelnen X-Gruppen, die gleich oder verschieden sein können, eine leicht austretende Gruppe bedeuten; und ggf. die Salzbildung einer auf diese Weise erhaltenen Verbindung der Formel (I); und/oder ggf. die Bildung einer freien Verbindung der Formel (I) aus einem Salz davon.

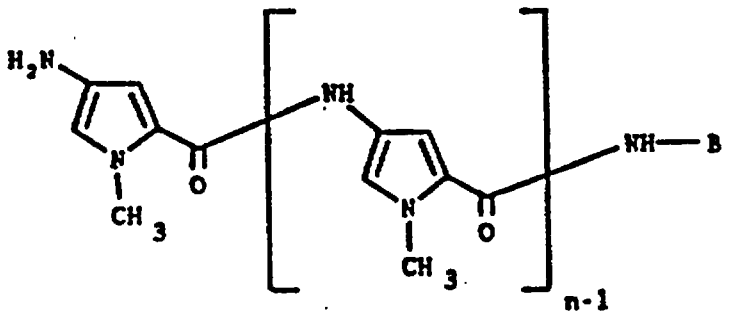
7. Pharmazeutische Zusammensetzung, enthaltend einen pharmazeutisch verträglichen Trägerstoff und/oder Verdünnungsmittel und als Wirkstoff eine Verbindung der Formel (I) oder ein pharmazeutisch verträgliches Salz davon nach einem der Ansprüche 1 bis 5.

8. Verbindung der Formel (I) oder ein pharmazeutisch verträgliches Salz davon nach einem der Ansprüche 1 bis 5 zur Verwendung als Angiogenese-Inhibitor.

9. Verwendung einer Verbindung der Formel (I) oder eines pharmazeutisch verträglichen Salzes davon nach einem der Ansprüche 1 bis 5 zur Herstellung eines Arzneimittels zur Verwendung bei der Behandlung von Angiogenese.

10. Verwendung einer Verbindung der Formel (I) oder eines pharmazeutisch verträglichen Salzes davon nach einem der Ansprüche 1 bis 5 zur Herstellung eines Arzneimittels zur prophylaktischen und/oder therapeutischen Anwendung bei einem Krankheitszustand, bei dem TNF-α eine schädliche Rolle spielt.

11. Verbindung der Formel (II)



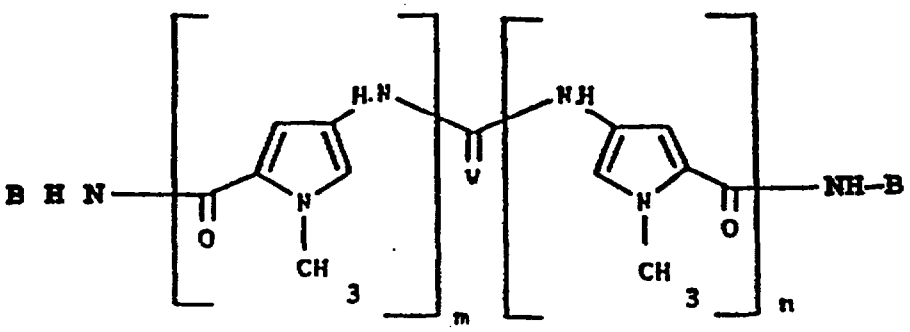
(II)

worin n und B die in Anspruch 1 oder 2 definierte Bedeutung haben, oder eines Salzes davon, mit der Maßgabe, daß B keine -$CH_2(CHA)_rCH_2A$-Gruppe gemäß der Definition in Anspruch 1 bedeutet.

* C L M S *

Patentansprüche für folgenden Vertragsstaat : ES

1. Verfahren zur Herstellung einer Verbindung der Formel (I)



(I)

in der m und n jeweils gleich sind und eine ganze Zahl von 1 bis 3 bedeuten; W Sauerstoff oder Schwefel bedeutet;

die einzelnen Gruppen B gleich sind und

a) eine durch eine oder mehrere Säuregruppen substituierte Phenyl- oder Naphthylgruppe bedeuten;

b) einen gesättigten oder ungesättigten, heteromonocyclischen oder heterobicyclischen Ring mit einem oder mehreren Heteroatomen, die unter Stickstoff, Sauerstoff und Schwefel ausgewählt sind, der durch eine oder mehrere Säuregruppen substituiert ist, bedeuten;

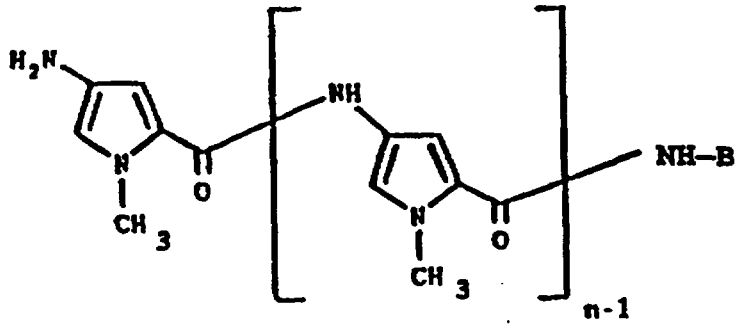
c) eine 2-Desoxy-D-glucosegruppe, die durch eine oder mehrere Säuregruppen substituiert ist, bedeuten; oder

d) eine $-CH_2(CHA)_rCH_2A$-Gruppe bedeuten, wobei die einzelnen A-Gruppen gleich oder verschieden sind und eine Säuregruppe bedeuten und r den Wert 0, 1 oder 2 hat;

wobei die einzelnen vorstehenden Säuregruppen unabhängig voneinander unter Sulfonsäure-, Schwefelsäure-, Sulfaminsäure-, Sulfinsäure-, Phosphorsäure-, Phosphonsäure-, Amidophosphorsäure- und Carbonsäuregruppen ausgewählt sind;

und der pharmazeutisch verträglichen Salze davon,

umfassend die Umsetzung einer Verbindung der Formel (II)



(II)

in der n und B die in Anspruch 1 definierte Bedeutung haben, oder eines Salzes davon mit einer Verbindung der Formel)III)



(III)

in der W die in Anspruch 1 definierte Bedeutung hat und die einzelnen X-Gruppen, die gleich oder verschieden sein können, eine leicht austretende Gruppe bedeuten; und ggf. die Salzbildung einer auf diese Weise erhaltenen Verbindung der Formel (I); und/oder ggf. die Bildung einer freien Verbindung der Formel (I) aus einem Salz davon.

2. Verfahren nach Anspruch 1, wobei m und n, die gleich sind, den Wert 2 haben;
W Sauerstoff bedeutet;
die einzelnen B-Gruppen, die gleich sind, a') eine durch 1 bis 3 Säuregruppen substituierte Phenyl- oder Naphthylgruppe; b') eine durch 1 bis 3 Säuregruppen substituierte Tetrahydropyranyl- oder Tetrahydrofuranylgruppe; oder c') eine durch 1 bis 3 Säuregruppen substituierte 2-Desoxy-D-glucose-gruppe bedeuten;
und die pharmazeutisch verträglichen Salze davon.

3. Verfahren nach Anspruch 1, wobei eine aus folgender Gruppe ausgewählte Verbindung hergestellt wird:
8,8'-(Carbonyl-bis-(imino-N-methyl-4,2-pyrrolcarbonylimino-(N-methyl-4,2-pyrrol)-carbonylimino))-bis-(1,3-naphthalindisulfonsäure);
8,8'-(Carbonyl-bis-(imino-N-methyl-4,2-pyrrolcarbonylimino-(N-methyl-4,2-pyrrol)-carbonylimino))-bis-(3,5-naphthalindisulfonsäure);
8,8'-(Carbonyl-bis-(imino-N-methyl-4,2-pyrrolcarbonylimino-(N-methyl-4,2-pyrrol)-carbonylimino))-bis-(2,5-naphthalindisulfonsäure);
8,8'-(Carbonyl-bis-(imino-N-methyl-4,2-pyrrolcarbonylimino-(N-methyl-4,2-pyrrol)-carbonylimino))-bis-(2,4-naphthalindisulfonsäure);
8,8'-(Carbonyl-bis-(imino-N-methyl-4,2-pyrrolcarbonylimino-(N-methyl-4,2-pyrrol)-carbonylimino))-bis-(1,6-naphthalindisulfonsäure);
8,8'-(Carbonyl-bis-(imino-N-methyl-4,2-pyrrolcarbonylimino-(N-methyl-4,2-pyrrol)-carbonylimino))-bis-(2,4,6-naphthalintrisulfonsäure);
8,8'-(Carbonyl-bis-(imino-N-methyl-4,2-pyrrolcarbonylimino-(N-methyl-4,2-pyrrol)-carbonylimino))-bis-(1,3,6-naphthalintrisulfonsäure);
8,8'-(Carbonyl-bis-(imino-N-methyl-4,2-pyrrolcarbonylimino-(N-methyl-4,2-pyrrol)-carbonylimino))-bis-(2,3,5-naphthalintrisulfonsäure);
2,2'-(Carbonyl-bis-(imino-N-methyl-4,2-pyrrolcarbonylimino-(N-methyl-4,2-pyrrol)-carbonylimino))-bis-(2-desoxy-D-glucose-6-sulfat); und
2,2'-(Carbonyl-bis-(imino-N-methyl-4,2-pyrrolcarbonylimino-(N-methyl-4,2-pyrrol)-carbonylimino))-bis-(2-desoxy-D-glucose-6-phosphat);
und die pharmazeutisch verträglichen Salze davon.

4. Verfahren nach Anspruch 3, wobei es sich bei dem Salz um das Natrium- oder Kaliumsalz handelt.

5. Verfahren nach Anspruch 1, wobei es sich bei der hergestellten Verbindung um 7,7'-(Carbonyl-bis-(imino-N-methyl-4,2-pyrrolcarbonylimino-(N-methyl-4,2-pyrrol)-carbonylimino))-bis-(1,3-naphthalindisulfonsäure)-tetrakaliumsalz handelt.

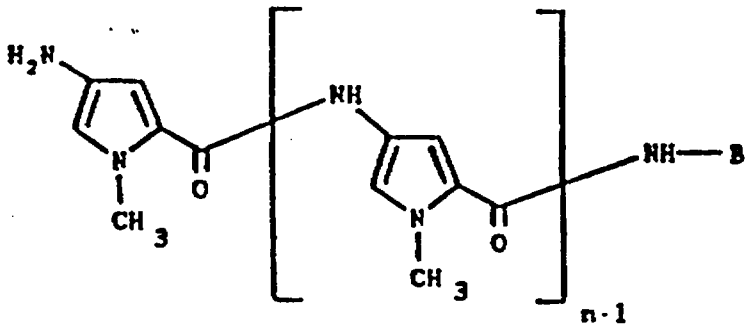
6. Verfahren zur Herstellung einer pharmazeutischen Zusammensetzung, umfassend das vermischen eines pharmazeutisch verträglichen Trägerstoffs und/oder Verdünnungsmittels und als Wirkstoff einer Verbindung der Formel (I) oder eines pharmazeutisch verträglichen Salzes davon nach einem der Ansprüche 1 bis 5.

7. Verwendung einer Verbindung der Formel (I) oder eines pharmazeutisch verträglichen Salzes davon nach einem der Ansprüche 1 bis 5 zur Herstellung eines Arzneimittels zur Verwendung bei der Behandlung von Angiogenese.

8. Verwendung einer Verbindung der Formel (I) oder eines pharmazeutisch verträglichen Salzes davon nach einem der Ansprüche 1 bis 5 zur Herstellung eines Arzneimittels zur prophylaktischen und/oder therapeutischen Anwendung bei einem Krankheitszustand, bei dem TNF-α eine schädliche Rolle spielt.

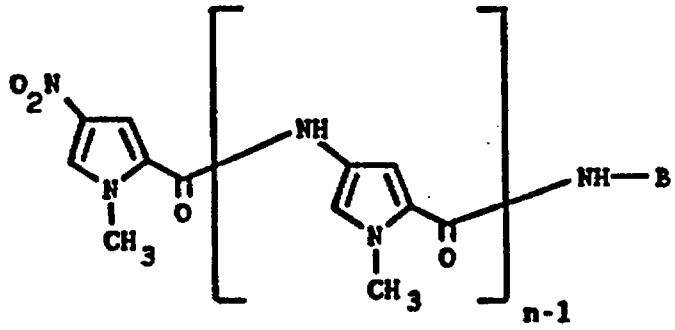
* C L M S *

9. Verfahren zur Herstellung einer Verbindung der Formel (II)



(II)

worin n und B die in Anspruch 1 oder 2 definierte Bedeutung haben, oder eines Salzes davon, mit der Maßgabe, daß B keine $-CH_2(CHA)_rCH_2A$-Gruppe gemäß der Definition in Anspruch 1 bedeutet, umfassend die Reduktion einer Verbindung der Formel (IV)

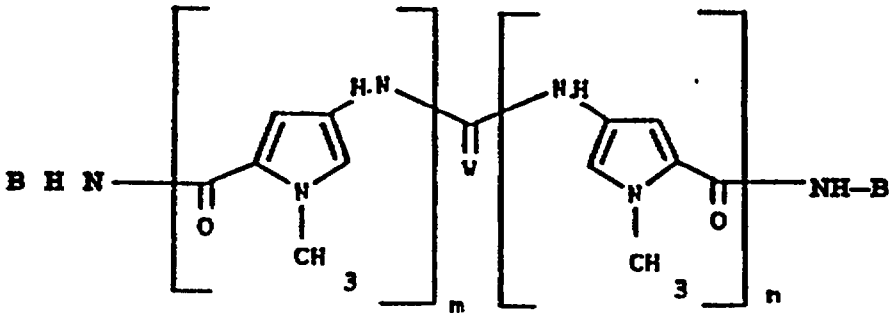


(IV)

worin n und B die vorstehend definierte Bedeutung haben.

Patentansprüche für folgenden Vertragsstaat : GR

1. Verfahren zur Herstellung einer Verbindung der Formel (I)



(I)

in der m und n jeweils gleich sind und eine ganze Zahl von 1 bis 3 bedeuten; W Sauerstoff oder Schwefel bedeutet;

die einzelnen Gruppen B gleich sind und

a) eine durch eine oder mehrere Säuregruppen substituierte Phenyl- oder Naphthylgruppe bedeuten;

b) einen gesättigten oder ungesättigten, heteromonocyclischen oder heterobicyclischen Ring mit einem oder mehreren Heteroatomen, die unter Stickstoff, Sauerstoff und Schwefel ausgewählt sind, der durch eine oder mehrere Säuregruppen substituiert ist, bedeuten;

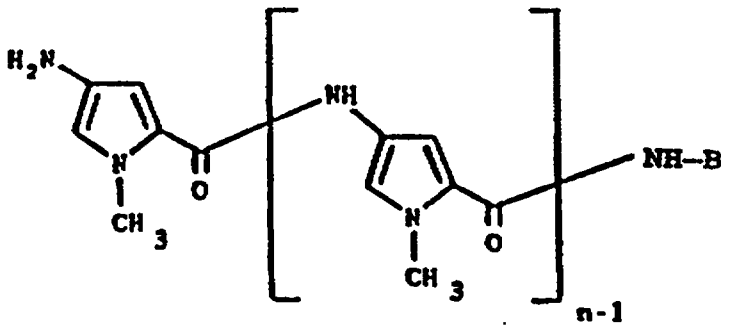
c) eine 2-Desoxy-D-glucosegruppe, die durch eine oder mehrere Säuregruppen substituiert ist, bedeuten; oder

d) eine $-CH_2(CHA)_rCH_2A$-Gruppe bedeuten, wobei die einzelnen A-Gruppen gleich oder verschieden sind und eine Säuregruppe bedeuten und r den Wert 0, 1 oder 2 hat;

wobei die einzelnen vorstehenden Säuregruppen unabhängig voneinander unter Sulfonsäure-, Schwefelsäure-, Sulfaminsäure-, Sulfinsäure-, Phosphorsäure-, Phosphonsäure-, Amidophosphorsäure- und Carbonsäuregruppen ausgewählt sind;

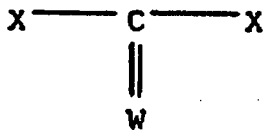
und der pharmazeutisch verträglichen Salze davon,

umfassend die Umsetzung einer Verbindung der Formel (II)



(II)

in der n und B die in Anspruch 1 definierte Bedeutung haben, oder eines Salzes davon mit einer Verbindung der Formel)III)



(III)

in der W die in Anspruch 1 definierte Bedeutung hat und die einzelnen X-Gruppen, die gleich oder verschieden sein können, eine leicht austretende Gruppe bedeuten; und ggf. die Salzbildung einer auf diese Weise erhaltenen Verbindung der Formel (I); und/oder ggf. die Bildung einer freien Verbindung der Formel (I) aus einem Salz davon.

2. Verfahren nach Anspruch 1, wobei m und n, die gleich sind, den Wert 2 haben;

W Sauerstoff bedeutet;

die einzelnen B-Gruppen, die gleich sind, a') eine durch 1 bis 3 Säuregruppen substituierte Phenyl- oder Naphthylgruppe; b') eine durch 1 bis 3 Säuregruppen substituierte Tetrahydropyranyl- oder Tetrahydrofuranylgruppe; oder c') eine durch 1 bis 3 Säuregruppen substituierte 2-Desoxy-D-glucosegruppe bedeuten;

und die pharmazeutisch verträglichen Salze davon.

3. Verfahren nach Anspruch 1, wobei eine aus folgender Gruppe ausgewählte Verbindung hergestellt wird:

8,8'-(Carbonyl-bis-(imino-N-methyl-4,2-pyrrolcarbonylimino-(N-methyl-4,2-pyrrol)-carbonylimino))-bis-(1,3-naphthalindisulfonsäure);

8,8'-(Carbonyl-bis-(imino-N-methyl-4,2-pyrrolcarbonylimino-(N-methyl-4,2-pyrrol)-carbonylimino))-bis-(3,5-naphthalindisulfonsäure);

8,8'-(Carbonyl-bis-(imino-N-methyl-4,2-pyrrolcarbonylimino-(N-methyl-4,2-pyrrol)-carbonylimino))-bis-(2,5-naphthalindisulfonsäure);

8,8'-(Carbonyl-bis-(imino-N-methyl-4,2-pyrrolcarbonylimino-(N-methyl-4,2-pyrrol)-carbonylimino))-bis-(2,4-naphthalindisulfonsäure);

8,8'-(Carbonyl-bis-(imino-N-methyl-4,2-pyrrolcarbonylimino-(N-methyl-4,2-pyrrol)-carbonylimino))-bis-(1,6-naphthalindisulfonsäure);

8,8'-(Carbonyl-bis-(imino-N-methyl-4,2-pyrrolcarbonylimino-(N-methyl-4,2-pyrrol)-carbonylimino))-bis-(2,4,6-naphthalintrisulfonsäure);

8,8'-(Carbonyl-bis-(imino-N-methyl-4,2-pyrrolcarbonylimino-(N-methyl-4,2-pyrrol)-carbonylimino))-bis-(1,3,6-naphthalintrisulfonsäure);

8,8'-(Carbonyl-bis-(imino-N-methyl-4,2-pyrrolcarbonylimino-(N-methyl-4,2-pyrrol)-carbonylimino))-

bis-(2,3,5-naphthalintrisulfonsäure);
2,2'-(Carbonyl-bis-(imino-N-methyl-4,2-pyrrolcarbonylimino-(N-methyl-4,2-pyrrol)-carbonylimino))-bis-(2-desoxy-D-glucose-6-sulfat); und
2,2'-(Carbonyl-bis-(imino-N-methyl-4,2-pyrrolcarbonylimino-(N-methyl-4,2-pyrrol)-carbonylimino))-bis-(2-desoxy-D-glucose-6-phosphat);
und die pharmazeutisch verträglichen Salze davon.

4. Verfahren nach Anspruch 3, wobei es sich bei dem Salz um das Natrium- oder Kaliumsalz handelt.

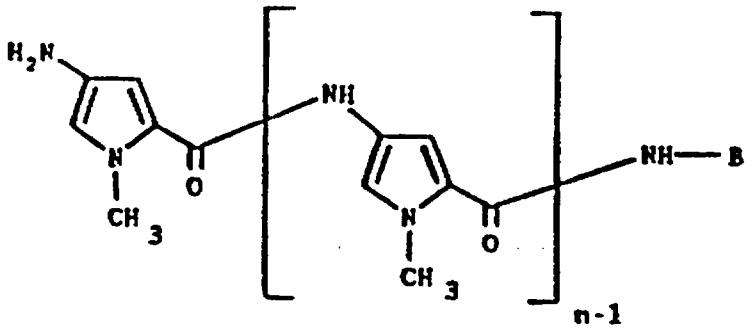
5. Verfahren nach Anspruch 1, wobei es sich bei der hergestellten Verbindung um 7,7'-(Carbonyl-bis-(imino-N-methyl-4,2-pyrrolcarbonylimino-(N-methyl-4,2-pyrrol)-carbonylimino))-bis-(1,3-naphthalindisulfonsäure)-tetrakaliumsalz handelt.

6. Verfahren zur Herstellung einer pharmazeutischen Zusammensetzung, umfassend das Vermischen eines pharmazeutisch verträglichen Trägerstoffs und/oder Verdünnungsmittels und als Wirkstoff einer Verbindung der Formel (I) oder eines pharmazeutisch verträglichen Salzes davon nach einem der Ansprüche 1 bis 5.

7. Verwendung einer Verbindung der Formel (I) oder eines pharmazeutisch verträglichen Salzes davon nach einem der Ansprüche 1 bis 5 zur Herstellung eines Arzneimittels zur Verwendung bei der Behandlung von Angiogenese.

8. Verwendung einer Verbindung der Formel (I) oder eines pharmazeutisch verträglichen Salzes davon nach einem der Ansprüche 1 bis 5 zur Herstellung eines Arzneimittels zur prophylaktischen und/oder therapeutischen Anwendung bei einem Krankheitszustand, bei dem TNF-α eine schädliche Rolle spielt.

9. Verbindung der Formel (II)



(II)

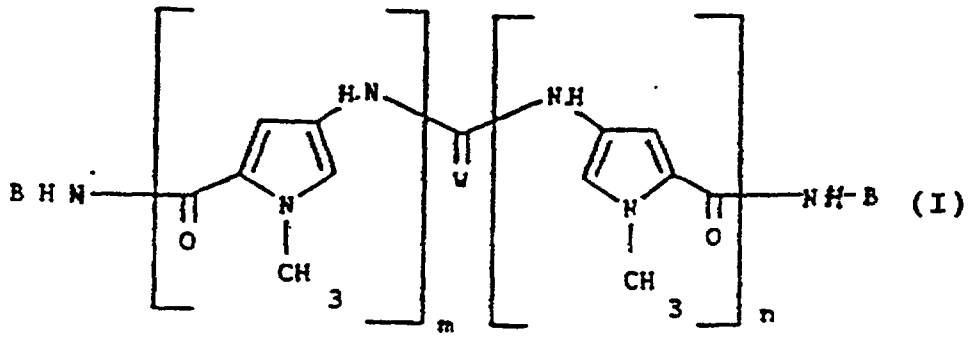
worin n und B die in Anspruch 1 oder 2 definierte Bedeutung haben, oder eines Salzes davon, mit der Maßgabe, daß B keine -$CH_2(CHA)_r$-CH_2A-Gruppe gemäß der Definition in Anspruch 1 bedeutet

* C L M S *

Revendications

Revendications pour les Etats contractants suivants : AT, BE, CH, LI, DE, DK, FR, GB, IT, NL, SE

1. Composé représenté par la formule (I) :



(I)

dans laquelle :

- m et n, qui sont identiques, représentent chacun un entier de 1 à 3 ;
- W représente oxygène ou soufre ;
- les groupes B, qui sont identiques, représentent chacun :
  (a) un groupe phényle ou naphtyle, substitué par un ou plusieurs groupes acides ;
  (b) un groupe hétéromonocyclique ou hétérobicyclique, saturé ou insaturé, contenant un ou plusieurs hétéroatomes choisis parmi l'azote, l'oxygène et le soufre, substitué par un ou plusieurs groupes acides ;
  (c) un groupe 2-désoxy-D-glucose, substitué par un ou plusieurs groupes acides ; ou
  (d) un groupe $-CH_2(CHA)_rCH_2A$, dans lequel les groupes A, qui sont identiques ou différents, représentent chacun un groupe acide, et r vaut 0, 1 ou 2 ;

et dans laquelle chacun des groupes acides ci-dessus est choisi indépendamment parmi les groupes acide sulfonique, sulfurique, sulfamique, sulfinique, phosphorique, phosphonique, phosphamique et carboxylique ;
et les sels pharmaceutiquement acceptables de ce composé.

2. Composé de la formule (I), selon la revendication 1, dans lequel :

- m et n, qui sont identiques, valent chacun 2 ;
- W représente oxygène ;
- les groupes B, qui sont identiques, représentent chacun :
  (a') un groupe phényle ou naphtyle, substitué par 1 à 3 groupes acides ;
  (b') un cycle tétrahydropyrannyle ou tétrahydrofurannyle, substitué par 1 à 3 groupes acides ; ou
  (c') un groupe 2-désoxy-D-glucose, substitué par 1 à 3 groupes acides ;

et les sels pharmaceutiquement acceptables de ce composé.

3. Composé choisi dans le groupe constitué par :

- le 8,8'-(carbonyl-bis(imino-N-méthyl-4,2-pyrrolecarbonyl-imino(N-méthyl-4,2-pyrrole)carbonyl-amino)bis(acide 1,3-naphtalènedisulfonique) ;
- le 8,8'-(carbonyl-bis(imino-N-méthyl-4,2-pyrrolecarbonyl-imino(N-méthyl-4,2-pyrrole)carbonyl-imino))bis(acide 3,5-naphtalènedisulfonique) ;
- le 8,8'-(carbonyl-bis(imino-N-méthyl-4,2-pyrrolecarbonyl-imino(N-méthyl-4,2-pyrrole)carbonyl-imino))bis(acide 2,5-naphtalènedisulfonique) ;
- le 8,8'-(carbonyl-bis(imino-N-méthyl-4,2-pyrrolecarbonyl-imino(N-méthyl-4,2-pyrrole)carbonyl-imino))bis(acide 2,4-naphtalènedisulfonique) ;
- le 8,8'-(carbonyl-bis(imino-N-méthyl-4,2-pyrrolecarbonyl-imino(N-méthyl-4,2-pyrrole)carbonyl-imino))bis(acide 1,6-naphtalènedisulfonique) ;
- le 8,8'-(carbonyl-bis(imino-N-méthyl-4,2-pyrrolecarbonyl-imino(N-méthyl-4,2-pyrrole)carbonyl-imino))bis(acide 2,4,6-naphtalènetrisulfonique) ;

* C L M S *

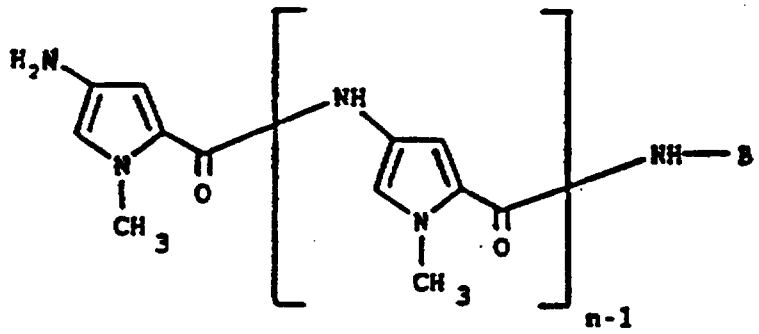
- le 8,8'-(carbonyl-bis(imino-N-méthyl-4,2-pyrrolecarbonyl-imino(N-méthyl-4,2-pyrrole)carbonyl-imino))bis(acide 1,3,6-naphtalènetrisulfonique) ;
- le 8,8'-(carbonyl-bis(imino-N-méthyl-4,2-pyrrolecarbonyl-imino(N-méthyl-4,2-pyrrole)carbonyl-imino))bis(acide 2,3,5-naphtalènetrisulfonique) ;
- le 2,2'-(carbonyl-bis(imino-N-méthyl-4,2-pyrrolecarbonyl-imino(N-méthyl-4,2-pyrrole)carbonyl-imino))bis(2-désoxy-D-glucose-6-sulfate) ; et
- le 2,2'-(carbonyl-bis(imino-N-méthyl-4,2-pyrrolecarbonyl-imino(N-méthyl-4,2-pyrrole)carbonyl-imino))bis(2-désoxy-D-glucose-6-phosphate) ;

et les sels pharmaceutiquement acceptables de ces composés.

4. Sel pharmaceutiquement acceptable d'un composé tel que défini à la revendication 3, dans lequel ledit sel est le sel de sodium ou de potassium.

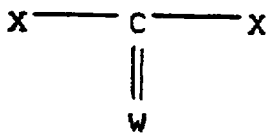
5. Sel tétrapotassique du 7,7'-(carbonyl-bis(imino-N-méthyl-4,2-pyrrolecarbonyl-imino(N-méthyl-4,2-pyrrole)carbonylimino))bis-(acide 1,3-naphtalènedisulfonique).

6. Procédé de préparation d'un composé représenté par la formule (I), ou d'un sel pharmaceutiquement acceptable de ce composé, tel que défini à l'une des revendications 1 à 5, le procédé comprenant la réaction d'un composé représenté par la formule (II) :



(II)

dans laquelle n et B sont tels que définis à la revendication 1,
ou d'un sel de celui-ci,
avec un composé représenté par la formule (III) :



(III)

dans laquelle :

- W est tel que défini à la revendication 1 ; et
- les groupes X, qui peuvent être identiques ou différents, représentent chacun un groupe bon partant,

et, si on le désire, la salification d'un composé de la formule (I) ainsi obtenu ; et/ou si on le désire, l'obtention d'un composé libre de la formule (I) à partir d'un sel de celui-ci.

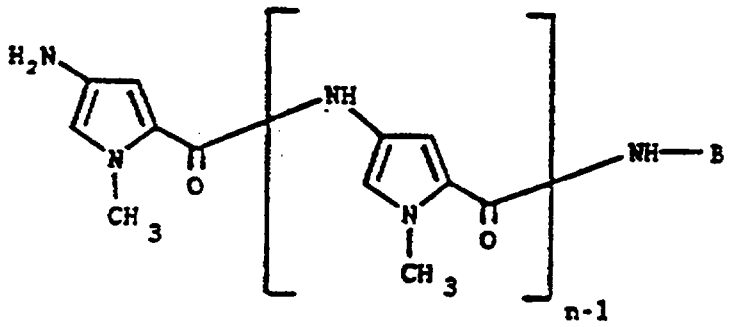
7. Composition pharmaceutique contenant un support et/ou diluant pharmaceutiquement acceptable et, en tant que principe actif, un composé de la formule (I), ou un sel pharmaceutiquement acceptable de celui-ci, tel que défini à l'une des revendications 1 à 5.

8. Composé de la formule (I), ou sel pharmaceutiquement acceptable de celui-ci, tel que défini à l'une des revendications 1 à 5, pour utilisation en tant qu'inhibiteur de l'angiogenèse.

9. Utilisation d'un composé de la formule (I), ou d'un sel pharmaceutiquement acceptable de celui-ci, tel que défini à l'une des revendications 1 à 5, dans la préparation d'un médicament pour utilisation dans le traitement de l'angiogenèse.

10. Utilisation d'un composé de la formule (I), ou d'un sel pharmaceutiquement acceptable de celui-ci, tel que défini à l'une des revendications 1 à 5, dans la préparation d'un médicament pour une utilisation prophylactique et/ou thérapeutique dans un état de maladie dans lequel le TNFα joue un rôle préjudiciable.

11. Composé représenté par la formule (II) :

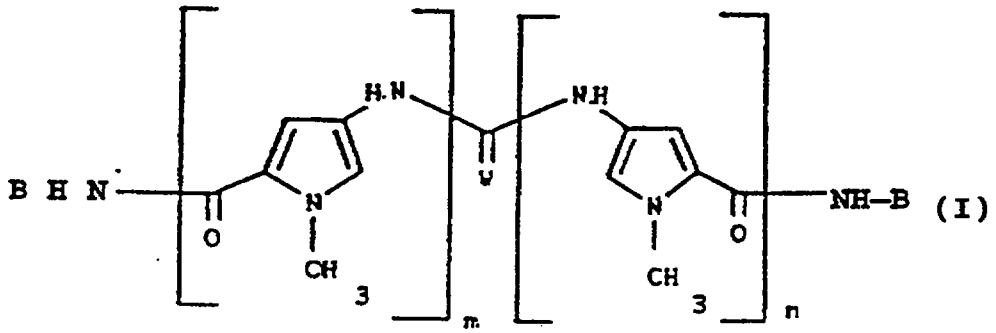


(II)

dans laquelle n et B sont tels que définis à la revendication 1 ou 2,
ou un sel de ce composé,
à la condition que B ne représente pas un groupe $-CH_2(CHA)_rCH_2A$, tel que défini à la revendication 1.

Revendications pour l'Etat contractant suivant : ES

1. Procédé de préparation d'un composé représenté par la formule (I) :



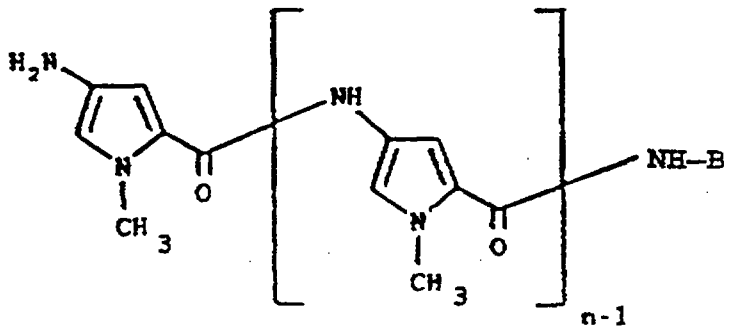
(I)

dans laquelle :

- m et n, qui sont identiques, représentent chacun un entier de 1 à 3 ;
- W représente oxygène ou soufre ;
- les groupes B, qui sont identiques, représentent chacun :
  (a) un groupe phényle ou naphtyle, substitué par un ou plusieurs groupes acides ;
  (b) un groupe hétéromonocyclique ou hétérobicyclique, saturé ou insaturé, contenant un ou plusieurs hétéroatomes choisis parmi l'azote, l'oxygène et le soufre, substitué par un ou plusieurs groupes acides ;
  (c) un groupe 2-désoxy-D-glucose, substitué par un ou plusieurs groupes acides ; ou
  (d) un groupe $-CH_2(CHA)_rCH_2A$, dans lequel les groupes A, qui sont identiques ou différents, représentent chacun un groupe acide, et r vaut 0, 1 ou 2 ;

et dans laquelle chacun des groupes acides ci-dessus est choisi indépendamment parmi les groupes acide sulfonique, sulfurique, sulfamique, sulfinique, phosphorique, phosphonique, phosphamique et

carboxylique ;
et des sels pharmaceutiquement acceptables de ce composé, lequel procédé comprend la réaction d'un composé représenté par la



(II)

formule (II) : dans laquelle n et B sont tels que définis ci-dessus,
ou d'un sel de celui-ci,
avec un composé représenté par la formule (III) :



(III)

dans laquelle :

- W est tel que défini ci-dessus ; et
- les groupes X, qui peuvent être identiques ou différents, représentent chacun un groupe bon partant,

et, si on le désire, la salification d'un composé de la formule (I) ainsi obtenu ; et/ou si on le désire, l'obtention d'un composé libre de la formule (I) à partir d'un sel de celui-ci.

2. Procédé selon la revendication 1, dans lequel :
   - m et n, qui sont identiques, valent chacun 2 ;
   - W représente oxygène ;
   - les groupes B, qui sont identiques, représentent chacun :
     (a') un groupe phényle ou naphtyle, substitué par 1 à 3 groupes acides ;
     (b') un cycle tétrahydropyrannyle ou tétrahydrofurannyle, substitué par 1 à 3 groupes acides ; ou
     (c') un groupe 2-désoxy-D-glucose, substitué par 1 à 3 groupes acides ;

   et les sels pharmaceutiquement acceptables de ce composé.

3. Procédé selon la revendication 1, dans lequel le composé préparé est choisi dans le groupe constitué par :
   - le 8,8'-(carbonyl-bis(imino-N-méthyl-4,2-pyrrolecarbonyl-imino(N-méthyl-4,2-pyrrole)carbonyl-amino))bis(acide 1,3-naphtalènedisulfonique) ;
   - le 8,8'-(carbonyl-bis(imino-N-méthyl-4,2-pyrrolecarbonyl-imino(N-méthyl-4,2-pyrrole)carbonyl-amino))bis(acide 3,5-naphtalènedisulfonique) ;
   - le 8,8'-(carbonyl-bis(imino-N-méthyl-4,2-pyrrolecarbonyl-imino(N-méthyl-4,2-pyrrole)carbonyl-imino))bis(acide 2,5-naphtalènedisulfonique) ;
   - le 8,8'-(carbonyl-bis(imino-N-méthyl-4,2-pyrrolecarbonyl-imino(N-méthyl-4,2-pyrrole)carbonyl-imino))bis(acide 2,4-naphtalènedisulfonique) ;
   - le 8,8'-(carbonyl-bis(imino-N-méthyl-4,2-pyrrolecarbonyl-imino(N-méthyl-4,2-pyrrole)carbonyl-amino))bis(acide 1,6-naphtalènedisulfonique) ;
   - le 8,8'-(carbonyl-bis(imino-N-méthyl-4,2-pyrrolecarbonyl-imino(N-méthyl-4,2-pyrrole)carbonyl-amino))bis(acide 2,4,6-naphtalènetrisulfonique) ;

- le 8,8'-(carbonyl-bis(imino-N-méthyl-4,2-pyrrolecarbonyl-imino(N-méthyl-4,2-pyrrole)carbonyl-amino))bis(acide 1,3,6-naphtalènetrisulfonique) ;
- le 8,8'-(carbonyl-bis(imino-N-méthyl-4,2-pyrrolecarbonyl-imino(N-méthyl-4,2-pyrrole)carbonyl-imino))bis(acide 2,3,5-naphtalènetrisulfonique) ;
- le 2,2'-(carbonyl-bis(imino-N-méthyl-4,2-pyrrolecarbonyl-imino(N-méthyl-4,2-pyrrole)carbonyl-imino))bis(2-désoxy-D-glucose-6-sulfate) ; et
- le 2,2'-(carbonyl-bis(imino-N-méthyl-4,2-pyrrolecarbonyl-imino(N-méthyl-4,2-pyrrole)carbonyl-imino))bis(2-désoxy-D-glucose-6-phosphate) ;

et les sels pharmaceutiquement acceptables de ces composés.

4. Procédé selon la revendication 3, dans lequel ledit sel est le sel de sodium ou le sel de potassium.

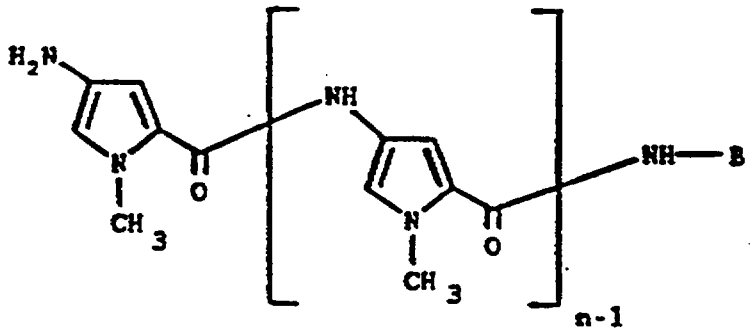
5. Procédé selon la revendication 1, dans lequel le composé préparé est le sel tétrapotassique du 7,7'-(carbonyl-bis(imino-N-méthyl-4,2-pyrrolecarbonyl-imino(N-méthyl-4,2-pyrrole)carbonylimino))bis-(acide1,3-naphtalènedisulfonique).

6. Procédé de préparation d'une composition pharmaceutique qui comprend l'opération consistant à mélanger ensemble un support et/ou diluant pharmaceutiquement acceptable et, en tant que principe actif, un composé de la formule (I), ou un sel pharmaceutiquement acceptable de celui-ci, tel que défini à l'une des revendications 1 à 5.

7. Utilisation d'un composé de la formule (I), ou d'un sel pharmaceutiquement acceptable de celui-ci, tel que défini à l'une des revendications 1 à 5, dans la préparation d'un médicament pour utilisation dans le traitement de l'angiogenèse.

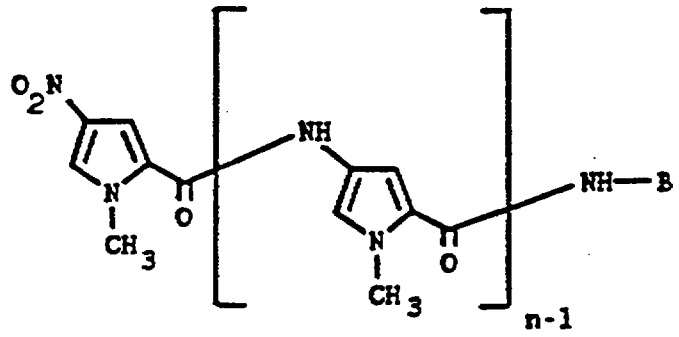
8. Utilisation d'un composé de la formule (I), ou d'un sel pharmaceutiquement acceptable de celui-ci, tel que défini à l'une des revendications 1 à 5, dans la préparation d'un médicament pour une utilisation prophylactique et/ou thérapeutique dans un état de maladie dans lequel le TNFα joue un rôle préjudiciable.

9. Procédé de préparation d'un composé de la formule (II) :



(II)

dans laquelle n et B sont tels que définis à la revendication 1 ou 2,
ou d'un sel de ce composé,
à la condition que B ne représente pas un groupe $-CH_2(CHA)_rCH_2A$, tel que défini à la revendication 1,
ledit procédé comprenant la réduction d'un composé de formule (IV) :

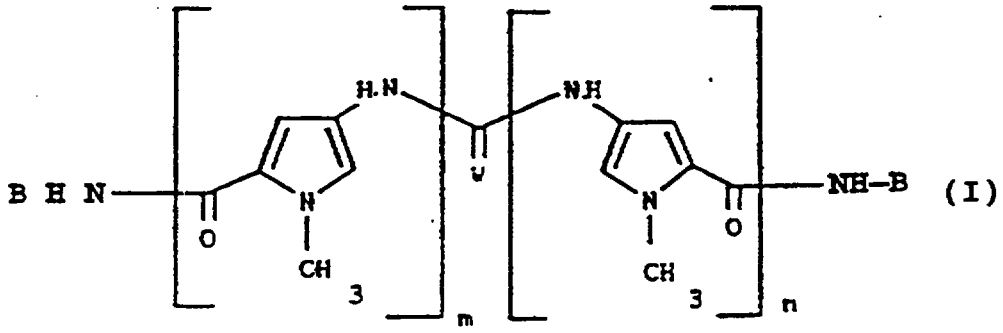


(IV)

dans laquelle n et B sont tels que définis ci-dessus.

Revendications pour l'Etat contractant suivant : GR

1. Procédé de préparation d'un composé représenté par la formule (I) :

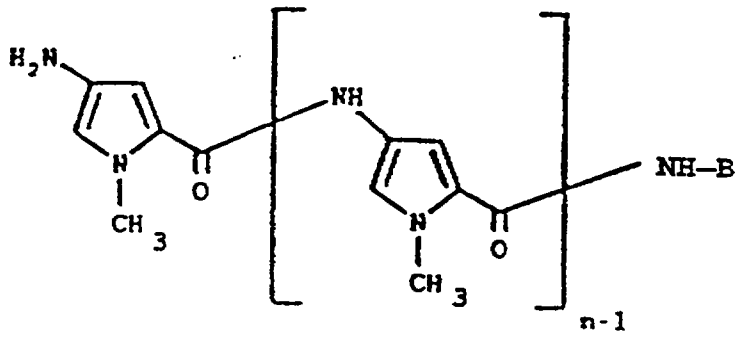


(I)

dans laquelle :

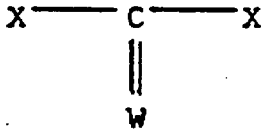
- m et n, qui sont identiques, représentent chacun un entier de 1 à 3 ;
- W représente oxygène ou soufre ;
- les groupes B, qui sont identiques, représentent chacun :
  (a) un groupe phényle ou naphtyle, substitué par un ou plusieurs groupes acides ;
  (b) un groupe hétéromonocyclique ou hétérobicyclique, saturé ou insaturé, contenant un ou plusieurs hétéroatomes choisis parmi l'azote, l'oxygène et le soufre, substitué par un ou plusieurs groupes acides ;
  (c) un groupe 2-désoxy-D-glucose, substitué par un ou plusieurs groupes acides ; ou
  (d) un groupe $-CH_2(CHA)_rCH_2A$, dans lequel les groupes A, qui sont identiques ou différents, représentent chacun un groupe acide, et r vaut 0, 1 ou 2 ;

et dans laquelle chacun des groupes acides ci-dessus est choisi indépendamment parmi les groupes acide sulfonique, sulfurique, sulfamique, sulfinique, phosphorique, phosphonique, phosphamique et carboxylique ;
et des sels pharmaceutiquement acceptables de ce composé, lequel procédé comprend la réaction d'un composé représenté par la formule (II) :



(II)

dans laquelle n et B sont tels que définis ci-dessus,
ou d'un sel de celui-ci,
avec un composé représenté par la formule (III) :



(III)

dans laquelle :

- W est tel que défini ci-dessus ; et
- les groupes X, qui peuvent être identiques ou différents, représentent chacun un groupe bon partant,

et, si on le désire, la salification d'un composé de la formule (I) ainsi obtenu ; et/ou si on le désire, l'obtention d'un composé libre de la formule (I) à partir d'un sel de celui-ci.

2. Procédé selon la revendication 1, dans lequel :
   - m et n, qui sont identiques, valent chacun 2 ;
   - W représente oxygène ;
   - les groupes B, qui sont identiques, représentent chacun :
     (a') un groupe phényle ou naphtyle, substitué par 1 à 3 groupes acides ;
     (b') un cycle tétrahydropyrannyle ou tétrahydrofurannyle, substitué par 1 à 3 groupes acides ; ou
     (c') un groupe 2-désoxy-D-glucose, substitué par 1 à 3 groupes acides ;

   et les sels pharmaceutiquement acceptables de ce composé.

3. Procédé selon la revendication 1, dans lequel le composé préparé est choisi dans le groupe constitué par :
   - le 8,8'-(carbonyl-bis(imino-N-méthyl-4,2-pyrrolecarbonyl-imino(N-méthyl-4,2-pyrrole)carbonyl-amino))bis(acide 1,3-naphtalènedisulfonique) ;
   - le 8,8'-(carbonyl-bis(imino-N-méthyl-4,2-pyrrolecarbonyl-imino(N-méthyl-4,2-pyrrole)carbonyl-imino))bis(acide 3,5-naphtalènedisulfonique) ;
   - le 8,8'-(carbonyl-bis(imino-N-méthyl-4,2-pyrrolecarbonyl-imino(N-méthyl-4,2-pyrrole)carbonyl-imino))bis(acide 2,5-naphtalènedisulfonique) ;
   - le 8,8'-(carbonyl-bis(imino-N-méthyl-4,2-pyrrolecarbonyl-imino(N-méthyl-4,2-pyrrole)carbonyl-imino))bis(acide 2,4-naphtalènedisulfonique) ;
   - le 8,8'-(carbonyl-bis(imino-N-méthyl-4,2-pyrrolecarbonyl-imino(N-méthyl-4,2-pyrrole)carbonyl-imino))bis(acide 1,6-naphtalènedisulfonique) ;
   - le 8,8'-(carbonyl-bis(imino-N-méthyl-4,2-pyrrolecarbonyl-imino(N-méthyl-4,2-pyrrole)carbonyl-imino))bis(acide 2,4,6-naphtalènetrisulfonique) ;
   - le 8,8'-(carbonyl-bis(imino-N-méthyl-4,2-pyrrolecarbonyl-imino(N-méthyl-4,2-pyrrole)carbonyl-imino))bis(acide 1,3,6-naphtalènetrisulfonique) ;
   - le 8,8'-(carbonyl-bis(imino-N-méthyl-4,2-pyrrolecarbonyl-imino(N-méthyl-4,2-pyrrole)carbonyl-amino))bis(acide 2,3,5-naphtalènetrisulfonique) ;

* C L M S *

- le 2,2'-(carbonyl-bis(imino-N-méthyl-4,2-pyrrolecarbonyl-imino(N-méthyl-4,2-pyrrole)carbonyl-amino))bis(2-désoxy-D-glucose-6-sulfate) ; et
- le 2,2'-(carbonyl-bis(imino-N-méthyl-4,2-pyrrolecarbonyl-imino(N-méthyl-4,2-pyrrole)carbonyl-imino))bis(2-désoxy-D-glucose-6-phosphate) ;

et les sels pharmaceutiquement acceptables de ces composés.

4. Procédé selon la revendication 3, dans lequel ledit sel est le sel de sodium ou le sel de potassium.

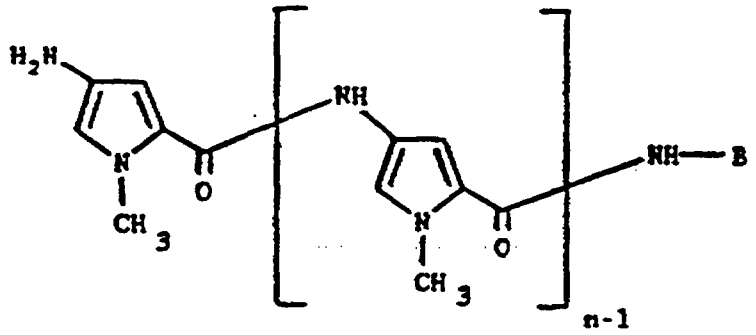
5. Procédé selon la revendication 1, dans lequel le composé préparé est le sel tétrapotassique du 7,7'-(carbonyl-bis(imino-N-méthyl-4,2-pyrrolecarbonyl-imino(N-méthyl-4,2-pyrrole)carbonylamino))bis-(acide1,3-naphtalènedisulfonique).

6. Procédé de préparation d'une composition pharmaceutique qui comprend l'opération consistant à mélanger ensemble un support et/ou diluant pharmaceutiquement acceptable et, en tant que principe actif, un composé de la formule (I), ou un sel pharmaceutiquement acceptable de celui-ci, tel que défini à l'une des revendications 1 à 5.

7. Utilisation d'un composé de la formule (I), ou d'un sel pharmaceutiquement acceptable de celui-ci, tel que défini à l'une des revendications 1 à 5, dans la préparation d'un médicament pour utilisation dans le traitement de l'angiogenèse.

8. Utilisation d'un composé de la formule (I), ou d'un sel pharmaceutiquement acceptable de celui-ci, tel que défini à l'une des revendications 1 à 5, dans la préparation d'un médicament pour une utilisation prophylactique et/ou thérapeutique dans un état de maladie dans lequel le TNFα joue un rôle préjudiciable.

9. Composé représenté par la formule (II) :



(II)

dans laquelle n et B sont tels que définis à la revendication 1 ou 2,
ou un sel de ce composé,
à la condition que B ne représente pas un groupe $-CH_2(CHA)_nCH_2A$, tel que défini à la revendication 1.