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BIOLOGICALLY ACTIVE UREIDO DERIVATIVES USEFUL AS ANTIMETASTATIC AGENTS

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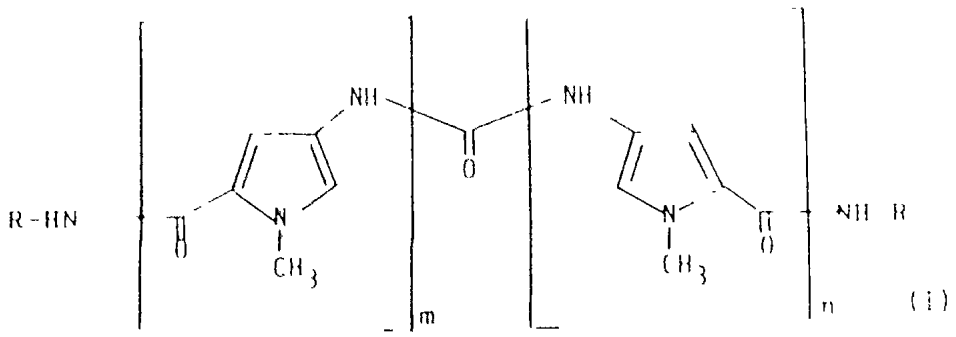
(56) Prior Art Documents
WO 91/10649

(57) Claim

1. A method of inhibiting tumoral cell adhesion in a mammal, said method comprising administering to said mammal an effective amount of a compound of formula (I)



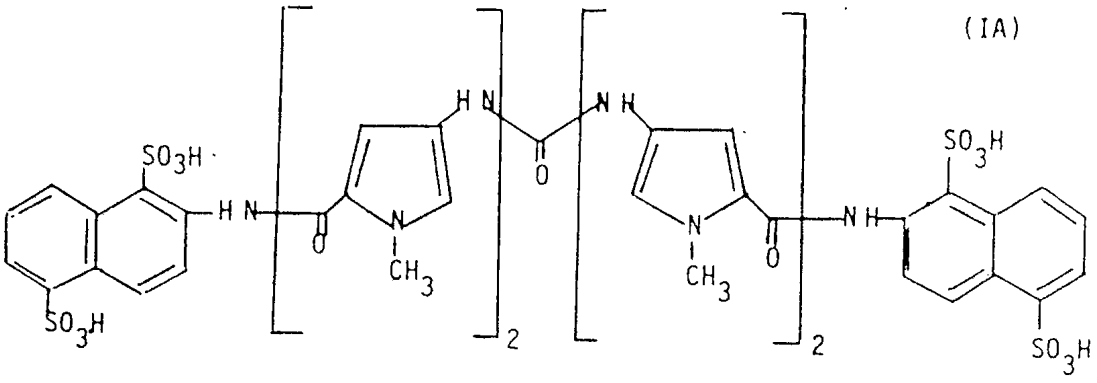
(I)

wherein
each of m and n, being the same, is an integer of 1 to 3; and each of the R groups, which are the same, is a naphthyl group substituted by 1 to 3 sulfonic groups, or a pharmaceutically acceptable salt thereof.

.../2

4. 2,2'-(carbonyl-bis(imino-N-methyl-4,2-pyrrole-carbonylimino(N-methyl-4,2-pyrrole)carbonylimino))-bis(1,5-naphthalenedisulfonic acid) of formula (IA)

(IA)



or a pharmaceutically acceptable salt thereof.

CORRECTED VERSION*

PCT

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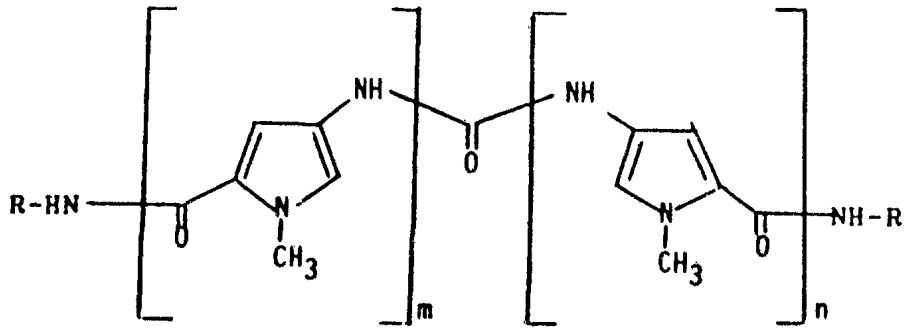
(54) Title: BIOLOGICALLY ACTIVE UREIDO DERIVATIVES USEFUL AS ANTIMETASTATIC AGENTS



(I)

(57) Abstract

The invention relates to the use of compounds of formula (I) wherein each of m and n, being the same, is an integer of 1 to 3; and each of the R groups, which are the same, is a naphthyl group substituted by 1 to 3 sulfonic groups, or pharmaceutically acceptable salts thereof, in the preparation of a medicament for use in preventing and/or treating the metastatic spread of tumors.

"BIOLOGICALLY ACTIVE UREIDO DERIVATIVES USEFUL AS ANTI-METASTATIC AGENTS"

The present invention relates to the use of ureido derivatives of substituted pyrroles as antimetastatic agents.

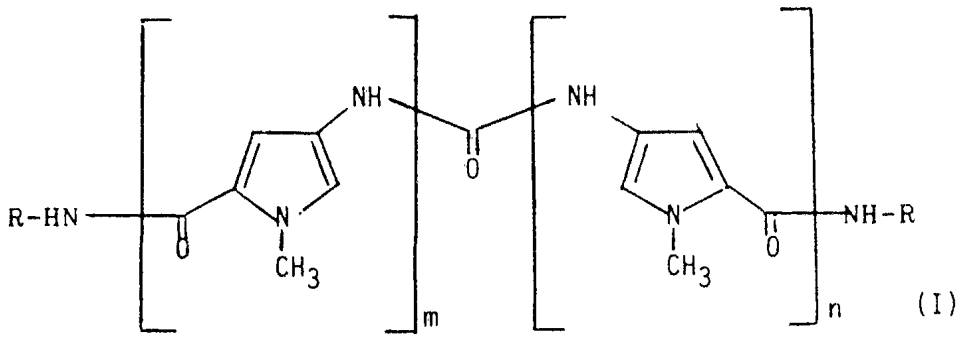
As known, malignancy of cancer is mainly due to metastasis. Because therapy usually fails to destroy multiple secondary tumors, their uncontrolled growth leads to death of patients. Only very few patients die from complications directly arising from the primary tumor. Accordingly, there is a need in therapy of drugs able to prevent and/or block the metastatic spread.

WO 91/10649 provides ureido derivatives of poly-4-amino-2-carboxy-1-methyl compounds which have angiogenesis inhibitor activity and have TNF-α neutralizing activity. Accordingly, these prior art compounds can be useful in treating several pathological conditions in mammals where the growth of new blood vessels is detrimental and in which TNF-α is known to play a detrimental role.

Now we have found that a selected class of compounds previously disclosed in the above mentioned international application are able to prevent and/or block the metastatic spread of tumors in mammals, including humans.

Accordingly, the present invention provides the use of

a compound of formula (I)



(I)

wherein

each of m and n, being the same, is an integer of 1 to 3; and each of the R groups, which are the same, is a naphthyl group substituted by 1 to 3 sulfonic groups, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for use in preventing and/or treating the metastatic spread of tumors by inhibiting tumoral cell adhesion.

The present invention also provides a compound of formula (I), as defined above, or a pharmaceutically acceptable salt thereof, for use in preventing and/or treating the metastatic spread of tumors.

The substituted naphthyl group is preferably a 5-, 6-, 7- or 8-naphthyl group, typically a 7- or 8-naphthyl group. When the naphthyl group is substituted by three sulfonic acid groups, the sulfonic acid substituents are preferably in the 1-, 3- and 5- or 1-, 3- and 6-positions. When it is substituted by 2 acid groups, the sulfonic acid substituents are preferably in the 1- and

3-, 1- and 5-, 3- and 5- or 3- and 6-positions. When it is substituted by one acid group the sulfonic acid substituent is preferably in the 1-, 3- or 5-position.

The invention also includes within its scope all the possible isomers, stereoisomers and their mixtures and the metabolites and the metabolic precursors or bioprecursors of the compounds of formula (I).

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, ß-phenethylamine, N-benzyl-ß-phenethylamine, N-benzyl-N,N-dimethylamine and other acceptable organic amines. Sodium and potassium salts are preferred.

As stated above, the present invention also includes within its scope pharmaceutically acceptable bioprecursors (otherwise known as pro-drugs) of the compounds of formula (I), i.e. compounds which have a different formula to formula (I) above but which nevertheless upon administration to a human being are converted directly or indirectly <u>in vivo</u> into a compound

of formula (I).

Preferred compounds of formula (I) are the compounds wherein m and n are each 2 and each of the R groups is as defined above, and the pharmaceutically acceptable salts thereof.

Examples of specific preferred compounds are:

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

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

7,7'-(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(1,3,6-naphthalentrisulfonic acid);

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

7,7'-(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(2,4-naphthalendisulfonic 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(5-naphthalensulfonic acid);

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

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

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

7,7'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis(2,6-naphthalendisulfonic acid);

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

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

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

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

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

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

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

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

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

7,7'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis(2,4,6-naphthalentrisulfonic acid);

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

and the pharmaceutically acceptable salts thereof.

As stated above, the compounds of the invention have been found to be active as antimetastatic agents. Accordingly, they can be used in mammals, including humans, for preventing and/or treating the metastatic spread of tumors metastasizing to bone, e.g. those of the breast, lung, prostate, kidney and thyroid, to liver and/or lung, e.g. melanoma and carcinoma arising in the gastrointestinal tract, pancreas and gallbladder. The antimetastatic activity of the compounds used in the invention is proven for instance by the fact that a representative compound of formula (I), 2,2'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))-bis(1,5-naphthalendisulfonic acid) (compound of formula (IA)), when administered i.v. to mice 48 hours before the injection of a tumoral cells suspension, provided the following inhibition activity data:

85 % inhibition on lung metastasis by murine melanoma B16F10;

100 % inhibition on lung metastasis by human sarcoma A375; and

82 % inhibition on liver metastasis by murine reticulumsarcoma M5076.

In addition, the compound of formula (IA), internal code FCE 27266, was found to be active in inhibiting spontaneous lung metastasis (87 %) on Lewis lung carcinoma when administered at 10 mg/kg i.p. for 17 days in mice.

The compounds of formula (I), or pharmaceutically acceptable salts thereof, can be administered by the usual routes, for example, parenterally, e.g. by intravenous injection or infusion, intramuscularly, subcutaneously, topically or orally, intravenous injection of infusion being preferred. The dosage depends on the age, weight and condition of the patient and on the administration route.

A suitable dosage for the compounds of formula (I), for example a compound of formula (IA), or pharmaceutically acceptable salts thereof, for administration to adult humans is from about 0.5 to about 300 mg per dose 1-4 times a day.

The pharmaceutical compositions used in the invention may comprise a compound of formula (I) or a pharmaceutically acceptable salt thereof, as the active substance, in association with one or more pharmaceutically acceptable excipients and/or carriers.

The pharmaceutical compositions 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 form 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.

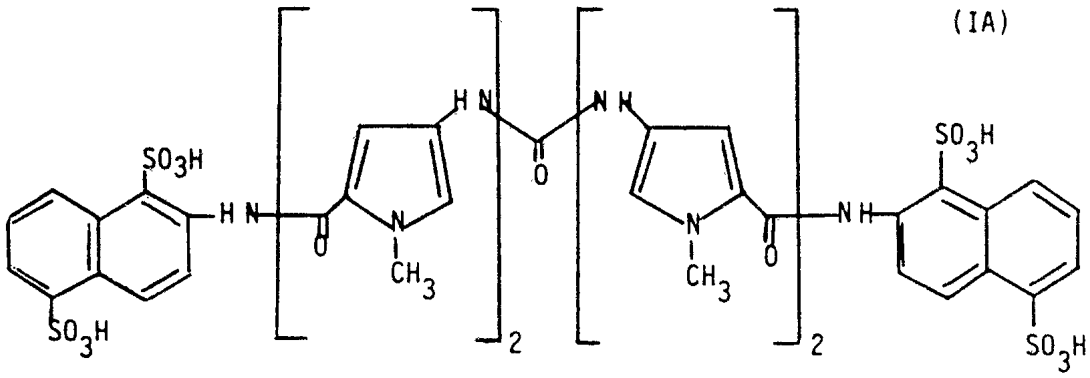
The compounds of formula (I), or pharmaceutically acceptable salts thereof, may be used in a method of treatment of the above mentioned pathological conditions comprising both separate and substantially contemporaneous administration of a composition containing a compound of formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutical composition containing a different pharmaceutically active agent, typically an antitumor agent.

Object of the present invention is also to provide products containing an antimetastatic agent of formula (I), as defined above, or a pharmaceutically acceptable salt thereof, and an antitumor agent as a combined preparation for simultaneous, separate or sequential use in preventing and/or treating metastatic spread of tumors.

Antitumor agents that can be formulated with a compound of formula (I), or a pharmaceutically acceptable salt thereof, or, alternatively, can be administered in a combined method of treatment are, e.g., doxorubicin, daunomycin, epirubicin, idarubicin, etoposide, fluorouracil, mephalan, cyclophosphamide, bleomycin, vinblastin and mitomycin or a mixture of two or more thereof.

The compounds of formula (I), or pharmaceutically acceptable salts thereof, can therefore be used in a treatment to ameliorate a cancer.

The present invention also provides the new ureido compound 2,2'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonyl-imino))-bis(1,5-naphthalendisulfonic acid), which can be represented by formula (IA):



(IA)

or a pharmaceutically acceptable salt thereof.

Typical examples of pharmaceutically acceptable salts of a compound of formula (IA) are those mentioned above in connection with the compounds of formula (I), the sodium and potassium salts being preferred.

The present invention also includes within its scope pharmaceutically acceptable bio-precursors (otherwise known as pro-drugs) of the compound of formula (IA), i.e. compounds which have a different formula to formula (I) above, but which nevertheless upon administration to a human being are converted directly or indirectly in

vivo into the compound of formula (IA).

The new compound of formula (IA) is embraced by the general formula disclosed in WO 91/10649 but is not specifically mentioned therein. The compound of formula (IA) and the pharmaceutically acceptable salts thereof, besides being active as antimetastatic agents, are also angiogenesis inhibitors. Accordingly, they can be 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.

Moreover, they are capable of neutralizing TNF-α and therefore 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 and rheumatoid arthritis.

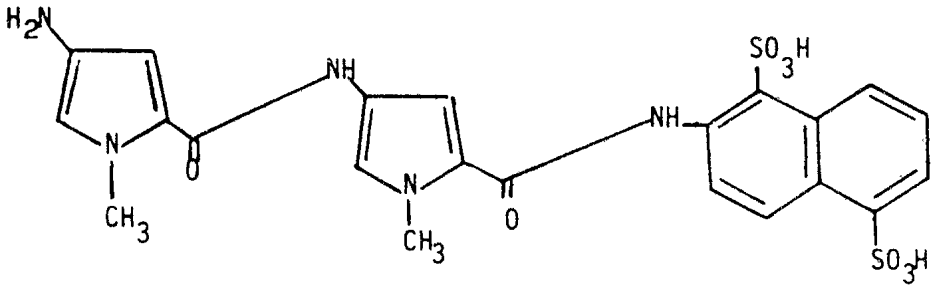
Dosages and pharmaceutical compositions similar to those described above for the compounds of formula (I) can also be used for the compound of formula (IA) and the pharmaceutically acceptable salts thereof when it is administered to adult humans as an angiogenesis inhibitor and/or anti-TNF-α activity agent.

The present invention additionally provides a compound of formula (IA), or a pharmaceutically acceptable salt

thereof, for use in a method of treatment of the human or animal body by therapy, in particular for use in preventing and/or treating the metastatic spread of tumors or for use as an angiogenesis inhibitor.

The present invention further provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and/or diluent and, as an active principle, the compound of formula (IA) or a pharmaceutically acceptable salt thereof.

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



(II)

or a salt thereof, with a compound of formula (III)

X-CO-X (III)

wherein each of the X groups, which may be the same or different, is a leaving group, and if desired, salifying the compound of formula (IA) thus obtained; and/or, if desired, obtaining the free compound of formula (IA) 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 pharmaceutically acceptable salts used in the invention, the sodium and potassium salts being the preferred.

Preferred examples of 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, trichlorophenoxy or trichloromethyloxy. The reaction of the 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 a 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 compound of formula (IA) 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 recrystallization from organic solvents such as lower aliphatic alcohols or dimethylformamide.

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

The present invention further provides the compound of formula (II) or a salt thereof.

The compound of formula (II) may be obtained according to known procedures, for instance as described in WO 91/10649.

The compounds of formula (I) and the pharmaceutically acceptable salts thereof can be obtained according to WO 91/10649, for instance by following a procedure similar to that described above in connection with the preparation of a compound of formula (IA) and the pharmaceutically acceptable salts thereof.

The following examples further illustrate but do not limit the present invention:

EXAMPLE 1

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

To a solution of 2-(amino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino)) (1,5-naphthalendisulfonic acid) disodium salt hydrochloride (1256 mg, 2 mmols) in water (60 ml) and dioxane (20 ml), NaOH 1N (2 ml) and sodium acetate (328 mg, 4 mmols) was added under stirring.

The whole was cooled to 5°C with an ice bath, then a solution of bis(trichloromethyl)carbonate (149 mg, 0.5 mmols) in dioxane (15 ml) was added dropwise in an hour. The mixture was stirred for 2 hours at room temperature. The solvents were evaporated under vacuum and the residue was chromatographed on a silica gel column with methylene chloride : methanol : water (300:200:20) as eluant, affording 856 mg of the title compound.

N.M.R. (DM δ O-d_6): 3.85 (3H, s); 3.91 (3H, s); 6.90 (1H, d, J=1.8); 6.98 (1H, d, J=1.8); 7.09 (1H, d, J=1.8); 7.35 (1H, dd, J=7, J=8.8); 7.47 (1H, d, J=1.8); 7.9 (1H, d, J=7); 9.15 (1H, bs); 8.67-8.82 (2H, dd, J=9.6); 8.99 (1H, d, J=8.8); 9.98 (1H, bs); 12.64 (1H, bs).

F.A.B. M.S.: m/z 1207, $[M-H]^-$; 1185, $[M-23]^-$; 1105 $(M-SO_3Na)^-$.

U.V. (H_2O): λ max 298; $E^{1\%}_{1cm}$ 522

By proceeding analogously, the following compounds can be prepared:

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

N.M.R. (DMSO-d_6): δ 3.85 (3H,s); 3.90 (3H,s); 6.81 (1H, d, J=1.8); 6.90 (1H, d, J=1.8); 7.12 (1H,d,J=1.8); 7.32 (1H, d, J=1.8); 7.70 (1H, dd, J=1.6, J=8.6); 7.80 (1H, d, J=8.6); 8.11 (1H, d, J=1.6); 8.15 (1H, bs), 8.58 (1H, d, J=1.7); 8.78 (1H, d, J=1.7); 10.05 (1H, bs); 10.94 (1H, bs).

F.A.B. M.S. m/z: 1209, M^++H; 1187, M^+-Ne+H;

U.V. (H_2O) n.m.: λ max ($E^{1\%}_{1cm}$): 321 (416); 231 (721).

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

N.M.R. (DMSO-d_6): δ 3.85 (3H,s); 3.93 (3H,s); 6.81 (1H, d, J=1.8); 6.91 (1H, d, J=1.8);

7.08 (1H, d, J=1.8); 7.51 (1H, d, J=1.8); 7.68 (1H, dd, J=1.6, J=8.6); 7.78 (1H, d, J=8.6); 8.04 (1H, s); 8.12 (1H, bs); 8.23 (1H, s); 8.89 (1H, s); 10.02 (1H, bs); 10.98 (1H, bs);

F.A.B. M.S. m/z: 1209, M^t+H; 1187, M^t-Ne+H;

U.V. (H_2O) n.m.: λ max ($E^{1\%}_{1cm}$) : 323.4 (540); 227.7 (732).

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;

N.M.R. (DMSO-d_6): δ 3.85 (3H, s); 3.89 (3H, s); 6.78 (1H, d, J=1.8); 7.08 (1H, d, J=1.8); 7.22 (1H, d, J=1.8); 7.35 (1H, d, J=1.8); 8.25 (1H, d, J=1.9); 8.30 (1H, bs); 8.36 (1H, bs); 9.00 (1H, bs); 9.07 (1H, d, J=1.6); 9.82 (1H, bs); 10.20 (1H, bs);

U.V. (H_2O) n.m.: λ max ($E^{1\%}_{1cm}$) : 320 (374); 254 (444).

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;

N.M.R. (DMSO-d_6): δ 3.84 (3H, s); 3.88 (3H, s); 6.81 (1H, d, J=1.8); 7.07 (1H, d, J=1.8); 7.11 (1H, d, J=1.8); 7.42 (1H, d, J=1.8); 7.87 (1H, d, J=1.9); 7.87 (1H, d, J=1.9); 8.06 (1H, d, J=1.9); 8.12 (1H, bs); 8.33 (1H, d, J=1.9); 8.54 (1H, d, J=1.9); 9.93 (1H, bs); 12.19 (1H, bs).

U.V. (H_2O) n.m.: λ max ($E^{1\%}_{1cm}$) : 320 (374); 254 (444).

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

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

N.M.R. (DMSO-d_6): 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) n.m.: λ max ($E^{1\%}_{1cm}$) : 316.8 (371); 248.95 (444)

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

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

N.M.R. (DMSO-d_6): δ 3.85 (3H, s); 3.89 (3H, s); 6.81 (1H, d, J=1.7); 7.06 (1H, d, J=1.7); 7.22 (1H, d, J=1.7); 7.33 (1H, d, J=1.7); 7.33 (1H, d, J=1.7); 7.38 (1H, dd, J=2.0, J=9.5); 7.92 (1H, bs); 8.10 (1H, d, J=1.7); 8.20 (1H, bs); 8.32 (1H, d, J=2.0); 8.69 (1H, d, J=9.4); 9.88 (1H, bs); 10.08 (1H, bs).

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

N.M.R. (DMSO-d_6): δ 3.85 (6H, s); 6.81 (1H, d, J=1.7 Hz); 7.06 (1H, d, J=1+Hz); 7.25 (1H, d, J=1.7 Hz); 7.34 (1H, d, J=1.7 Hz); 7.4 ÷ 7.6 (2H, m); 8.14 (1H, bs); 8.25 (2H, s); 8.73 (1H, dd, J=13 Hz, J=8.3 Hz); 9.92 (1H, bs); 10.07 (1H, bs).

U.V. (H_2O) n.m.: λ max ($E^{1\%}_{1cm}$) : 307 (435); 231 (932).

F.A.B. m/z : 1209 (M^++1); 1231 (M^++Ne); 1128 (M^+-SO_3)

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;

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

N.M.R. (DMSO-d_6): δ 3.80 (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).

U.V. (H_2) nm: λ max ($E^{1\%}_{1cm}$) : 311 (266); 233 (551)

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

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

N.M.R. (DMSO-d_6): δ 3.85 (6H, s); 6.84 (1H, d, J=1.8); 7.05 (1H, d, J=1.8); 7.25 (1H, d, J=1.8); 7.35 (1H, d, J=1.8); 7.46-7.56 (3H, m); 7.92-8.00 (2H, m); 8.15 (1H, bs); 8.87 (1H, m); 9.89 (1H, bs); 10.03 (1H, bs);

U.V. (H_2O) n.m.: λ max ($E^{1\%}_{1cm}$) : 310 (531); 227 (1043)

F.A.B. M.S. m/z : 1005,(M^++H); 1027 (M^++Ne); 512.

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

N.M.R. (DMSO-d_6): δ 3.84 (3H, s); 3.86 (3H, s); 6.81 (1H, d, J=1.8); 7.08 (2H, bs); 7.41 1H, d, J=1.8); 7.50 (1H, t, J=7.0); 7.78 (1H, d, J=7.0); 8.02 (1H, d, J=7.0); 8.11 (2H, m); 8.53 (1H, d, J=2.02); 9.93 (1H, bs); 12.21 (1H, bs);

U.V. (H_2O) n.m.: λ max ($E^{1\%}_{1cm}$) : 309.05 (403); 229.65, 735

F.A.B. M.S. m/z : 1209, M^++H; 1231,M^++Ne; 1187, M^+-Ne+H; 1129; 640; 618; 614; 592.

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

N.M.R. (DMSO-d_6): δ 3.85 (6H, s); 6.83 (1H, d, J=1.8); 7.06 (1H, d, J=1.8); 7.26 (1H, d, J=1.8); 7.38 (1H, d, J=1.08); 7.50

(1H, d, J=7.8); 7.72 (1H, dd, J=1.7, J=8.9); 7.98 (1H, d, J=7.8); 8.25 (1H, bs); 9.19 (1H, d, J=1.7); 9.91 (1H, bs); 10.03 (1H, bs);

U.V. (H_2O) n.m.: λ max ($E^{1\%}_{1cm}$) : 310 (431); 231 (1027)

F.A.B. M.S. m/z: 1209, M^++H; 640; 618; 614; 592;

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

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

N.M.R. (DMSO-d_6): 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 (1.12, 1H, s); 8.27 (1H, dd); 9.07 (1H, dd); 9.90 (1H, bs); 12.27 (1H, bs).

U.V. (H_2O) n.m.: λ max ($E^{1\%}_{1cm}$) : 316 (331); 229 (478)

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

8,8'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-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-d_6): 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).

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

F.A.B. M.S. m/z: 1005, M^++H; 1027, M^++2Na

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

N.M.R. (DMSO-d_6): δ 3.84 (3H, s); 3.85 (3H, s); 6.82 (1H, d, J=1.8); 7.06 (1H, d, J=1.8); 7.09 (1H, d, J=1.8); 7.39-7.54 (3H, m); 7.74 (1H, dd, J=1.3, J=.3, J=8.2); 7.93-8.02 (2H, m); 8.13 (1H, bs); 8.26 (1H, dd, J=1.5, J=7.3); 9.93 (1H, bs); 12.20 (1H, bs);

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

U.V. (H_2O) n.m.: λ max ($E^{1\%}_{1cm}$) : 312 (490); 224 (831)

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-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(2,3-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-methyl-4,2-pyrrole)carbonylimino))bis(2,6-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(3,6-naphthalendisulfonic acid) tetrasodium salt;

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;

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

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

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.

EXAMPLE 2

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

A solution of 2,2'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonyl-imino))-bis(1,5-naphthalenedisulfonic acid)tetrasodium 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.

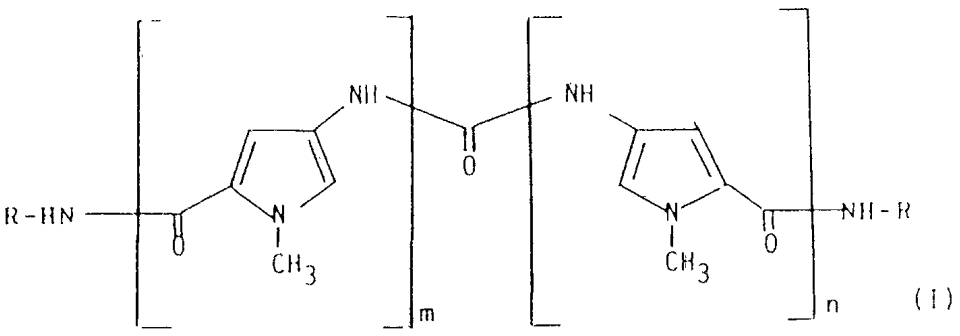
EXAMPLE 3

Intramuscular injection 40 mg/ml.

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

CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A method of inhibiting tumoral cell adhesion in a mammal, said method comprising administering to said mammal an effective amount of a compound of formula (I)



(I)

wherein
each of m and n, being the same, is an integer of 1 to 3; and each of the R groups, which are the same, is a naphthyl group substituted by 1 to 3 sulfonic groups, or a pharmaceutically acceptable salt thereof.

2. The method according to claim 1, wherein in the compound of formula (I) m and n are each 2.

3. The method according to claim 1, wherein the compound is: 7,7'-(carbonyl-bis(imino-N-methyl-4,2-pyrrole-carbonylimino(N-methyl-4,2-pyrrole)carbonyl-imino))bis(3,5-naphthalendisulfonic acid);

7,7'-(carbonyl-bis(imino-N-methyl-4,2-pyrrole-carbonylimino(N-methyl-4,2-pyrrole)carbonylimino))-bis(3,6-naphthalendisulfonic acid);

7,7'-(carbonyl-bis(imino-N-methyl-4,2-pyrrole-carbonylimino(N-methyl-4,2-pyrrole)carbonylimino))-bis(1,3,5-naphthalentrisulfonic acid);

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

7,7'-(carbonyl-bis(imino-N-methyl-4,2-pyrrole-carbonylimino(N-methyl-4,2-pyrrole)carbonylimino))-bis(1,3-naphthalendisulfonic acid);

7,7'-(carbonyl-bis(imino-N-methyl-4,2-pyrrole-carbonylimino(N-methyl-4,2-pyrrole)carbonylimino))-bis(2,4-naphthalendisulfonic acid);

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

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

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

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

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

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

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

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

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

7,7'-(carbonyl-bis(imino-N-methyl-4,2-pyrrole-carbonylimino(N-methyl-4,2-pyrrole)carbonylimino))-bis(1,6-naphthalendisulfonic acid);

7,7'-(carbonyl-bis(imino-N-methyl-4,2-pyrrole-carbonylimino(N-methyl-4,2-pyrrole)carbonylimino))-bis(2,6-naphthalendisulfonic acid);

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

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

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

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

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

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

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

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

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

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

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

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

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

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

7,7'-(carbonyl-bis(imino-N-methyl-4,2-pyrrole-carbonylimino(N-methyl-4,2-pyrrole)carbonylimino))-bis(1,4,6-naphthalentrisulfonic acid);

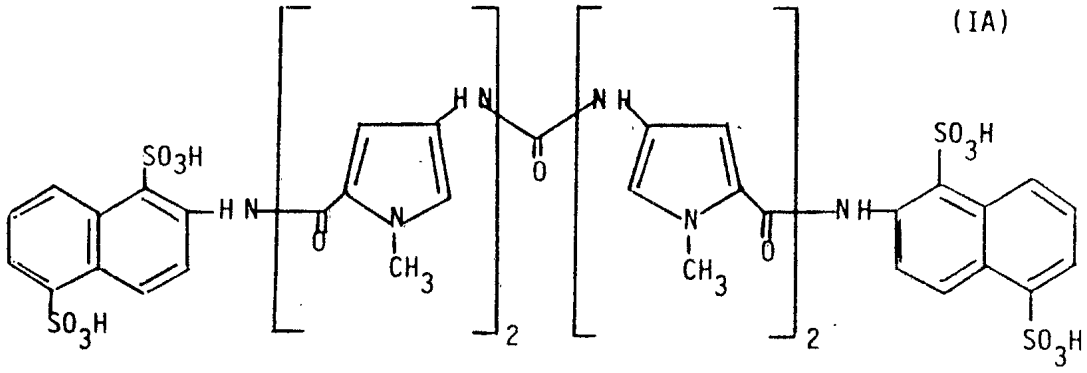
7,7'-(carbonyl-bis(imino-N-methyl-4,2-pyrrole-carbonylimino(N-methyl-4,2-pyrrole)carbonylimino))-bis(1,3,6-naphthalentrisulfonic acid);

7,7'-(carbonyl-bis(imino-N-methyl-4,2-pyrrole-carbonylimino(N-methyl-4,2-pyrrole)carbonylimino))-bis(2,4,6-naphthalentrisulfonic acid); or

7,7'-(carbonyl-bis(imino-N-methyl-4,2-pyrrole-carbonylimino(N-methyl-4,2-pyrrole)carbonylimino))-bis(2,3,5-naphthalentrisulfonic acid);

or a pharmaceutically acceptable salt thereof.

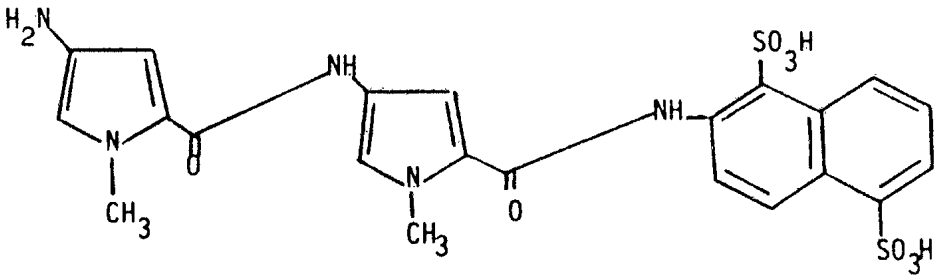
4. 2,2'-(carbonyl-bis(imino-N-methyl-4,2-pyrrole-carbonylimino(N-methyl-4,2-pyrrole)carbonylimino))-bis(1,5-naphthalenedisulfonic acid) of formula (IA)



(IA)

or a pharmaceutically acceptable salt thereof.

5. A process for the preparation of the compound of formula (IA), or a pharmaceutically acceptable salt thereof, according to claim 4, which process comprises reacting a compound of formula (II):



(II)

or a salt thereof, with a compound of formula (III)

X-CO-X (III)

wherein each of the X groups, which may be the same

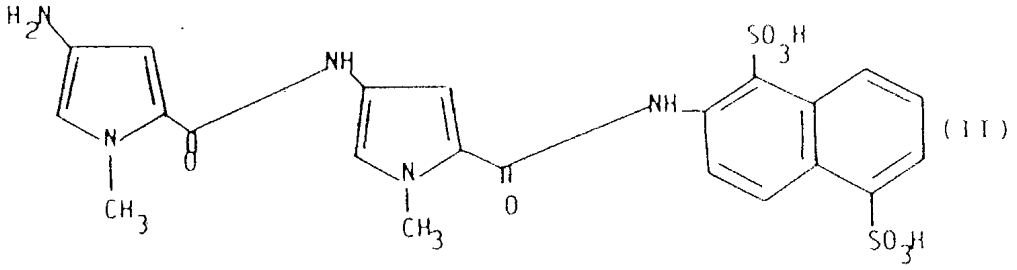
or different, is a leaving group, and, if desired, salifying the compound of formula (IA) thus obtained; and/or, if desired, obtaining the free compound of formula (IA) from a salt thereof.

6. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and/or diluent and, as an active principle, the compound of formula (IA) as defined in claim 4 or a pharmaceutically acceptable salt thereof.

7. the method of any one of claims 1 to 3 wherein products containing an anti-tumor cell adhesion agent of formula (I), or a pharmaceutically acceptable salt thereof,

and an anti-tumor agent are administered either as a combined preparation simultaneously, or are administered separately or sequentially.

8. The compound of formula (II)



(II)

or salt thereof.

DATED THIS 9TH DAY OF APRIL 1996

FARMITALIA CARLO ERBA S.R.L.

By Its Patent Attorneys:

GRIFFITH HACK & CO.,

Fellows Institute of Patent Attorneys of Australia

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/EP 94/00268

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 A61K31/40 A61K31/785

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO,A,91 10649 (FARMITALIA CARLO ERBA S.R.L.) 25 July 1991 see page 11 ---	1-3,9
A	EP,A,0 527 042 (FARMITALIA CARLO ERBA S.R.L.) 5 August 1992 see page 8 ---	1-3,9
A	DRUG DES. DISCIV., vol.8, no.1, 1991 pages 3 - 35 D.C. BILLINGTON 'Angiogenesis and its inhibition: Potential new therapies in oncology and non-neoplastic diseases' see the whole document --- -/--	1-3,9

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"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 when the document is taken alone

"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

Date of the actual completion of the international search	Date of mailing of the international search report
17 May 1994	04.08.94

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	KRAUTBAUER, B

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCT/EP 94/00268

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CANCER RES., vol.52, no.23, 1992 pages 6702 - 6704 B.A. TEICHER ET AL. 'Antiangiogenic agents potentiate cytotoxic cancer therapies against primary and metastatic disease' see the whole document -----	1-3,9

2

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP 94/00268

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

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

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
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:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

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

For further information please see annex.

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

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ 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 claims Nos.:

1-3,9 partially

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/

Continuation of BOX II:

1. Use of compounds falling under formula I except the compound of formula 1a, in the preparation of a medicament for use in preventing and/or treating the metastatic spread of tumors; products containing these compounds in combination with antitumor agents.
Claims 1-3,9 partially.

2. Compound 1a, the process of its preparation, a pharmaceutical composition containing it, its use in preventing and/or treating the mestastatic spread of tumors and as angiogenesis inhibitor; products containing compound 1a in combination with antitumor agents; compound II used in the process of preparation of compound 1a.
Claims 4-8,10 completely, claims 1-3,9 partially.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int ional Application No
PCT/EP 94/00268

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9110649	25-07-91	AU-B-	647446	24-03-94
		AU-A-	7059991	05-08-91
		CN-A-	1053230	24-07-91
		EP-A-	0462258	27-12-91
		JP-T-	4504426	06-08-92
		US-A-	5260329	09-11-93
EP-A-0527042	10-02-93	AU-B-	646173	10-02-94
		AU-A-	2037492	11-02-93
		JP-A-	5208988	20-08-93
		NZ-A-	243627	27-04-94