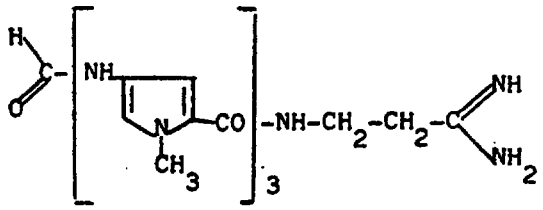
Description

The present invention refers to new antitumour alkylating and antiviral agents related to the known antibiotic distamycin A,



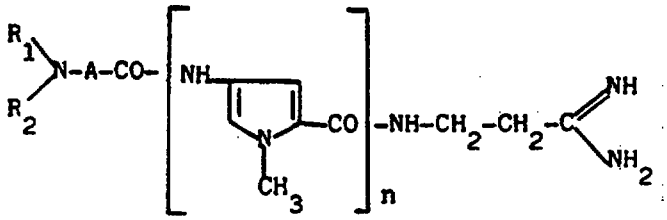
(distamycin A)

which belongs to the family of the pyrroleamidine antibiotics and is reported to interact reversibly and selectively with DNA-AT sequences interfering with both replication and transcription [Nature 203, 1064 (1964); FEBS Letters 7 (1970) 90; Prog. Nucleic Acids Res.Mol.Biol., 15, 285 (1975)].

DE-A-1795539 describes the preparation of distamycin derivatives in which the formyl group of distamycin is replaced by hydrogen or the acid residue of an organic C_1-C_4 aliphatic acid or of cyclopentylpropionic acid.

The present invention relates to new distamycin A analogs in which the distamycin formyl group is substituted by aromatic, alicyclic or heterocyclic moieties bearing alkylating groups, to a process for their preparation, to pharmaceutical compositions containing them and to the use of said compounds and compositions as antitumour and antiviral agents.

The invention herein provides compounds of the general formula (I)

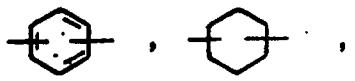


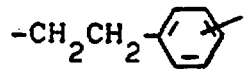
(I)

wherein

n is 2, 3 or 4;

A is a divalent radical chosen from

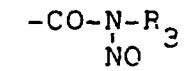




and -Het-, wherein Het is a pentatomic or hexatomic heteromonocyclic ring, except pyrrole, containing at least one heteroatom selected from O, S and N, the said radical being unsubstituted or substituted by one or more substituents chosen from C_1-C_6 alkyl, C_1-C_6 alkoxy, cyano and trifluoromethyl;

and either one of R_1 and R_2 is hydrogen and the other is

a) a group



in which R_3 is C_1-C_6 alkyl unsubstituted or substituted by halogen atoms; phenyl; or cyclohexyl; or

b) a group $-CO-(CH_2)_m-R_4$ in which m is zero, 1, 2 or 3 and R_4 is hydrogen, halogen, hydroxy, aziridinyl or oxiranyl;

or R_1 and R_2 are the same and they are both a C_1-C_6 alkyl group unsubstituted or substituted by halogen, hydroxy or C_1-C_6 alkoxy.

The invention includes also the pharmaceutically acceptable salts of the compounds of formula (I) as well as all the possible isomers covered by the formula (I), both separately and in mixture.

The alkyl groups and the aliphatic moieties of the alkoxy groups may be branched or straight chain.

A C_1-C_6 alkyl group is, preferably, C_1-C_4 alkyl, in particular, e.g., methyl, ethyl, n-propyl, iso-propyl, n-butyl and tert.butyl.

A C_1-C_6 alkoxy is,preferably, C_1-C_4 alkoxy, in particular, for instance, methoxy, ethoxy, n-propoxy or tert.butoxy.

A halogen atom is, preferably, chlorine, bromine or fluorine. When A represents a heteromonocyclic ring as defined above, it is, preferably, a pentatomic or hexatomic saturated or unsaturated, most preferably unsaturated, heteromonocyclic ring containing at least one, preferably one or two, heteroatom chosen from O, S and N.

Examples of said heteromonocyclics are thiophene, thiazole, pyridine, isoxazole, furane, triazole and imidazole. Preferably these rings are either unsubstituted or substituted by C_1-C_6 alkyl, in particular methyl; 1-methyl-imidazole is an example of substituted heteromonocyclic.

Pharmaceutically acceptable salts of the compounds of formula (I) are their salts with pharmaceutically acceptable, either inorganic or organic, acids.

Examples of inorganic acids are hydrochloric, hydrobromic, sulfuric and nitric acid; examples of organic acids are acetic, propionic, succinic, malonic, citric, tartaric, methanesulfonic and p-toluenesulfonic acid.

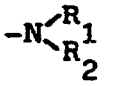
A particularly preferred n value is 3.

Particularly preferred A values are



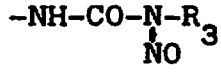
and -Het- wherein Het is as defined above, especially one of the specific heteromonocyclics indicated before, in particular, for instance, thiophene, thiazole and 1-methyl-imidazole.

Particularly preferred values for the group



are either

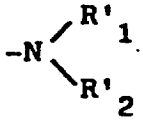
(a')



wherein R_3 is unsubstituted or halo-substituted C_1-C_6 alkyl, for example methyl, ethyl or, respectively, 2-chloroethyl, or

(b') $-NH-CO-(CH_2)_m-R_4$ wherein m is zero, 1, 2 or 3, especially zero, and R_4 is aziridinyl or oxiranyl; or

(c')

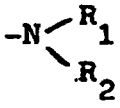


wherein R'_1 and R'_2 are the same and are each a halo-substituted C_1-C_6 alkyl, 2-chloroethyl for example.

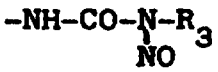
A particularly preferred class of compounds of the invention are the compounds of formula (I) wherein n is 3; A is a divalent radical chosen from



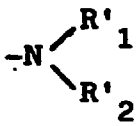
and the group -Het- wherein -Het- is a pentatomic or hexatomic heteromonocyclic ring, except pyrrole, containing one or two heteroatoms chosen from O, S and N, either unsubstituted or substituted by C_1-C_6 alkyl; and the group



is either (i)



wherein R_3 is unsubstituted or halo-substituted C_1-C_6 alkyl, or (ii)



wherein R'_1 and R'_2 are the same and are each a halo-substituted C_1-C_6 alkyl, and the pharmaceutically acceptable salts thereof.

In the above preferred class, preferred Het values are thiophene, thiazole, pyridine, isoxazole, furane, triazole, imidazole and 1-methyl-imidazole, particularly thiophene, thiazole and 1-methyl-imidazole; when R_3 is unsubstituted C_1-C_6 alkyl, methyl and ethyl are preferred, especially methyl; when R_3 and/or R'_1 and R'_2 are a halo-substituted C_1-C_6 alkyl, this is, preferably, 2-chloroethyl.

Examples of specific compounds under this invention, especially in the form of salts with hydrochloric acid, are the following:

β-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-(N'-methyl-N'--nitrosoureido-benzene)-1-carboxamido]pyrrole-2-carboxamido] pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine;

β-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-N'-(2-chloroethyl)-N'-nitrosoureido-benzene)-1-carboxamido]-pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine;

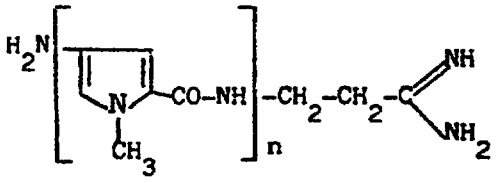
β-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-N,N-bis(2-chloroethyl)aminothiophen-2-carboxmido]pyrrole-2-carboxamido] pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine;

β-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-N,N-bis(2-chloro-ethyl)amino-benzene-1-carboxamido]pyrrole-2-carboxamido] pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine, and

β-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3-N,N-bis(2-chloro-ethyl)amino-benzene-1-carboxamido]pyrrole-2-carboxamido] pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine.

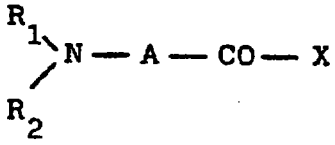
The compounds of the invention are prepared by a process comprising reacting a compound of formula

(II)



(II)

wherein n is as defined above, with a compound of formula (III)



(III)

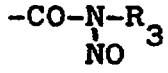
wherein R_1, R_2 and A are as defined above and X is hydroxy or a leaving group selected from halogen, a 2,4,5-trichlorophenoxy, 2,4-dinitrophenoxy, succinimido-N-oxy and imidazolyl group, and, if desired, salifying a compound of formula (I) or obtaining a free compound from a salt, and/or if desired, separating a mixture of isomers of formula (I) into the single isomers.

The leaving group X in the compounds (III) may be, for example, chlorine.

The reaction between a compound of formula (II) and a compound of formula (III) wherein X is -OH is preferably carried out in a molecular ratio from 1:1 to 1:2 in an organic solvent such as e.g., dimethylsulphoxide, hexamethylphosphotriamide, dimethylacetamide, dimethylformamide, ethyl alcohol, benzene or pyridine, in the presence of an organic or inorganic base such as, e.g., triethylamine, diisopropyl ethylamine or sodium carbonate or bicarbonate, and of a condensing agent such as, e.g., N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide or preferably, N,N'-dicyclohexylcarbodiimide. The reaction temperature may vary from about -10 °C to about 50 °C and the reaction time from about 1 to about 24 hours.

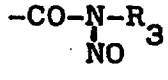
The reaction between a compound of formula (II) and a compound of formula (III), wherein X is another leaving group, e.g. halogen, 2,4,5-trichlorophenoxy or succinimido-N-oxy or imidazolyl, may be carried out in analogous conditions but without the condensing agent.

For the reaction between a compound of formula (II) and a compound of formula (III) wherein one of R_1 and R_2 is hydrogen and the other is a group



as defined above under a), and X is -OH, preferred solvents are, e.g., dimethylsulphoxide, hexamethylphosphotriamide, dimethylacetamide or, preferably, dimethylformamide; preferred bases are organic bases such as, e.g., triethylamine or diisopropyl ethylamine; and preferred reaction times are from about 1 to about 12 hours.

For the reaction between a compound of formula (II) and a compound of formula (III), wherein one of R_1 and R_2 is hydrogen and the other is a group



as defined above under a), and X is a halogen atom or another leaving group, e.g., 2,4,5-trichlorophenoxy or succinimido-N-oxy or imidazolyl, preferred solvents are, e.g., dimethylformamide or pyridine; preferred bases are organic bases, e.g. diisopropylethylamine; preferred temperatures are from about 0 °C to about 25 °C and preferred reaction times are from about two hours to about ten hours.

For the reaction between a compound of formula (II) and a compound of formula (III) wherein one of R_1 and R_2 is hydrogen and the other is a group $-CO-(CH_2)_m-R_4$ as defined above under b), X being either -OH or halogen or another leaving group, preferred solvents are, e.g., dimethylsulphoxide, hexamethyl-

phosphotriamide, dimethylacetamide or, preferably, dimethylformamide; preferred bases are organic bases such as, e.g, triethylamine or diisopropyl ethylamine; and preferred reaction times are from about 2 to about 24 hours.

For the reaction between a compound of formula (II) and a compound of formula (III) wherein R_1 and R_2 are the same and are both hydrogen or both a C_1-C_6 alkyl group unsubstituted or substituted by halogen, hydroxy or C_1-C_6 alkoxy, and X is halogen or another leaving group, preferred bases are both organic and inorganic bases such as, e.g., triethylamine or diisopropyl ethylamine or sodium carbonate or bicarbonate; preferred solvents are, for instance, ethyl alcohol, benzene, dimethylformamide, pyridine, dimethylacetamide, hexamethylphosphotriamide; preferred temperature is the room temperature and preferred reaction time is around 18 hours.

Analogous conditions, though with the additional presence of a condensing agent, are the preferred ones also for the reaction between a compound (II) and a corresponding compound (III) wherein X is -OH: dicyclohexylcarbodiimide is a preferred condensing agent and dimethylformamide is a preferred solvent.

The compounds of formula (II) are known compounds or may be prepared by known methods from known compounds: see, for instance,Arcamone et al. Gazzetta Chim.Ital. 97, 1097 (1967). The compounds of formula (III) are known compounds too or may be prepared from known compounds through reactions well described in the organic chemistry: see for example J.Med. Chem. 9, 882 (1966) and 25, 178 (1982).

The salification of a compound of formula (I) as well as the preparation of a free compound from a salt may be carried out by known standard methods.

Well known procedures such as, e.g. fractional crystallization or chromatography may also be followed for separating a mixture of isomers of formula (I) into the single isomers.

The new compounds of formula (I) prepared according to the above described procedures may be as well purified by conventional methods such as, e.g., silica gel or alumina column chromatography, and/or by recrystallization from an organic solvent such as, e.g., a lower aliphatic alcohol, e.g. methyl, ethyl or isopropyl alcohol, or dimethylformamide.

The compounds of the invention can be useful as antineoplastic and antiviral agents. They show, in particular, cytostatic properties towards tumor cells so that they can be useful, e .g., to inhibit the growth of various tumors. such as,for instance, carcinomas, e.g. mammary carcinoma, lung carcinoma, bladder carcinoma, colon carcinoma, ovary and endometrial tumors. Other neoplasias in which the compounds of the invention could find application are, for instance, sarcomas, e.g. soft tissue and bone sarcomas, and the hematological malignancies such as, e.g. leukemias.

The following table reports in vitro anti-tumor activity data referring to the compounds of the invention β-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-N,N-bis(2-chloro-ethyl)amino-benzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine hydrochloride (internal code FCE 24517) and β-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-N,N-bis(2-chloro-ethyl)aminothiophen-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine hydrochloride (internal code FCE 24690), in comparison with distamycin A,which is deemed to be the closest, and the most widely known and studied, reference compound.

The in vitro antitumor activity was evaluated by cytotoxicity studies carried out on murine L1210 leukemia cells, L-PAM resistant leukemia cells and P388 leukemia cells, as well as on HeLa cells. Cells were derived from in vivo tumors and established in cell culture. Cells were used until the tenth passage. Cytotoxicity was determined by counting surviving cells after 4 hours treatment and 48 hours growth in drug-free medium. For HeLa cells the colony inhibition test according to Cancer Chemother. Pharmacol. 1:249-254, 1978, was used.

The percentage of cell growth in the treated cultures was compared with that of controls. ID_{50} values (doses inhibiting 50% of the cellular growth in respect to controls) were calculated on dose-response curves.

TABLE

Compound	ID_{50} (μg/ml)			
	L1210[1)]	L1210/LPAM[1)]	P388[2)]	HeLa[3)]
distamycin A	198	136	25	3.9
FCE 24517	0.985	0.430	0.21	0.014
FCE 24690	1.365	0.985	0.22	0.037

1) Cytotoxicity evaluated after 4 hours treatment;
2) Cytotoxicity evaluated after 48 hours treatment;
3) Colony inhibition test carried out after 24 hours treatment.

The compounds of the invention show also a remarkable effectiveness in interfering with the reproductive activity of the pathogenic viruses and protect tissue cells from viral infections.

For example they show activity against DNA viruses such as, for instance, herpes, e.g. herpes simplex and herpes zoster, viruses, virus vaccinia, RNA viruses such as, e.g. Rhinovirus and Adenoviruses, and against retroviruses such as, for instance, Sarcoma viruses, e.g., Murine sarcoma virus, and Leukemia viruses, e.g. Friend leukemia virus. Thus, for example, herpes, coxsackie and respiratory syncytial viruses were tested in fluid medium as follows. Serial twofold dilutions of the compounds from 200 to 1.5 mcg/ml were distributed in duplicate 0.1 ml/well in 96 wells microplates for tissue culture.

Cell suspensions ($2x10^5$ cells/ml) infected with about $5x10^{-3}$ $TCID_{50}$ of virus/cell were immediately added 0.1 ml/well.

After 3-5 day incubation at 37°C in $CO_2$5%, the cell cultures were evaluated by microscopical observation and Minimum Inhibiting Concentration (MIC) were determined, MIC being the minimum concentration which determines a reduction of cytopathic effect in comparison with the infected controls.

The compounds of the invention can be administered by the usual routes, for example, pareriterally, 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 0.1 to about 200-250 mg pro dose 1-4 times a day.

As already said, the pharmaceutical compositions of the invention contain a compound of formula (I) as the active substance, in association with one or more pharmaceutically acceptable excipients.

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 of 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 oleaginous 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 tumors and viral infections in a patient in need of it, comprising administering to the said patient a composition of the invention.

The following examples illustrate but do not limit the invention.

The abbreviations DMF and DMSO stand for dimethylformamide and, respectively, dimethylsulfoxide.

Example 1

β-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-(N'-methyl-N'-nitrosoureidobenzene)-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine, hydrochloride.

A solution of 0.1 ml of triethylamine in 1 ml of DMF was added in 5' to a stirred solution of 0.41 g of N-deformyl distamycin in 2.5 ml of DMF at room temperature and under nitrogen. After 15' 0.17 g of 4-(N-nitroso-N-methylureido)benzoic acid and 0.16 g of dicyclohexylcarbodiimide were added in small portions. The reaction mixture was stirred two hours and 25 ml of ethyl ether were added. The solid collected by filtration was purified by chromatography on silica gel with mixtures of ethylacetate, methanol and acetic acid, yielding 0.175 g of the title compound,

m.p. 205-210 °C (dec.) (from isopropanol).

FD-MS: m/z 572 [6, $(M\text{-}C_2H_2N_2O_2)^{+\cdot}$]; 555 [7.5, $(M\text{-}NH_3\text{-}C_2H_2N_2O_2)^{+\cdot}$]; 502 (100);

PMR (DMSO-d_6) δ:

10.90 (broad signal, 1H)
10.31 (s, 1H)
9.99, 9.92 (s, 2H)
8.97, 8.63 (broad signal, 4H)
8.22 (t, J = 5.5Hz, 1H)
7.97, 7.86 (two doublets, J = 8.8Hz, 4H)
7.32, 7.24, 7.18, 7.11, 7.06, 6.94 (broad signal, 6H)
3.86, 3.83, 3.80 (s, 9H)
3.48 (m, 2H)
3.17 (s, 3H)
2.60 (m, 2H).

By analogous procedure it can be also prepared the corresponding N'-(2-chloro-ethyl)-N'-nitrosoureido benzoyl derivative of N-deformyldistamycin, i.e. the compound β-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-(N'-(2-chloro-ethyl-N'-nitrosoureido-benzene)-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]-pyrrole-2-carboxamido]propionamidine, hydrochloride,

m.p. 182 °C (dec.),

MS-FD : M^+ (707);M^+-17 (690); M^+-70 (637)

PMR (DMS)-d_6) δ :
2.39 (t,2H)
3.50 (dt,2H)
3.69 (t,2H)
3.79 (s,3H)
3.85 (s,3H)
3.89 (s,3H)
4.19 (t,2H)
6.89-7.25 (m,8H)
7.88 (m,2H)
9.01 (b,4H)
9.92 (s,1H)
9.94 (s,1H)
10.06 (s,1H)

UV (EtOH 95%;C = 0.00172%):

λ_{max}	ε
240	30,294
310	41,587

Example 2

β-[1-methyl-4-[1-methyl-4-[1-methyl-4-(4-N,N-bis(2-chloroethyl)aminothiophen-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido] propionamidine, hydrochloride

Step one - The intermediate 4-[N,N-bis-(2-chloroethyl)-aminothiophen-2-carboxylic acid.
Starting from 1.74 g of methyl-4-nitrothiophen-2-carboxylate, by reduction with zinc in methanol solution saturated with hydrogen chloride [according to Can. J. Chem. 44, 2888

(1966) for the reduction of the 5-nitrothiophen derivative] 0.90 g of methyl-4-aminothiophen-2-carboxylate were obtained,m.p. 81-82 °C (from diisopropylether).

4 g of cold ethylene oxide were introduced to a solution of 0.9 g of methyl-4-aminothiophen-2-carboxylate in 12.5 ml of 40% aqueous acetic acid at 5° under stirring. The mixture maintained overnight at room temperature in a sealed flask was concentrated to small volume and then diluted with 25 ml of water. Solid sodium bicarbonate was added and the mixture was extracted with ethyl acetate.

By evaporation of the organic solvent 1.3 g of methyl-4-[N,N-bis-(2-hydroxyethyl)]-aminothiophen-2-carboxylate were obtained as a light brown oil which solidifies on standing,m.p. 68-69 °C (from ethylacetate-hexane 60/40).

The bis-hydroxyethylamino derivative obtained (1.3 g) was dissolved in 1.96 ml of phosphorous oxychloride and the mixture was refluxed 45 minutes. After evaporation under vacuum the dark residue was treated with 7.75 ml of concentrated hydrochloric acid at 100° for three hours. The mixture was cooled, 21 ml of cold water were added and the resulting solution was extracted with ethyl acetate.

Evaporation of the organic solvent and purification of the solid residue by chromatography on a silica gel column eluting with a mixture of ethyl acetate-methanol afforded 0.49 g of 4-[N,N-bis-(2-chloroethyl)]-aminothiophen-2-carboxylic acid, m.p. 135-137 °C (from benzene-hexane 60/40);

EI/MS: m/z 267 (11,M^+);218 (100); 63 (57);

PMR ($CDCl_3$) δ :

9.50 (broad signal, 1H)

7.45 (d, J = 2.3Hz, 1H)

6.30 (d, J = 2.3Hz, 1H)

3.63 (s, 8H).

Step two - The title compound

A solution of 0.1 ml of triethylamine in 0.5 ml of DMF was added to a solution of 0.45 g of deformyl distamycin dihydrochloride in 4.5 ml of DMF at room temperature and under nitrogen.

The mixture was treated with 0.23 g of 4-[N,N-bis-(2-chloroethyl)]-aminothiophen-2-carboxylic acid and 0.77 g of dicyclohexylcarbodiimide in small portions. The resulting mixture was stirred overnight, then filtered and evaporated to dryness under vacuum.

The solid residue was purified by chromatography on silica gel column eluting with mixtures of ethyl acetate and ethanol (9:1 and 8:2 by volume). 0.22 g of the title compound were obtained, m.p.199-204 °C (after recrystallization from isopropyl alcohol);

FD-MS: m/z 703 MH^+ ;

PMR (DMSO-d_6) δ :

10.28 (broad signal, 1H)

9.94, 9.98 (s, 2H)

8.9-9.3 (broad signal, 4H)

8.24 (t, J = 5.5Hz, 1H)

7.67, 6.44 (two doublets, J = 1.6Hz, 2H)

7.24, 7.18, 7.07, 7.04, 6.92 (d, J = 1.8Hz, 6H)

3.85, 3.83, 3.79 (s, 9H)

3.8-3.6 (m, 8H)

3.47 (m, 2H)

2.57 (m, 2H).

By analogous procedure the following compounds can be prepared:

β-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-[N,N-bis(2-chloroethyl)]-aminoimidazole-1-methyl-2-carboxamido]-pyrrole-2-carboxamido] pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine hydrochloride;

β-[1-methyl-4-[1-methyl-4-[1-methyl-4-[5-[N,N-bis-(2-chloroethyl)]-aminoimidazole-1-methyl-2-carboxamido]-pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine hydrochloride;

β-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-[N,N-bis(2-chloroethyl) aminothiazole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine hydrochloride;

β-[1-methyl-4-[1-methyl-4-[1-methyl-4-[5-(N,N-bis(2-chloroethyl)aminothiazole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine hydrocloride.

Example 3

β[1-methyl-4-[1-methyl-4-[1-methyl-4-(4-N,N-bis(2-chloroethylamino benzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido propionamidine, hydrochloride

A solution of 0.195 g of sodium bicarbonate in 3 ml of water was added to a cooled solution of 0.4 g of deformyl distamycin in 21 ml of ethanol. To this mixture a solution of 0.32 g of 4-N,N-(2-chloroethyl)-aminobenzoyl chloride in 3 ml of benzene was added dropwise. The mixture was stirred three hours at 5° and then twelve hours at room temperature. Evaporation under vacuum gave a solid residue which was chromatographed on silica gel column eluting with mixtures of chloroform-methanol (9:1 and 7:3 by volume) yielding 0.22 g of the title compound,m.p.295° C dec. (from isopropyl alcohol and ethyl ether;
FD-MS: m/z 697 (34, MH^+); 679 (100, $M-NH_3$);
PMR (DMSO-d_6)δ:
T= 50° C
9.91 (s, 1H)
9.82, 9.79 (s, 2H)
8.94, 8.61 (broad signal, 4H)
8.11 (t. J= 5.5Hz, 1H)
785, 6,82 (two doublets, J= 8.9Hz, 4H)
7.26, 7.20, 7.15, 7.07, 7.05, 6.94 (d, J= 1.6Hz, 6H)
3.85, 3.84, 3.81 (s, 9H)
3.78 (s, 8H)
3.51 (m, 2H)
2.64 (t, J= 6.6Hz, 2H).

By analogous procedure the following compounds can be obtained:
β-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3-N,N-bis(2-chloroethyl)amino-benzene-1-carboxamido]pyrrole-2-carboxamido] pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine hydrochloride, m.p. 170° C (dec.);

MS-FD:	M^+-17 (679); M^+-70 (626); M^+-2 (CH_2CH_2Cl) (571);
PMR (DMSO-d_6) δ:	2.63 (t,3H)
	3.35-4.00 (m,19H)
	6.80-7.40 (m,10H)
	8.20 (t,1H)
	8.88 (b,4H)
	9.90 (1.1H)
	9.94 (s,1H) 10.15 (s,1H

UV (EtOH 95%: C=0.003107%):

λ_{max}	ε
235	35,896
262	35,309
310	39,200;

β-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-oxiranecarbonylamino-benzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine hydrochloride;
β-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3-oxiranecarbonylamino-benzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine hydrochloride;
β-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-[1-(aziridine) carbonylamino-benzene-1-carboxamido]pyrrole-2-carboxamido] pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine hydrochloride;
β-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3-[1-(aziridine) carbonylamino-benzene-1-carboxamido]pyrrole-2-carboxamido] pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine hydrochloride.

Example 4

Tablets each weighing 0.250 g and containing 50 mg of the active substance can be manufactured as follows:

Composition (for 10,000 tablets)	
β-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-N,N-bis(2-chloro-ethyl)amino-benzene-1-carboxamido]pyrrole-2-carboxamido] pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine hydrochloride	500 g
Lactose	1,400 g
Corn starch	500 g
Talc powder	80 g
Magnesium stearate	20 g.

The β-[1-methyl-4-[1-methyl-4[1-methyl-4-[4-N,N-bis(2-chloro-ethyl)amino-benzene-1-carboxamido]-pyrrole-2-carboxamido] pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine hydrochloride, the lactose and half the corn starch are mixed;
the mixture is then forced through a sieve of 0.5 mm mesh size.

Corn starch (10 g) is suspended in warm water (90 ml) and the resulting paste is used to granulate the powder. The granulate is dried, comminuted on a sieve of 1.4 mm mesh size, then the remaining quantity of starch, talc and magnesium stearate is added, carefully mixed and processed into tablets.

Example 5

Capsules, each dosed at 0.200 g and containing 20 mg of the active substance can be prepared as follows:

Composition for 500 capsules:	
β-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-N,N-bis(2-chloro-ethyl)amino-benzene-1-carboxamido]pyrrole-2-carboxamido] pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine hydrochloride	10 g
Lactose	80 g
Corn starch	5 g
Magnesium stearate	5 g.

This formulation can be encapsulated in two-piece hard gelatin capsules and dosed at 0.200 g for each capsule.

Example 6

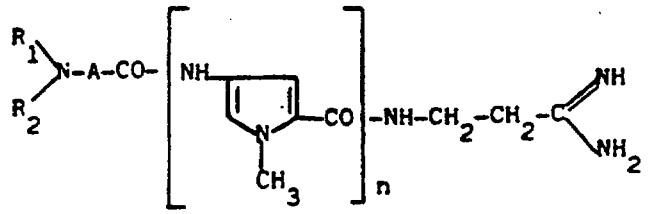
Intramuscular injection 25 mg/ml

An injectable pharmaceutical composition can be manufactured by dissolving 25 g of β-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-N,N-bis(2-chloro-ethyl-)aminothiophen-2-carboxamido]pyrrole-2-carboxamido]-pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine hydrochloride in sterile propyleneglycol (1000 ml) and sealing ampoules of 1-5 ml.

Claims

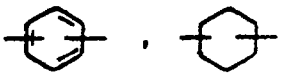
Claims for the following Contracting States : BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

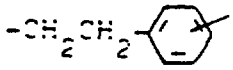
1. A distamycin A analog of formula (I)



(I)

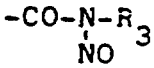
wherein
n is 2, 3 or 4;
A is a divalent radical chosen from





and -Het-, wherein Het is a pentatomic or hexatomic heteromonocyclic ring, except pyrrole, containing at least one heteroatom selected from O, S and N, the said radical being unsubstituted or substituted by one or more substituents chosen from C_1-C_6 alkyl, C_1-C_6 alkoxy, cyano and trifluoromethyl; and either one of R_1 and R_2 is hydrogen and the other is

a) a group



in which R_3 is C_1-C_6 alkyl unsubstituted or substituted by halogen atoms; phenyl; or cyclohexyl; or

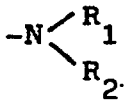
b) a group $-CO-(CH_2)_m-R_4$ in which m is zero, 1, 2 or 3 and R_4 is hydrogen, halogen, hydroxy, aziridinyl or oxiranyl;

or R_1 and R_2 are the same and they are both a C_1-C_6 alkyl group unsubstituted or substituted by halogen, hydroxy or C_1-C_6 alkoxy, and the pharmaceutically acceptable salts thereof.

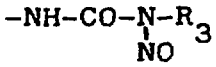
2. A compound according to claim 1 wherein n is 3;
A is a divalent radical chosen from



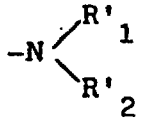
and the group -Het- wherein -Het- is a pentatomic or hexatomic heteromonocyclic ring, except pyrrole, containing one or two heteroatoms chosen from O, S and N, either unsubstituted or substituted by C_1-C_6 alkyl; and the group



is either (i)



wherein R_3 is unsubstituted or halo-substituted C_1-C_6 alkyl, or (ii)

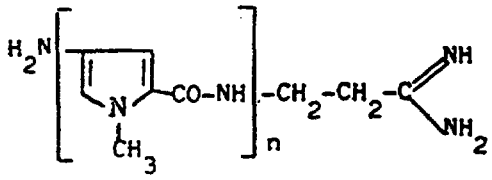


wherein R'_1 and R'_2 are the same and are each a halo-substituted C_1-C_6 alkyl.

3. A compound according to claim 2 wherein the pentatomic or hexatomic heteromonocyclic ring is thiophene, thiazole, pyridine, isoxazole, furane, triazole, imidazole or 1-methyl-imidazole.

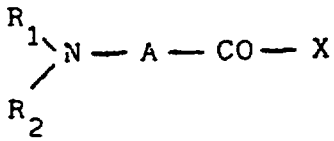
4. A compound according to claim 1 selected from:
β-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-(N'-methyl-N'-nitrosoureido-benzene)-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine hydrochloride;
β-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-N'-(2-chloroethyl)-N'-nitrosoureido-benzene)-1-carboxamido]-pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine hydrochloride;
β-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-N,N-bis(2-chloroethyl)aminothiophen-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido] propionamidine hydrochloride;
β-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-N,N-bis(2-chloroethyl)amino-benzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido] propionamidine hydrochloride; and
β[1-methyl-4-[1-methyl-4-[1-methyl-4-[3-N,N-bis(2-chloroethyl)amino-benzene-1-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido] propionamidine hydrochloride;

5. A process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof, according to claim 1, the process comprising reacting a compound of formula (II)



(II)

wherein n is as defined in claim 1, with a compound of formula (III)



(III)

wherein R_1, R_2 and A are as defined in claim 1 and X is hydroxy or a leaving group selected from halogen, a 2,4,5-trichlorophenoxy, 2,4-dinitrophenoxy, succinimido-N-oxy and imidazolyl group, and, if desired, salifying a compound of formula (I) or obtaining a free compound from a salt, and/or, if desired, separating a mixture of isomers of formula (I) into the single isomers.

6. A pharmaceutical composition containing a compound of formula (I) or a pharmaceutically acceptable salt thereof, according to claim 1, as the active principle, and a pharmaceutically acceptable carrier and/or diluent.

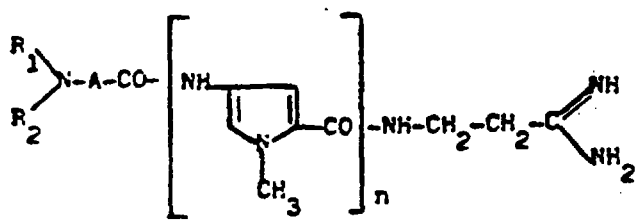
7. A compound of formula (I) or pharmaceutically acceptable salt thereof according to claim 1 for use as an antitumor or antiviral agent.

8. A pharmaceutical composition according to claim 6 for use as an antitumor or antiviral agent.

9. The use of a compound of formula (I) or pharmaceutically acceptable salt thereof according to claim 1 in the preparation of a pharmaceutical composition for use as an antitumor or antiviral agent.

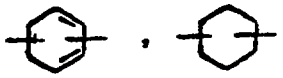
Claims for the following Contracting States : AT, ES, GR

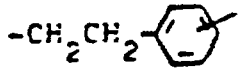
1. A process for the preparation of a distamycin A analog of formula (I)



(I)

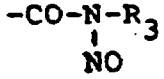
wherein
n is 2, 3 or 4;
A is a divalent radical chosen from





and -Het-, wherein Het is a pentatomic or hexatomic heteromonocyclic ring, except pyrrole, containing at least one heteroatom selected from O, S and N, the said radical being unsubstituted or substituted by one or more substituents chosen from C_1-C_6 alkyl, C_1-C_6 alkoxy, cyano and trifluoromethyl; and either one of R_1 and R_2 is hydrogen and the other is

a) a group



in which R_3 is C_1-C_6 alkyl unsubstituted or substituted by halogen atoms; phenyl; or cyclohexyl; or
b) a group -CO-$(CH_2)_m$-R_4 in which m is zero, 1, 2 or 3 and R_4 is hydrogen, halogen, hydroxy, aziridinyl or oxiranyl;

or R_1 and R_2 are the same and they are both a C_1-C_6 alkyl group unsubstituted or substituted by halogen, hydroxy or C_1-C_6 alkoxy; or a pharmaceutically acceptable salts thereof; which process comprises reacting a compound of formula (II)

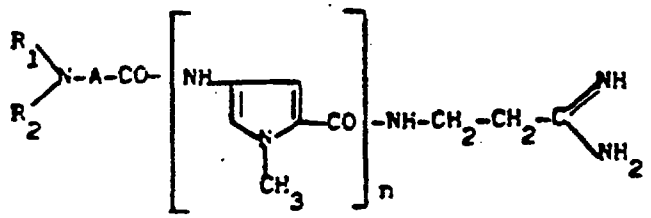
7. A compound of formula (I) or pharmaceutically acceptable salt thereof according to claim 1 for use as an antitumor or antiviral agent.

8. A pharmaceutical composition according to claim 6 for use as an antitumor or antiviral agent.

9. The use of a compound of formula (I) or pharmaceutically acceptable salt thereof according to claim 1 in the preparation of a pharmaceutical composition for use as an antitumor or antiviral agent.

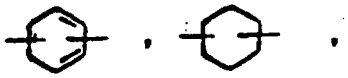
Claims for the following Contracting States : AT, ES, GR

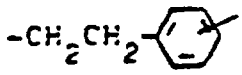
1. A process for the preparation of a distamycin A analog of formula (I)



(I)

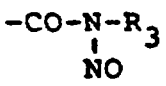
wherein
n is 2, 3 or 4;
A is a divalent radical chosen from





and -Het-, wherein Het is a pentatomic or hexatomic heteromonocyclic ring, except pyrrole, containing at least one heteroatom selected from O, S and N, the said radical being unsubstituted or substituted by one or more substituents chosen from C_1-C_6 alkyl, C_1-C_6 alkoxy, cyano and trifluoromethyl; and either one of R_1 and R_2 is hydrogen and the other is

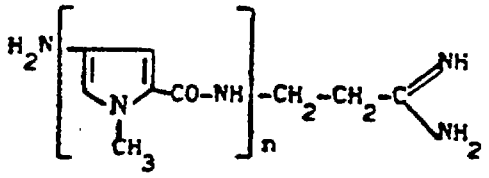
a) a group



in which R_3 is C_1-C_6 alkyl unsubstituted or substituted by halogen atoms; phenyl; or cyclohexyl; or

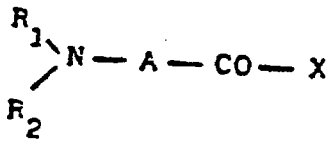
b) a group $-CO-(CH_2)_m-R_4$ in which m is zero, 1, 2 or 3 and R_4 is hydrogen, halogen, hydroxy, aziridinyl or oxiranyl;

or R_1 and R_2 are the same and they are both a C_1-C_6 alkyl group unsubstituted or substituted by halogen, hydroxy or C_1-C_6 alkoxy; or a pharmaceutically acceptable salts thereof; which process comprises reacting a compound of formula (II)



(II)

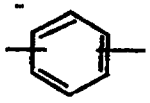
wherein n is as defined above with a compound of formula (III)



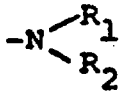
(III)

wherein R_1, R_2 and A are as defined above and X is hydroxy or a leaving group selected from halogen, a 2,4,5-trichlorophenoxy, 2,4-dinitrophenoxy, succinimido-N-oxy and imidazolyl group, and, if desired, salifying a compound of formula (I) or obtaining a free compound from a salt, and/or, if desired, separating a mixture of isomers of formula (I) into the single isomers.

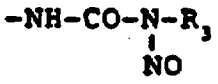
2. A process according to claim 1, wherein in the compound of formula (II) n is 3 and in the compound of formula (III) A is a divalent radical chosen from



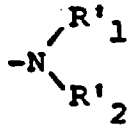
and the group -Het- wherein -Het- is a pentatomic or hexatomic heteromonocyclic ring, except pyrrole, containing one or two heteroatoms chosen from O, S and N, either unsubstituted or substituted by C_1-C_6 alkyl; and the group



is either (I)



wherein R_3 is unsubstituted or halo-substituted C_1-C_6 alkyl, or (ii)



wherein R'_1 and R'_2 are the same and are each a halo-substituted C_1-C_6 alkyl.

3. A process according to claim 2 wherein the pentatomic or hexatomic heteromonocyclic ring is thiophene, thiazole, pyridine, isoxazole, furane, triazole, imidazole or 1-methyl-imidazole.

4. A process according to any one of the preceding claims, wherein X is formula (III) is hydroxy, the

molecular ratio of the compound of formula (II): the compound of formula (III) is from 1:1 to 1:2 and the reaction is effected in an organic solvent in the presence of an organic or inorganic base and of a condensing agent.

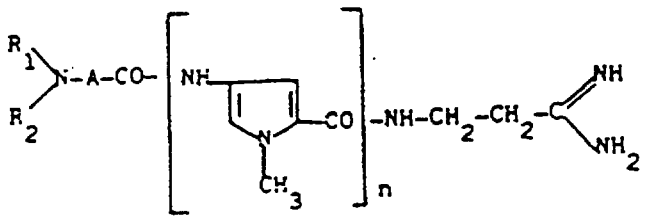
5. A process according to any one of claims 1 to 3, wherein X in formula (III) is a leaving group, the molecular ratio of the compound of formula (II): the compound of formula (III) is from 1:1 to 1:2 and the reaction is effected in an organic solvent in the presence of an organic or inorganic base but in the absence of a condensing agent.

6. A process according to any one of claims 1 to 3 and 5, wherein X is chlorine.

Patentansprüche

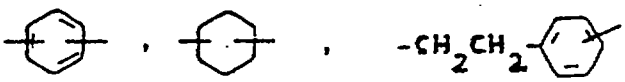
Patentansprüche für folgende Vertragsstaaten : BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Distamycin A Analogon der Formel (I)



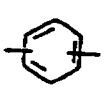
(I)

worin n 2, 3 oder 4 ist; worin A ein divalentes Radikal ist, ausgewählt aus



und -Het-, worin Het ein fünf- oder sechsatomiger, heteromonocyklischer Ring, ausgenommen Pyrrol, ist, der zumindest ein Heteroatom enthält, ausgewählt aus O, S und N, wobei das Radikal unsubstituiert ist oder durch einen oder mehrere Substituenten substituiert ist, ausgewählt aus C_1-C_6 Alkyl, C_1-C_6 Alkoxy, Cyano und Trifluoromethyl; und worin eines von R_1 und R_2 Wasserstoff ist und das andere ist a) eine Gruppe -CO-N(NO)-R_3, worin R_3 ein C_1-C_6 Alkyl ist, das unsubstituiert oder durch Halogenatome substituiert ist; Phenyl oder Cyclohexyl ist; oder b) eine Gruppe -CO-$(CH_2)_m$-R_4, worin m Null, 1, 2 oder 3 ist und worin R_4 Wasserstoff, Halogen, Hydroxy, Aziridinyl oder Oxiranyl ist; oder worin R_1 oder R_2 gleich sind und beide eine C_1-C_6 Alkylgruppe bedeuten, die unsubstituiert oder durch Halogen, Hydroxy oder C_1-C_6 Alkoxy substituiert ist, und die pharmazeutisch akzeptablen Salze davon.

2. Verbindung nach Anspruch 1,
dadurch **gekennzeichnet,** daß n 3 ist; daß A ein bivalentes Radikal ist, ausgewählt aus



und der Gruppe -Het-, worin Het ein fünfatomiger oder sechsatomiger, heteromonozyklischer Ring ist, ausgenommen Pyrrol, der 1 oder 2 Heteroatome enthält, ausgewählt aus O, S oder N, entweder unsubstituiert oder durch C_1-C_6-Alkyl substituiert; und wobei die Gruppe -N(R_1)(R_2) entweder (i) NM-CO-N(NO)-R_3, worin R_3 unsubstituiertes oder halo-substituiertes C_1-C_6 Alkyl ist, oder (ii) -N(R'_1)(R'_2) ist, worin R'_1 und R'_2 gleich sind und jeweils ein halosubstituiertes C_1-C_6 Alkyl sind.

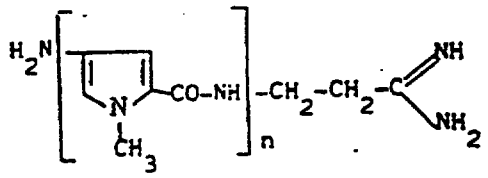
3. Verbindung nach Anspruch 2,
dadurch **gekennzeichnet,** daß der fünfatomige oder sechsatomige heteromonocyklische Ring Thio-

* C L M S *

phen, Thiazol, Pyridin, Isoxazol, Furan, Triazol, Imidazol oder 1-Methylimidazol ist.

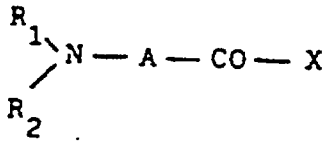
4. Verbindung nach Anspruch 1,
ausgewählt aus:
beta-(1-Methyl-4-(1-methyl-4-(1-methyl-4-(4-(N'-methyl-N'-nitrosoureidobenzol)-1-carboxamido)pyrrol-2-carboxamido) pyrrol-2-carboxamido)pyrrol-2-carboxamido)propionamidinhydrochlorid;
beta-(1-Methyl-4-(1-methyl-4-(1-methyl-4-(4-N'-(2-chloro ethyl)- N'-nitrosoureido-benzol)-1-carboxamido) pyrrol-2-carboxamido) pyrrol-2-carboxamido)pyrrol-2-carboxamido)propionamidinhydrochlorid;
beta-(1-Methyl-4-(1-methyl-4-(1-methyl-4-(4-N,N-bis-(2-chloro- ethyl)aminothiophen-2-carboxamido) pyrro)2-carboxamido) pyrrol-2-carboxamido)pyrrol-2-carboxamido)propionamidinhydrochlorid;
beta-(1-Methyl-4-(1-methyl-4-(1-methyl-4-(4-N,N-bis(2-ch loro- ethyl)amino-benzol-1-carboxamido)-pyrrol-2-carbox- amido) pyrrol-2-carboxamido)pyrrol-2-carboxamido)propionamidinhydrochlorid, und
beta-(1-Methyl-4-(1-methyl-4-(1-methyl-4-(3-N,N-bis(2-ch loro-ethyl)amino-benzol-1-carboxamido)pyrrol-2-carboxamido)pyrrol-2-carboxamido)pyrrol-2-carboxamido)propionamidinhydrochlorid.

5. Verfahren zur Herstellung einer Verbindung der Formel (I) oder eines pharmazeutisch akzeptablen Salzes davon, nach Anspruch 1, umfassend die Reaktion einer Verbindung der Formel (II)



(II)

worin n wie in Anspruch 1 definiert ist, mit einer Verbindung der Formel (III)



(III)

worin R_1, R_2 und A wie in Anspruch 1 definiert sind und worin X Hydroxy oder eine Abspaltgruppe ist, ausgewählt aus Halogen, einer 2,4,5-Trichlorophenoxy-, 2,4-Dinitrophenoxy-, Succinimido-N-oxy- und Imidazolylgruppe, und, falls erwünscht, Salzbilden einer Verbindung der Formel (I) oder Erhalt einer freien Verbinung aus einem Salz und/oder, falls erwünscht, Trennen einer Mischung von Isomeren der Formel (I) in die einzelnen Isomeren.

6. Pharmazeutische Zusammensetzung, umfassend eine Verbindung der Formel (I) oder ein pharmazeutisch akzeptables Salz davon nach Anspruch 1, als den aktiven Bestandteil und einen pharmazeutisch akzeptablen Träger und/oder Verdünnungsmittel.

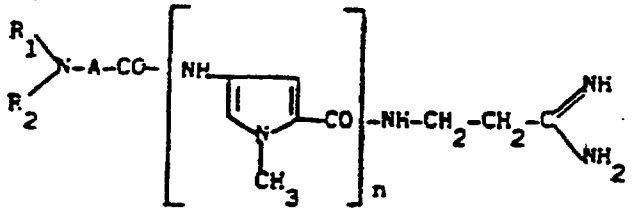
7. Verbindung der Formel (I) oder pharmazeutisch akzeptables Salz davon nach Anspruch 1 für die Verwendung als ein Antitumor- oder Antivirusmittel.

8. Pharmazeutische Zusammensetzung nach Anspruch 6, zur Verwendung als ein Antitumor- oder Antivirusmittel.

9. Verwendung einer Verbindung der Formel (I) oder pharmazeutisch akzeptables Salz davon nach Anspruch 1, für die Herstellung einer pharmazeutischen Zusammensetzung für die Verwendung als ein Antitumor- oder Antivirusmittel.

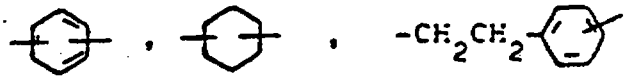
Patentansprüche für folgende Vertragsstaaten : AT, ES, GR

1. Verfahren zur Herstellung eines Distamycin A Analogons der Formel (I)



(I)

worin n 2, 3 oder 4 ist; worin a ein divalentes Radikal ist, ausgewählt aus



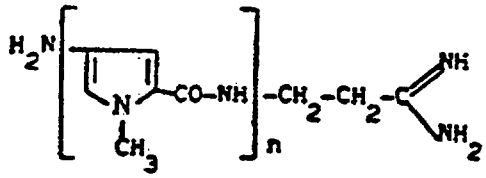
und -Het-, worin Het ein fünf- oder sechsatomiger, heteromonocyklischer Ring, ausgenommen Pyrrol, ist, der zumindest ein Heteroatom enthält, ausgewählt aus O, S und N, wobei das Radikal unsubstituiert ist oder durch einen oder mehrere Substituenten substituiert ist, ausgewählt aus C_1-C_6 Alkyl, C_1-C_6 Alkoxy, Cyano und Trifluoromethyl; und worin eines von R_1 und R_2 Wasserstoff ist und das andere ist

a) eine Gruppe -CO-N(NO)-R_3, worin R_3 ein C_1-C_6 Alkyl ist, das unsubstituiert oder durch Halogenatome substituiert ist; Phenyl oder Cyclohexyl ist; oder

b) eine Gruppe -CO-$(CH_2)_m$-R_4, worin m Null, 1, 2 oder 3 ist und worin R_4 Wasserstoff, Halogen, Hydroxy, Aziridinyl oder Oxiranyl ist; oder worin R_1 oder R_2 gleich sind und beide eine C_1-C_6 Alkylgruppe bedeuten, die unsubstituiert oder durch Halogen, Hydroxy oder C_1-C_6 Akoxy substituiert ist, oder die pharmazeutisch akzeptablen Salze davon,

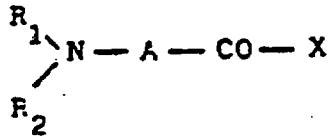
gekennzeichnet durch

Reaktion einer Verbindung der Formel (II)



(II)

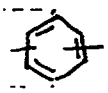
worin n wie oben definiert ist, mit einer Verbindung der Formel (III)



(III)

worin R_1, R_2 und A wie in Anspruch 1 definiert sind und worin X Hydroxy oder eine Abspaltgruppe ist, ausgewählt aus Halogen, einer 2,4,5-Trichlorophenoxy-, 2,4-Dinitrophenoxy-, Succinimido-N-oxy- und Imidazolylgruppe, und, falls erwünscht, Salzbilden einer Verbindung der Formel (I) oder Erhalt einer freien Verbinung aus einem Salz und/oder, falls erwünscht, Trennen einer Mischung von Isomeren der Formel (I) in die einzelnen Isomeren.

2. Verfahren nach Anspruch 1,
dadurch **gekennzeichnet,** daß in der Verbindung der Formel (II) n 3 ist; und daß in der Verbindung der Formel (III) A ein bivalentes Radikal ist, ausgewählt aus



und der Gruppe -Het-, worin Het ein fünfatomiger oder sechsatomiger, heteromonozyklischer Ring ist, ausgenommen Pyrrol, der 1 oder 2 Heteroatome enthält, ausgewählt aus O, S oder N, entweder unsubstituiert oder durch die C_1-C_6-Alkyl substituiert; und wobei die Gruppe -N(R_1)(R_2) entweder (i) NH-CO-N(NO)-R_3, worin R_3 unsubstituiertes oder halo-substituiertes C_1-C_6 Alkyl ist, oder (ii) -N(R'_1)-(R'_2) ist, worin R'_1 und R'_2 gleich sind und jeweils ein halosubstituiertes C_1-C_6 Alkyl sind.

3. Verfahren nach Anspruch 2,
dadurch **gekennzeichnet,** daß der fünfatomige oder sechsatomige heteromonozyklische Ring Thiophen, Thiazol, Pyridin, Isoxazol, Furan, Triazol, Imidazol oder 1-Methylimidazol ist.

4. Verfahren nach einem der vorhergehenden Ansprüche,
dadurch **gekennzeichnet,** daß X in der Formel (III) Hydroxy ist, daß das Molekularverhältnis der Verbindung der Formel (II) zu der Verbindung der Formel (III) von 1:1 bis 1:2 ist und daß die Reaktion in einem organischen Lösungsmittel in der Gegenwart einer organischen oder anorganischen Base und eines Kondensierungsmittels bewirkt wird

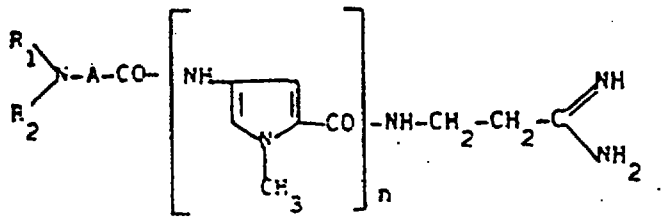
5. Verfahren nach einem der Ansprüche 1 bis 3,
dadurch **gekennzeichnet,** daß X in der Formel (III) eine Abspaltgruppe ist, daß das Molekularverhältnis der Verbindung der Formel (II) zu der Verbindung der Formel (III) von 1:1 bis 1:2 ist und daß die Reaktion in einem organischen Lösungsmittel in der Gegenwart einer organischen oder anorganischen Base , aber in der Abwesenheit eines Kondensierungsmittels durchgeführt wird.

6. Verfahren nach einem der Ansprüche 1 bis 3 und 5,
dadurch **gekennzeichnet,** daß X Chlor ist.

Revendications

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

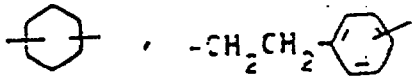
1. Analogue de la distamycine A, représenté par la formule (I) :



(I)

dans laquelle :
- n vaut 2, 3 ou 4 ;
- A représente un radical divalent choisi parmi

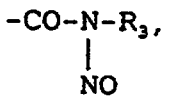




et -Het-, où Het représente un groupe hétéromonocyclique pentatomique ou hexatomique,

excepté le pyrrole, contenant au moins un hétéroatome choisi parmi O, S et N, ledit radical étant non substitué ou substitué par un ou plusieurs substituants choisis parmi alkyle en C_1-C_6, alcoxy en C_1-C_6, cyano et trifluorométhyle ; et

- l'un ou l'autre parmi R_1 et R_2 représente hydrogène, et l'autre représente :
  (a) un groupe



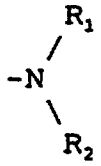
dans lequel R_3 représente alkyle en C_1-C_6 non substitué ou substitué par des atomes d'halogène ; phényle ; ou cyclohexyle ; ou
(b) un groupe $-CO-(CH_2)_m-R_4$, dans lequel m vaut zéro, 1, 2 ou 3, et R_4 représente hydrogène, halogène, hydroxy, aziridinyle ou oxirannyle ;
ou bien R_1 et R_2 sont identiques et représentent tous deux un groupe alkyle en C_1-C_6 non substitué ou substitué par halogène, hydroxy ou alcoxy en C_1-C_6 ;

et ses sels pharmaceutiquement acceptables.

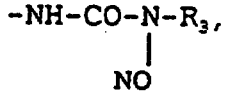
2. Composé selon la revendication 1, dans lequel:
   - n vaut 3 ;
   - A représente un radical divalent choisi parmi



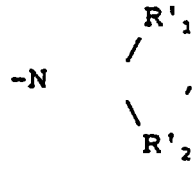
et le groupe -Het-, dans lequel -Het- représente un groupe hétéromonocyclique pentatomique ou hexatomique, excepté le pyrrole, contenant un ou deux hétéroatomes choisis parmi O, S et N, soit non substitué, soit substitué par alkyle en C_1-C_6 ; et
   - le groupe



représente ou bien (i)



dans lequel R_3 représente alkyle en C_1-C_6 non-substitué ou halo-substitué, ou bien (ii)



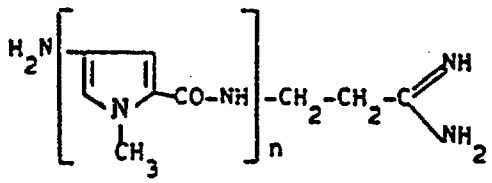
où R'_1 et R'_2 sont identiques et représentent chacun un alkyle en C_1-C_6 halo-substitué.

* C L M S *

3. Composé selon la revendication 2, dans lequel le groupe hétéromonocyclique pentatomique ou hexatomique est le thiophène, le thiazole, la pyridine, l'isoxazole, le furanne, le triazole, l'imidazole ou le méthyl-1 imidazole.

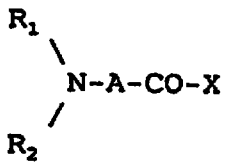
4. Composé selon la revendication 1, choisi parmi :
   - le chlorhydrate de β-[méthyl-1 [méthyl-1 [méthyl-1 [(N'-méthyl N'-nitrosouréido)-4 benzène-carboxamido-1]-4 pyrrole-carboxamido-2]-4 pyrrole-carboxamido-2]-4 pyrrole-carboxamido-2] propionamidine ;
   - le chlorhydrate de β-[méthyl-1 [méthyl-1 [méthyl-1 [N'-(chloro-2 éthyl) N'-nitrosouréido-4 benzène-carboxamido-1]-4 pyrrole-carboxamido-2]-4 pyrrole-carboxamido-2]-4 pyrrole-carboxamido-2]-4 pyrrole-carboxamido-2] propionamidine ;
   - le chlorhydrate de β-[méthyl-1 [méthyl-1 [méthyl-1 [N,N-bis (chloro-2 éthyl) amino-4 thiophène-carboxamido-2]-4 pyrrole-carboxamido-2]-4 pyrrole-carboxamido-2]-4 pyrrole-carboxamido-2] propionamidine ;
   - le chlorhydrate de β-[méthyl-1 [méthyl-1 [méthyl-1 [N,N-bis (chloro-2 éthyl) amino-4 benzène-carboxamido-1]-4 pyrrole-carboxamido-2]-4 pyrrole-carboxamido-2]-4 pyrrole-carboxamido-2] propionamidine ; et
   - le chlorhydrate de β-[méthyl-1 [méthyl-1 [méthyl-1 [N,N-bis (chloro-2 éthyl) amino-3 benzène-carboxamido-1]-4 pyrrole-carboxamido-2]-4 pyrrole-carboxamido-2]-4 pyrrole-carboxamido-2] propionamidine.

5. Procédé de fabrication d'un composé représenté par la formule (I), ou d'un sel pharmaceutiquement acceptable de ce composé, tel que défini à la revendication 1, le procédé comprenant :
   - la réaction d'un composé représenté par la formule (II)



(II)

dans laquelle n est tel que défini à la revendication 1, avec un composé représenté par la formule (III) :



(III)

dans laquelle :
   - R_1, R_2 et A sont tels que définis à la revendication 1 ; et
   - X représente hydroxy ou un groupe partant choisi parmi halogène, un groupe trichloro-2,4,5 phénoxy, dinitro-2,4 phénoxy, succinimido-N-oxy et imidazolyle ; et
   - si on le désire, la salification d'un composé de la formule (I) ou l'obtention d'un composé libre à partir d'un sel, et/ou, si on le désire, la séparation d'un mélange d'isomères de la formule (I) en les isomères individuels.

6. Composition pharmaceutique contenant un composé de la formule (I), ou un sel pharmaceutiquement acceptable de ce composé, tel que défini à la revendication 1, en tant que principe actif, et un support et/ou diluant pharmaceutiquement acceptable.

7. Composé de la formule (I), ou sel pharmaceutiquement acceptable de ce composé, tel que défini à la revendication 1, pour utilisation en tant qu'agent antitumoral ou antiviral.

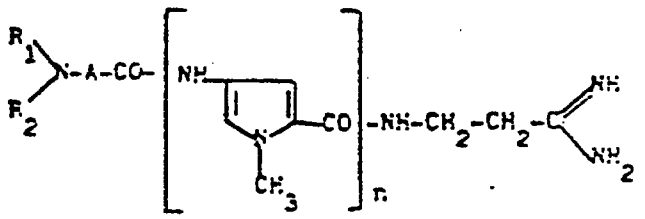
8. Composition pharmaceutique selon la revendication 6, pour utilisation en tant qu'agent anti-tumoral ou

antiviral.

9. Utilisation d'un composé de la formule (I), ou d'un sel pharmaceutiquement acceptable de ce composé, tel que défini à la revendication 1, pour la préparation d'une composition pharmaceutique pour utilisation en tant qu'agent antitumoral ou antiviral.

Revendications pour les Etats contractants suivants : AT, ES, GR

1. Procédé de préparation d'un analogue de la distamycine A, représenté par la formule (I) :

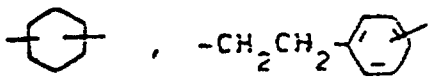


(I)

dans laquelle :

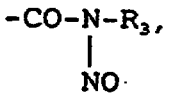
- n vaut 2, 3 ou 4 ;
- A représente un radical divalent choisi parmi





et -Het-, où Het représente un groupe hétéromonocyclique pentatomique ou hexatomique, excepté le pyrrole, contenant au moins un hétéroatome choisi parmi O, S et N, ledit radical étant non substitué ou substitué par un ou plusieurs substituants choisis parmi alkyle en C_1-C_6, alcoxy en C_1-C_6, cyano et trifluorométhyle ; et

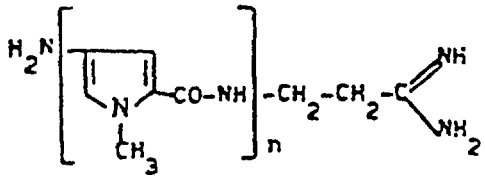
- l'un ou l'autre parmi R_1 et R_2 représente hydrogène, et l'autre représente :
  (a) un groupe



dans lequel R_3 représente alkyle en C_1-C_6 non substitué ou substitué par des atomes d'halogène ; phényle ; ou cyclohexyle ; ou
(b) un groupe $-CO-(CH_2)_m-R_4$, dans lequel m vaut zéro, 1, 2 ou 3, et R_4 représente hydrogène, halogène, hydroxy, aziridinyle ou oxirannyle ;
ou bien R_1 et R_2 sont identiques et représentent tous deux un groupe alkyle en C_1-C_6 non substitué ou substitué par halogène, hydroxy ou alcoxy en C_1-C_6 ;

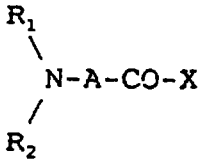
ou de ses sels pharmaceutiquement acceptables ;
lequel procédé comprend :

- la réaction d'un composé représenté par la formule (II)



(II)

dans laquelle n est tel que défini ci-dessus, avec un composé représenté par la formule (III) :



(III)

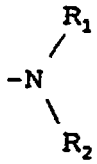
dans laquelle :

- R_1, R_2 et A sont tels que définis ci-dessus ; et
- X représente hydroxy ou un groupe partant choisi parmi halogène, un groupe trichloro-2,4,5 phénoxy, dinitro-2,4 phénoxy, succinimido-N-oxy et imidazolyle ; et
- si on le désire, la salification d'un composé de la formule (I) ou l'obtention d'un composé libre à partir d'un sel, et/ou, si on le désire, la séparation d'un mélange d'isomères de la formule (I) en les isomères individuels.

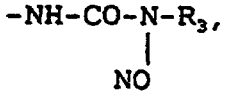
2. Procédé selon la revendication 1, dans lequel, dans le composé de la formule (II), n vaut 3, et, dans le composé de la formule (III),
   - A représente un radical divalent choisi parmi



et le groupe -Het-, dans lequel -Het- représente un groupe hétéromonocyclique pentatomique ou hexatomique, excepté le pyrrole, contenant un ou deux hétéroatomes choisis parmi O, S et N, soit non substitué, soit substitué par alkyle en C_1-C_6 ; et
   - le groupe

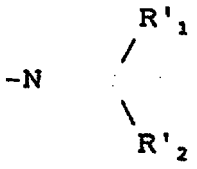


représente ou bien (i)



dans lequel R_3 représente alkyle en C_1-C_6 non-substitué ou halo-substitué, ou bien (ii)

* C L M S *



où R'_1 et R'_2 sont identiques et représentent chacun un alkyle en C_1-C_6 halo-substitué.

3. Procédé selon la revendication 2, dans lequel le groupe hétéromonocyclique pentatomique ou hexatomique est le thiophène, le thiazole, la pyridine, l'isoxazole, le furanne, le triazole, l'imidazole ou le méthyl-1 imidazole.

4. Procédé selon l'une quelconque des revendications précédentes, dans lequel X dans la formule (III) représente hydroxy, le rapport moléculaire composé de formule (II) : composé de formule (III) est de 1:1 à 1:2, et la réaction est effectuée dans un solvant organique, en présence d'une base organique ou minérale et d'un agent de condensation.

5. Procédé selon l'une quelconque des revendications 1 à 3, dans lequel X dans la formule (III) représente un groupe partant, le rapport moléculaire composé de formule (II) : composé de formule (III) est de 1:1 à 1:2, et la réaction est effectuée dans un solvant organique, en présence d'une base organique ou minérale, mais en l'absence d'un agent de condensation.

6. Procédé selon l'une quelconque des revendications 1 à 3 et 5, dans lequel X représente le chlore.