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(71) Applicants *(for all designated States except US):* A. MENARINI INDUSTRIE FARMACEUTICHE RIUNITE S.R.L.[IT/IT]; Via Sette Santi, 3, I-50131 Florence (IT). BRISTOL-MYERS SQUIBB S.P.A. [IT/IT]; Via Paolo Di Dono, 73, I-00143 Rome (IT).

(72) Inventors; and
(75) Inventors/Applicants *(for US only) :* ANIMATI, Fabio [IT/IT]; Via di Monteverde, 25, I-00152 Rome (IT). ARCAMONE, Federico [IT/IT]; Via 4 Novembre, 26, I-20014 Nerviano (IT). LOMBARDI, Paolo [IT/IT]; 16a Strada, 22, I-20020 Cesate (IT). ROSSI, Cristina [IT/IT]; Via Paolo Buzzi, 6, I-00143 Rome (IT).

(74) Agents: GERVASI, Gemma et al.; Notarbartolo & Gervasi S.r.l., Viale Bianca Maria, 33, I-20122 Milan (IT).

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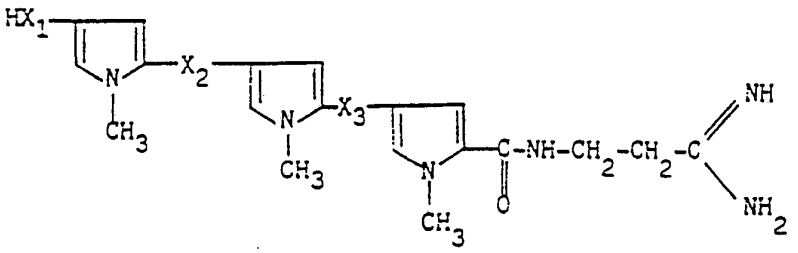


(I)

(57) Abstract

The present invention relates to polyaminopyrrolecarboxamido derivatives of general formula (I) and pharmaceutical acceptable salts thereof, wherein $X_1$, $X_2$ and $X_3$, same or different, represent either -CONH- or NHCO- group, the case wherein $X_1 = X_2 = X_3$ = -CONH- being excluded, to processes for their preparation and to pharmaceutical compositions having antiviral and antitumoral properties containing them.

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## + DESIGNATIONS OF "SU"

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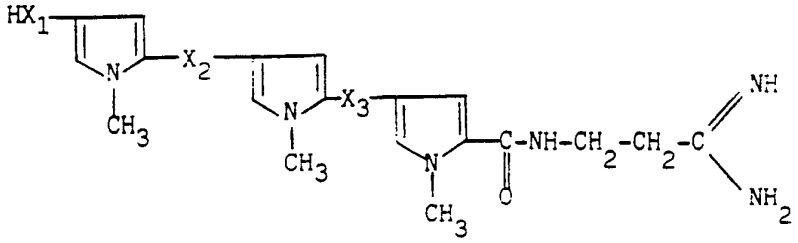
POLY-AMINOPYRROLECARBOXAMIDO DERIVATIVES, PROCESSES FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM.

DESCRIPTION

Field of the invention

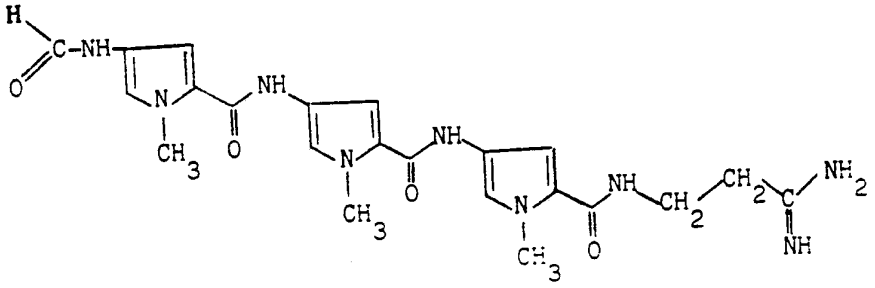
The present invention relates to compounds having the general formula (I)



and their pharmaceutically acceptable salts, wherein $X_1$, $X_2$ and $X_3$, same or different, represent either -CONH- or -NHCO- group, the case wherein $X_1$=$X_2$=$X_3$=-CONH- being excluded, to,processes for their preparation and to pharmaceutical compositions having antiviral and antitumour properties containing them.

Prior art

The antiviral antibiotic Distamycin



Distamycin

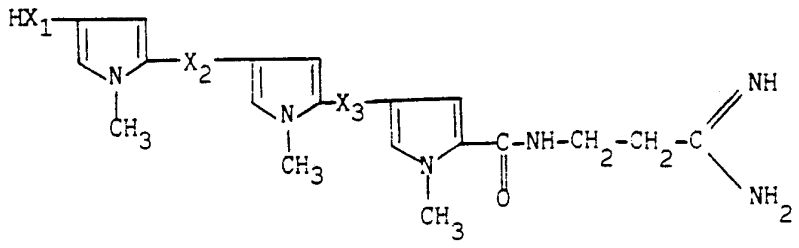
is a well known compound which belongs to the family of pyrrole-amidine antibiotics and its capability of interacting reversibly and selectively with dNA-AT sequences, interfering with both replication and transcription processes of genetic message, is reported in the literature. Literature referring to Distamycin includes, for example, Nature 203, 1064 (1964). However the compound as defined above, although it is endowed with interesting antiviral properties, did not found any application in the clinical practice since its use is limited to herpes virus cutaneous infections [see F.E. Hahn in Antibiotics III, Mechanisms of Action of Antimicrobial and Antitumor Agents, by Corcoran J.W. and Hahn, F.E., Springer, New York, 1975, p.79]. Moreover in the field of products with antiviral properties it is very important to obtain ever new pharmaceutical products having a more favourable therapeutical index and broader action spectrum and therefore suitable to be adapted to more and more numerous new infective or not infective patologies. Consequently the application field of these pharmaceutical products can be developed and extended.

Detailed description of the invention

The present invention provides new compounds correlated to Distamycin and having not only antiviral but also antitumoral properties. More particularly the present invention relates to Distamycin analogous compounds in which one or more carboxamido bonds are replaced by a retro-carboxamido bond. We have surprisingly found that such compounds present specific and differentiated

antitumor and antiviral properties when compared with Distamicyn and its analogous.

The invention relates to compounds of general formula (I)

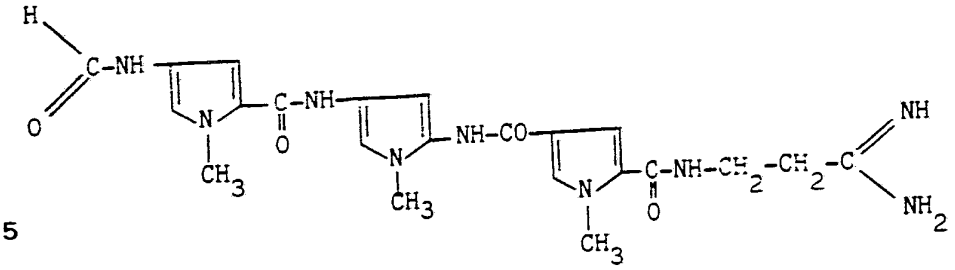


and their pharmaceutically acceptable salts, wherein $X_1$, $X_2$ and $X_3$, same or different, represent either the -CONH- or NHCO- group wherein the case $X_1$=$X_2X_3$=-CONH- being excluded.

The invention relates also to pharmaceutical compositions containing the above mentioned compounds or to pharmaceutically acceptable salts thereof formed with inorganic acids such as hydrochloric, hydrobromic, sulphuric, nitric and the like or with organic acids such as acetic, propionic, succinic, malonic, citric, tartaric, methanesulphonic, p-toluenesulphonic.

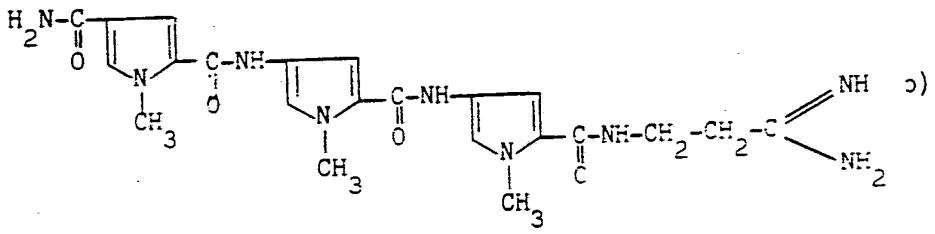
Among the preferred compounds according to the present invention are the following:

3-[1-methyl-4-[1-methyl-4-[1-methyl-4-(formylamino)-pyrrole-2-carboxamido] pyrrole-2-aminocarbonyl] pyrrole-2-carboxamido]propionamidine (Ia) [I, $X_1$=$X_2$=-CONH-, $X_3$=-NHCO-]



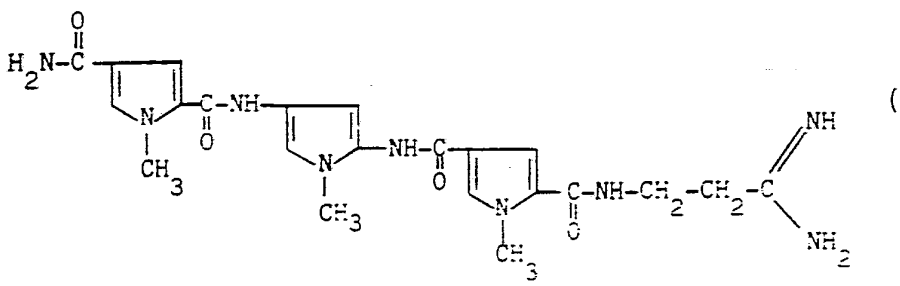
(Ia)

3-[1-methyl-4-[11-methyl-4-[1-methyl-4-(carboxamide)-pyrrole-2-carboxamido] pyrrole-2-carboxamido] pyrrole-2-carboxamido]propionamidine (Ib) [I, $X_1$=-NHCO-, $X_2$=$X_3$=-CONH-]



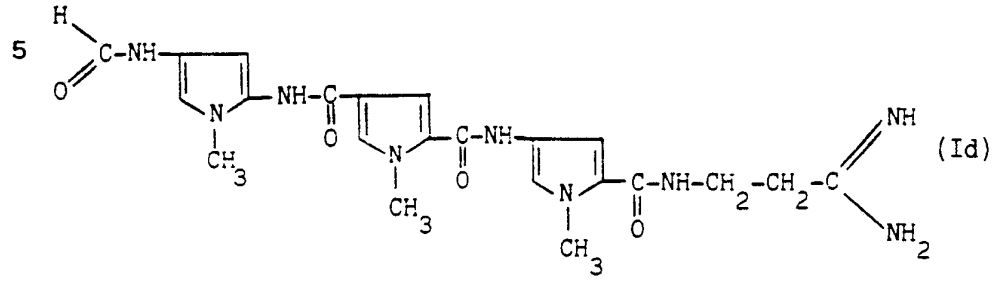
Ib)

3-[1-methyl-4-[1-methyl-4-[1-methyl-4-(carboxamide)-pyrrole-2-carboxamido] pyrrole-2-aminocarbonyl] pyrrole-2-carboxamido]propionamidine (Ic) [I, $X_1$=$X_3$-NHCO-, $X_2$=-CONH-]



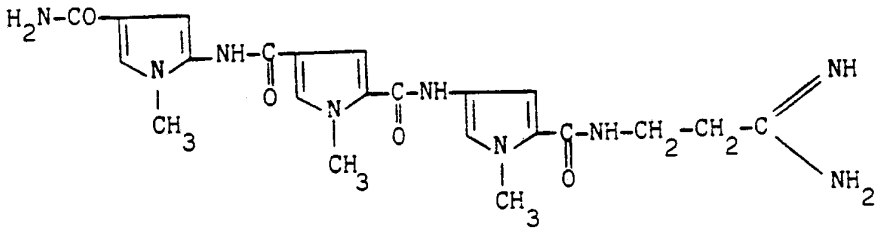
(Ic)

3-[1-methyl-4-[1-methyl-4-[q-methyl-4-(formylamino)pyrrole-2-aminocarbonyl] pyrrole-2-carboxamido] pyrrole-2-carboxamido]propionamidine (Id) [I, $X_1$=$X_3$=-CONH-, $X_2$=-NHCO-]



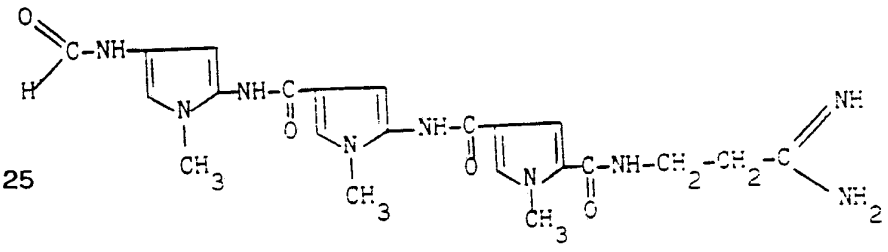
(Id)

3-[1-methyl-4-[1-methyl-4-[1-methyl-4-(carboxamide)-pyrrole-2-aminocarbonyl] pyrrole-2-carboxamido] pyrrole-2-carboxamido]propionamidine (Ie) [I, $X_1$=$X_2$=-NHCO-, $X_3$=-CONH-]



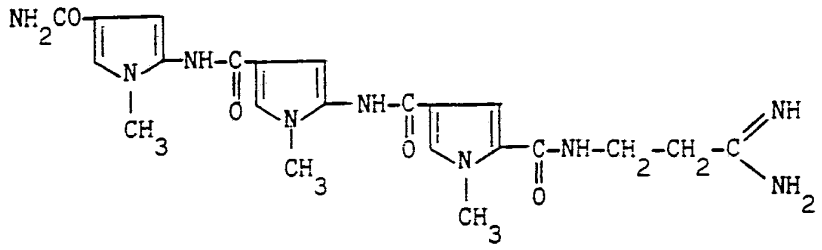
(Ie)

3-[1-methyl-4-[1-methyl-4-[1-methyl-4-(formylamino)-pyrrole-2-aminocarbonyl] pyrrole-2-aminocarbonyl] pyrrole-2-carboxamido]propionamidine (If) [I, $X_1$=-CONH-, $X_2$=$X_3$=-NHCO-]



(If)

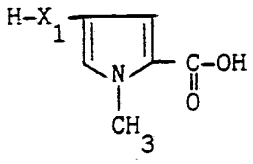
3-[1-methyl-4-[1-methyl-4-[1-methyl-4-(carboxamide)-pyrrole-2-aminocarbonyl] pyrrole-2-aminocarbonyl] pyrrole-2-carboxamido]propionamidine (Ig) [I, $X_1$=$X_2$=$X_3$=-NHCO-]



(Ig)

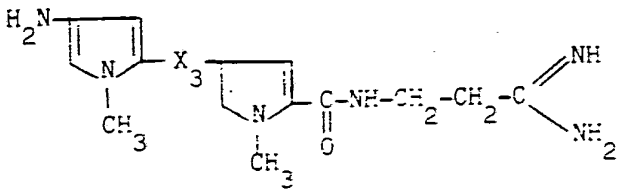
The compounds of formula (I) may be prepared by the following processes:

(A) reacting a compound of formula (II)



(II)

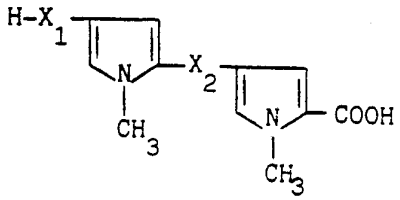
wherein $X_1$ is as defined above, or a reactive derivative thereof, with a compound of formula (III)



(III)

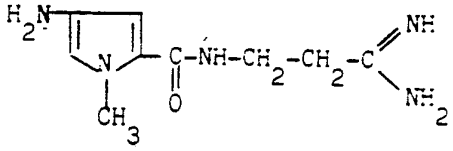
wherein $X_3$ is as defined above, so obtaining the compounds of formulas from (Ia) to (Ic); or

(B) reacting a compound of formula (IV)



(IV)

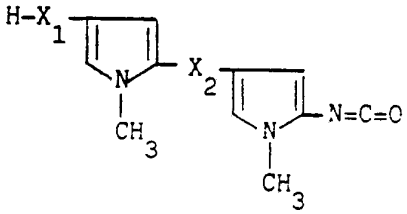
wherein $X_1$ and $X_2$ are as defined above, or a reactive derivative thereof, with a compound of formula (V)



(V)

so obtaining the compounds of formulas (Id) and (Ie); or

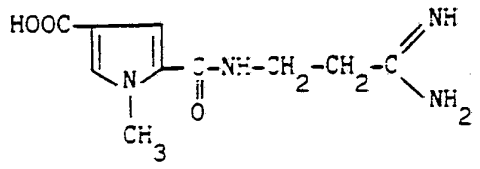
(C) reacting a compound of formula (VI)



(VI)

wherein $X_1$ and $X_2$ are as defined above, or a reactive precursor

thereof, with a compound of formula (VII)



(VII)

obtaining the compound of formulas (If) and (Ig).

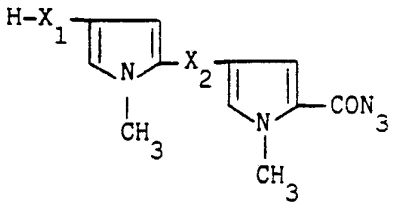
A reactive derivative of a compound of formula (II) may be, e,g., an acyl halide, in particular the chloride, or the acyl azide, or the acyl imidazole of the acid (II); or an activated ester such as e.g., the succinimido ester of the acid (II); or the anhydride thereof. Preferably, the reaction between a compound of formula (II) and a compound of formula (III) is performed using a reactive derivative of the compound of formula (II), e.g. of the kind previously specified, and then the reaction is preferably carried out in a biphasic water - inert organic solvent system, e.g. Schotten-Baumann amidation; or in an inert anhydrous organic solvent such asm, for instance, benzene, toluene halogenated hydrocarbons, ethanol, methanol, tetrahydrofuran, dioxane, dimethylformamide; or in aqueous dioxane, ethanol, methanol. Either an inorganic base, such as, e.g., an hydroxide, carbonate or bicarbonate of an alkali metal, preferably sodium, potassium or barium, or an organic base such as triethanolamine, diisopropylethylamine pyridine or N,N-dimethylaminopyridine may be present. If preferred, the reaction

between a compound of formula (II) and a compound of formula(III) may be performed in an inert organic solvent in the presence of a condensing agent such as, e.g., dicyclohexylcarbodiimide or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimidehydrochloride.

Usual procedures described in organic chemistry for amidation or peptide bond formation may be followed.

A reactive derivative of a compound of formula (IV) may be, e.g., an acyl halide, in particular the chloride, or the corresponding acyl azide, or the acyl imidazole or an activated ester such as, the succinimido ester of the acid; or an anhydride thereof. The reaction may be performed under conditions analogous to those reported before for the reaction between a compound of formula (II) and a compound of formula (III).

A reactive precursor of a compound of formula (VI) may be, e.g., the compound of formula (VIII)

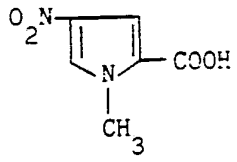


(VIII)

Therefore the reaction between an isocyanate of formula (VI) and an amidinoacid of formula (VII) is preferably performed using an acyl - azide of formula (VIII) as a reactive precursor of an isocyanate of

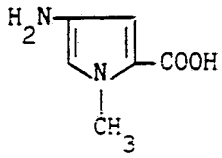
formula (VI). The reaction may be carried out in an aromatic hydrocarbon solvent, such as benzene or toluene, at from 50°C to 100°C and may take from 5 to 20 hours. A molar quantity of an organic base such as triethylamine, pyridine and similar may be present in the reaction to salify an acid of formula (VIII). The formation of an isocyanate from a reactive precursor, e,g, an acyl azide, is well known process in organic chemistry, e.g., the Curtius reaction.

In process (A), a compound of formula (II), wherein $X_1$ is -CONH-, is a known compound and may be obtained, for instance by a process which includes the reduction of the known nitroacid of formula (IX)



(IX)

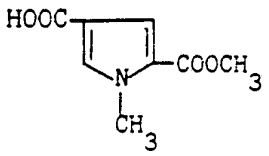
and the formylation of the corresponding aminoacid of formula (X)



(X)

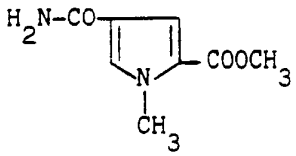
as described in, e.g., J. Org. Chem., 46, 3492 (1981). Preferably, the formylation of an aminoacid of formula (X) is carried out with

N-formylimidazole in a biphasic water-organic solvent system in presence of an inorganic base, such as, for instance, sodium bicarbonate (Schotten-Baumann amidation). A compound of formula (II), wherein $X_1$ is -NHCO-, may be obtained by a process which includes the amidation of the known pyrrole bicarboxylic acid monomethylester of formula (XI) prepared as described, for instance, in J. Org. Chem., 43, 4849 (1978); 51, 3125 (1986)



(XI)

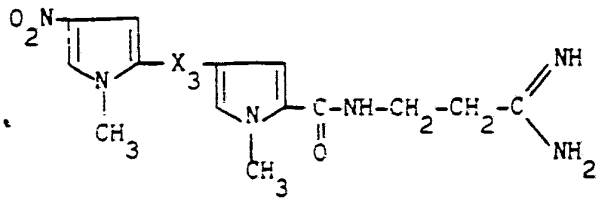
and the hydrolysis of the methyl ester group of the corresponding pyrrolecarboxamide of formula (XII)



(XII)

The amidation reaction and the hydrolysis are performed by usual procedures described in organic chemistry.

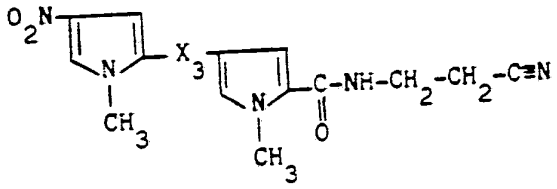
A compound of formula (III), wherein $X_3$ is as defined above may be prepared by reducing a compound of formula (XIII)



(XIII)

wherein $X_3$ is as defined above. The reduction of a nitroamidino compound of formula (XIII) may be carried out by catalytic hydrogenation as described, for instance, in J. Org. Chem. 50, 3774 (1985) for the preparation of the known compound of formula (III), wherein $X_3$ is - CONH-.

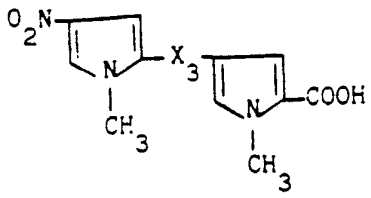
A compound of formula (XIII), wherein $X_3$ is as defined above, may be prepared by the Pinner reaction performed on a compound of formula (XIV)



(XIV)

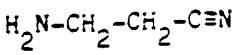
wherein $X_3$ is as defined above. The Pinner reaction may be carried out as described, for instance, in J. Org. Chem., 50, 3724 (1985) for the preparation of the known amidino compound of formula (XIII), wherein $X_3$ is -CONH-.

A compound of formula (XIV), wherein $X_3$ is as defined above, may be prepared by reaction a compound of formula (XV)



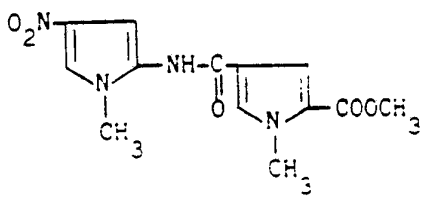
(XV)

ore a reactive derivative thereof, with a compound of formula (XVI)



XVI)

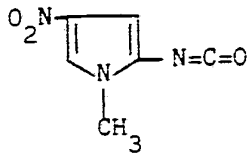
A reactive derivative of a nitroacid of formula (XV) may be the same reported in this specification for the compound of formula (II) and the reaction may be performed under conditions analogous to those reported for the amidation reaction between a compound of formula (II) and a compound of formula (III). A nitroacid of formula (XV), wherein $X_3$ is -CONH-, is a known compound and it may be prepared ad described in, for instance, J. Org. Chem., 50, 3774 (1985). A nitroacid of formula (XV), wherein $X_3$ is -NHCO- may be prepared by hydrolysing a corresponding methyl ester of formula (XVII)



(XVII)

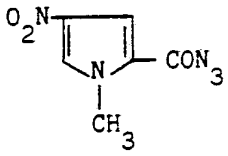
The hydrolysis of a compound of formula (XVII) may be performed following methods and procedures known in the organic chemistry, for instance, by using sodium hydroxide in methanol.

A compound of formula (XVII) may be prepared by reacting a compound of formula (XVIII)



(XVIII)

or a reactive precursor thereof, with a compound of formula (XI). A reactive precursor of a compound of formula (XVIII) may be, e.g., a compound of formula (XIX)



(XIX)

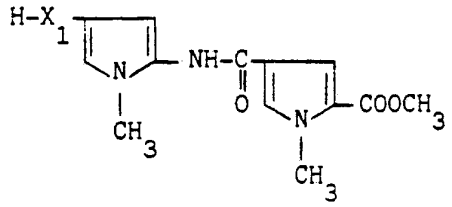
The reaction between an isocyanate of formula (XVIII) and an acid of formula (XI) may be preferably performed using an acyl azide of formula (XIX) as a reactive precursor of the corresponding isocyanate, under conditions analogous to those reported above for the reactions between an isocyanate of formula (VI) and an acid of

formula (VII).

An acyl azide of formula (XIX) may be prepared from the corresponding acids of formula (IX) by usual procedures described in organic chemistry, for instance in Tetrahedron, 30, 2151 (1974).

In processo (B), a compound of formula (IV), wherein $X_1$ is as defined above and $X_2$ is -CONH-, may be prepared by reacting a compound of formula (II), or a reactive derivative thereof, with a compound of formula (X). The amidation reaction may be performed under conditions analogous to those reported above for the reaction between a compound of formula (II) and a compound of formula (III).

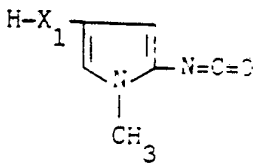
A compound of formula (IV), wherein $X_1$ is as defined above and $X_2$ is -NHCO-, may be prepared by hydrolysing a corresponding methyl ester of formula (XX)



(XX)

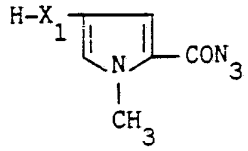
The hydrolysis of a compound of formula (XX) may be performed following methods and procedures known in organic chemistry for the hydrolysis of methyl esters.

A compound of formula (XX) may be prepared by reacting a compound of formula (XXI)



(XXI)

or a reactive precursor thereof, with a bicarboxylic acid monomethylester of formula (XI). A reactive precursor of a compound of formula (XXI) may be, e.g., a compound of formula (XXII)

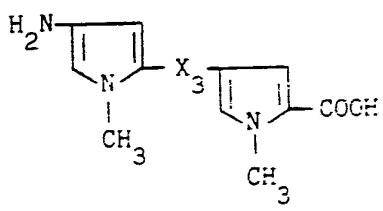


(XXII)

The reaction between an isocyanate of formula (XXI) and an acid of formula (XI) may be preferably performed using an acyl azide of formula (XXII) as a reactive precursor of the corresponding isocyanate, under conditions analogous to those already described for the reaction between an isocyanate of formula (VI) and an acid of formula (VII).

An acyl azide of formula (XXII), wherein $X_1$ is as defined above, may be prepared from the corresponding acid of formula (II) by usual procedures described in organic chemistry.

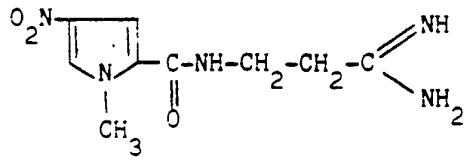
If preferred, a compound of formula (IV) wherein $X_1$ is -CONH- and $X_2$ is as defined above, may be prepared by a process which includes the reduction of a nitroacid of formula (XV), wherein $X_3$ is as defined above, and the formylation of a corresponding aminoacid of formula (XXIII)



(XXIII)

The reduction of a nitroacid of formula (XV) and the formylation of an aminoacid of formula (XXIII) are carried out under conditions analogous to those already described for the reduction of a nitroacid of formula (IX) and the formylation of an aminoacid of formula (X).

A compound of formula (V), may be prepared by reducing a compound of formula (XXIV)



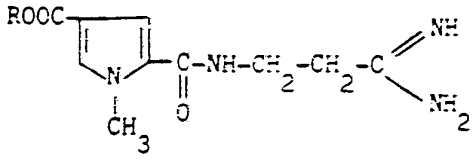
(XXIV)

The reduction of a nitroamidino compound of formula (XXIV) may be carried out under conditions analogous to those already reported for the reduction of a nitroamidino compound of formula (XIII). A compound of formula (XXIV) is known and may be prepared for example as described in J. Med. Chem. 32, 1074 (1989).

In process (C), a compound of formula (VI) wherein $X_1$ and $X_2$ are as defined above, may be obtained from the corresponding reactive precursor of formla (VIII) by the Curtius reaction. An acyl azide of formula (VIII) may be prepared from the corresponding acid of formula (IV), wherein $X_1$ and $X_2$ are as defined above, in a anner analogous to that reported in this specification for the preparation

of the acyl azides of formula (XIX), e;g; as described in Tetrahedron, 30, 2151 (1974).

A compound of formula (VII), may be obtained by the reductive hydrolysis of the ester groups of a compound of formula (XXV)

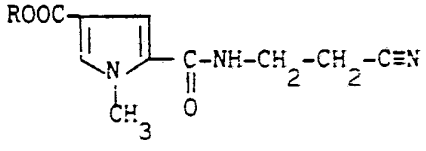


(XXV)

wherein R is a carboxylic acid protecting group such as 2,2,2-trichloroethyl, benzyl, phenacyl and the similars.

The removal of the protecting group R may be carried out by, for instance, zinc and acetic acid; catalytic hydrogenation over palladium charcoal in water, methanol, ethanol, formic acid, acetic acid and mixture thereof.

A compound of formula (XXV) may be prepared by the Pinner reaction performed on a compound of formula (XXVI).

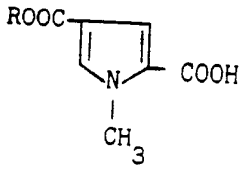


(XXVI)

The Pinner reaction may be carried out as described, for isntance,

in J. Org. Chem., 50, 3724 (1985).

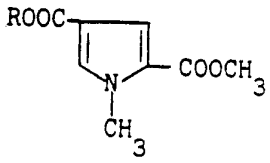
A compound of formula (XXVI) may be obtained by the reaction of a compound of formula (XXVII)



(XXVII)

wherein R is as defined above, or a reactive derivative thereof, with a compound of formula (XVI). A reactive derivative of an acid of formula (XXVII) may be the same already described for the compounds of formula (II) and the reaction may be carried out under conditions analogous to those reported for the amidation reaction between a compound of formula (II) and a compound of formula (III).

A compound of formula (XXVII), wherein R is as defined above, may be prepared by hydrolising the corresponding methyl ester of formula (XXVIII)



(XXVIII)

The hydrolysis of a compound of formula (XXVIII) may be performed following methods and procedures known in organic chemistry, for instance, by using sodium hydroxide in methanol.

A compound of formula (XXVIII) may be prepared by reacting a compound of formula (XI), or a reactive derivative thereof, with 2,2,2-trichloroethanol, benzyl alcohol, benzyl chloride, benzyl bromide, benzyl iodide, phenacyl bromide by usual procedures described in organic chemistry, for instance in T.W. Greene, Protective Groups in Organic Synthesis, Wiley - Interscience Publication, 1981.

Moreover the present invention relates to a pharmaceutical composition comprising as active principle a compound of formula I (a - g) or a pharmaceutical acceptable salt thereof having a pharmaceutically acceptable carrier or diluent. A therapeutically effective amount of a compound, according to the invention, for example, in the case of adults, 0.1 - 100 mg pro dose 1-4 times per day, is combined with an inert carrier. Usual carriers can be used and the compositions can be formulated according to usual methods. The compounds according to the invention are useful for the therapeutical treatment of both humans and animals. In particular the compounds according to the invention are useful as antitumor and/or antiviral agents if administered in therapeutical effective amounts, as above defined, to the patient.

The invention will be better understood in the light of the following examples wich are intended to illustrate the invention without limiting the same.

EXAMPLE 1

1-methyl-2-carbomethoxy-4-carboxypyrrole (XI)

1 g (5.08 Mmol) of 1-methyl-2,4-dicarbomethoxypyrrole was added to 0.34 ml of a solution of 20% $SO_3/H_2SO_4$ in 2 ml of $H_2SO_4$ at such a rate that the reaction temperature remained between 30-35°C. After the addition was over, the flask was placed in a 50°C oil bath for one hour. The yellow reaction mixture was poured into 50 g of ice and neutralized carefully with aqueous NaOH.

The resulting cold solution was brought to pH 8.5 with $NaHCO_3$ and extracted with $CHCl_3$ to remove the diester. The aqueous phase was acidified to pH and extracted with $CHCl_3$. After evaporation of the solvent, 550 mg (60% yield), mp 184-186°C were obtained. $^1$H-NMR DMSO-$d_6$ δ:

3.75 (s, 3H)

3.95 (s, 3H)

7.1 (d, 1H)

7.7 (d, 1H)

12.2 (bs, 1H)

**EXAMPLE 2**

1-methyl-2-methoxycarbonyl-4-carboxamido-pyrrole (XII)

1.02 g (10 mM) of $ET_3N$ and 2.75 g (10 mM) of DPPA were added under stirring to a suspension of 1.83 g (10 mM) XI in 20 ml of $CH_3CN$. After 4 hours of additional stirring at room temperature 25 mM of $NH_4OH$ were added to the reaction mixture. After 8 hours of additional stirring, the reaction mixture was evaporated under vacuum. The resulting brownish oil was taken up with water to give a white solid which was filtered and washed with water. 1.09 g (60%

yield) of the compound (XII), mp 153-155° were obtained.

$^1$H-NMR $(CD_3)_2CO$, δ : 3.75 (s, 3H)
3.95 (s, 3H)
6.7 (br amide 2H)
7.35 (d, 1H)
7.55 (d, 1H)

EXAMPLE 3

1-methyl-2-carboxy-4-carboxamido-pyrrole (II, $X_1$ = -NHCO-)

5.5 ml of NaOH 1 M were added under stirring to a suspension of XII (1 g; 5.5 mM) in 20 ml of water, after 1 h stirring, the product was completely dissolved and the reaction mixture was acidified with HCl 6N.

The resulting white precipitate was filtered and washed with water.

750 mg of the compound (ii, $X_1$ = -NHCO-) were obtained (81% yield), mp 237 - 239°C

$^1$H-NMR DMSO-$d_6$ δ : 3.85 (s, 3H)
6.5 (br, 3H)
7.3 (d, 1H)
7.65 (d, 1H)

EXAMPLE 4

1-methyl-2-azidocarbonyl-4-nitro-pyrrole (XIX)

1.02 g (1.02 mM) of $Et_3N$ and of DPPA 2.75 g (10 mM) were added under stirring to a suspension of IX (1.7 g, 10 mM) in 20 ml of $CH_3CN$. After 2 hours of additional stirring at room temperature, the

mixture was partitioned between $CHCl_3$ and 5% aqueous $NaHCO_3$.

The separated organic phase is dried over $Na_2SO_4$ and evaporated to give 1.75 g (90% yield) of the product (XIX), mp 134-135°C

$^1$H-NMR $(CD_3)_2CO$ δ : 4.05 (s, 3H)

7.35 (d, 1H)

8.15 (d, 1H)

**EXAMPLE 5**

1-methyl-2-carboxy-4-formylamino-pyrrole (II, $X_1$ = -CONH-)

A solution of IX (1 g, 6 mM) in 20 ml of aqueous $Na_2CO_3$ 1M was hydrogenated in a Brown apparatus at room temperature over a Pd/C catalyst (10%) (250 mg) until the hydrogen absorption ceased (7-8 h).The catalyst was filtered off and to the resulting yellow solution containing the unstable (X) was dropped a solution in benzene of freshly prepared N-formylimydazole, under vigorous stirring. After this addition the resulting two-phase system was stirred for 15 minutes, then the organic phase was separated. The yellow aqueous solution, cooled at 0-5°C, was cautiously acidified with formic acid to pH 3,5 under vigorous stirring. The precipitated acid was filtered and washed with small portions of ice-water.

810 mg (80% yield) of the product (II, $X_1$ = -CONH-) were obtained.

mp : 208-210°C

$^1$H-NMR DMSO-$d_6$ δ : 3.85 (s, 3H)

6.75 (d, 1H)

7.35 (d, 1H)

8.15 (s, 1H)

**EXAMPLE 6**

1-methyl-4-(1-methyl-4-nitro-pyrrole-2-amminocarbonyl)-2-methoxycarbonyl-pyrrole (XVII)

A stirred suspension of XI (1 g; 5.5 mM), $Et_3N$ (556.5 mg; 5.5 mM) and of XXII (1.08 g; 5.5 mM) was refluxed under stirring in nitrogen atmosphere for about 8 hours. The reaction mixture was cooled and a yellow product precipitated which was filtered and washed with small portions of benzene. 1.18 g (70% yield) of the compound (XX) were obtained, mp : 165-167°C

$^1$H-NMR DMSO-$d_6$ δ : 3.50 (s, 3H)
3.77 (s, 3H)
3.89 (s, 3H)
6.52 (d, 1H)
7.46 (d, 1H)
7.76 (d, 1H)
7.93 (d, 1H)
9.79 (d, 1H)

**EXAMPLE 7**

1-methyl-4-(1-methyl-4-nitro-pyrrole-2-amminocarbonyl)-2-carboxy-pyrrole (XV, $X_3$ = -NHCO-)

A stirred suspension of (XX) (1 g; 3.2 mM) and NaOH 1M (3.5 mM) in 50 ml of MeOH was heated at 55°C for about 8 hours.

After cooling the reaction mixture was evaporated under vacuum and water was added. The not reacted starting material precipitated and

was filtered off. The filtrate was carefully acidified by HCl 6 M and the compound (XV) ($X_3$ = -NHCO-) precipitated.

There were obtained 420 mg (45% yield), mp 264-266°C

$^1$H-NMR DMSO-$d_6$ δ : 3.50 8s, 3H)
3.88 (s, 3H)
6.52 (d, 1H)
7.4 (d, 1H)
7.7 (d, 1H)
7.9 (d, 1H)
9.76 (s, 1H)
12.6 (s, 1H)

**EXAMPLE 8**

3-[1-methyl-4-(1-methyl-4-nitro-pyrrole-2-amnocarbonyl)-pyrrole-2-carboxyamido]propionitrile (XIV, $X_3$ = -NHCO-)

To a stirred suspension of XV ($X_3$ = -NHCO-) (1 g; 3.43 mM) in 20 ml of $CH_3CN$ were added 348 mg (3.43 mM) of $Et_3N$ and 945 mg (3.43 mM) of DPPA.

4 mM of $H_2N$-$CH_2$-$CH_2$-CN and 4 mM of $Et_3N$ were added to the reaction mixture after 4 hours of additional stirring at room temperature.

The mixture was left to react for about 12 hours. The reaction mixture was evaporated under vacuum. A brownish oil was obtained which for addition of water gave a yellow solid that was filtered and washed with water.

1,01 g (yield 85%) of the product (XIV, $X_3$ = -NHCO-) were obtained; mp 202°C with decomposition.

| | | |
|---|---|---|
| $^1$H-NMR DMSO-$d_6$, δ : | 2.71 | (t, 2H) |
| | 3.40 | (q, 2H) |
| | 3.50 | (d, 3H) |
| | 3.89 | (s, 3H) |
| | 6.51 | (d, 1H) |
| | 7.28 | (d, 1H) |
| | 7.68 | (d, 1H) |
| | 7.92 | (d, 1H) |
| | 8.58 | (t, 1H) |
| | 9.78 | (s, 1H) |

EXAMPLE 9

3-[1-methyl-4-(1-methyl-4-nitro-pyrrole-2-aminocarbonyl)-pyrrole-2-carboxyamido]propionamidine-hydrochloride (XIII, $X_3$ = -NHCO-) A suspension of XIV ($X_3$ = -NHCO-) (1 g; 2.9 mM) in 25 ml of anhydrous EtOH was treated under stirring with gaseous dry HCl with efficient cooling (dry icr acetone) until saturated. The mixture was stirred for 1.5 h at room temperature, then the solvent was removed and to the residual product was added dry ethanol and dry $NH_3$ gas condensed into the reaction vessel. After 1 h at room temperature the solvent was removed under reduced pressure, ethylacetate was added and a yellow precipitate was obtained (865 mg, 75% yield); mp: 235°C with decomposition.

| | | |
|---|---|---|
| $^1$H-NMR DMSO-$d_6$ δ: | 2.65 | (t, 2H) |
| | 3.45 | (m, 2H) |
| | 3.5 | (s, 3H) |
| | 3.9 | (s, 3H) |
| | 6.5 | (d, 1H) |
| | 7.3 | (d, 1H) |
| | 7.74 | (d, 1H) |
| | 7.95 | (d, 1H) |
| | 8.4 | (t, 1H) |
| | 8.7-9.1 | (bd, 4H) |
| | 9.85 | (s, 1H) |

**EXAMPLE 10**

3-[1-methyl-4-[1-methyl-4-(1-methyl-4-(formylamino)-pyrrole-2-carboxyamido)pyrrole-2-aminocarbonyl]pyrrole-2-carboxyamido]propionamidine (Ia, $X_1$ = $X_2$ = -CONH-, $X_3$ = -NHCO-)

A solution of XIII ($X_3$ = -NHCO-) (1 g; 2.5 mM) in 20 ml of MeOH, additioned with 2.5 ml of HCl 1M, was hydrogenated in a Brown apparatus at room temperature over a Pd/C catalyst (10%) (250 mg) untill the hydrogen absorption ceased (4-5 hours). The catalyst was filtered off and the resulting filtrate containing the unstable hydrochloride of III ($X_3$ = -NHCO-) was evaporated under vacuum.

To the crude product, being suspended in EtOH, was added a solution in THF of the chloride obtained from the acid II ($X_1$ = -CONH-) and 5 mM of diisopropylethylamine. After 30 minutes ethyl acetate was

added to completely precipitate the product. 930 mg were obtained (70% yield)

(Ia, $X_1 = X_2 = -CONH-$, $X_3 = -NHCO-$).

$^1H$-NMR DMSO-$d_6$ δ : 2.51 (t, 2H)
3.37 (q, 2H)
3.69 (s, 3H)
3.73 (s, 6H)
5.81 (d, 1H)
6.54 (d, 1H)

**EXAMPLE 11**

3-[1-methyl-4-[1-methyl-4-(1-methyl-4-(carboxyamido))-pyrrole-2-carboxyamido)pyrrole-2-carboxyamido]pyrrole-2-carboxyamido]propionamidine (Ib , $X_1$ = -NHCO-, $X_2 = X_3$ =-CONH-] A solution of XIII ($X_3$ = -CONH-) (1 g; 2.5 mM) in 20 ml of MeOH, additioned with 2.5 ml of HCl 1M, was hydrogenated in a Brown apparatus at rom temperature over a Pd/C catalyst (10%) (250 mg) until the hydrogen absorption ceased (4-5 hours). The catalyst was filtered off and the resulting filtrate containing the unstable hydrochloride of III ($X_3$ = -CONH-) was evaporated under vacuum.

To the crude product, being suspended in EtOH, was added a solution in THF of the chloride obtained from the acid II ($X_1$ = -NHCO-) and 5 mM of diisopropylethylamine. After 30 minutes ethyl acetate was added to completely precipitate the product. 970 mg were obtained (75% yield)

(Ib, $X_1$ = -NHCO- , $X_2 = X_3$ = -CONH-)

| | | | |
|---|---|---|---|
| $^1$H-NMR DMSO-$d_6$ δ : | 2.62 (t,2H) | 7.27 (d,1H) |
| | 3.51 (q,2H) | 7.29 (d,1H) |
| | 3.83 (s,3H) | 6.98-7.42 (bd,2H) |
| | 3.86 (s,3H) | 8.65-8.96 (bd,4H) |
| | 3.89 (s,3H) | 8.25 (t,1H) |
| | 6.95 (d, 1H) | 9.98 (bs,1H) |
| | 7.05 (d,1H) | 10.12 (bs,1H) |
| | 7.21 (d,1H) | |

**EXAMPLE 12**

3-[1-methyl-4-[1-methyl-4-(1-methyl-4-(carboxyamido))-pyrrole-2-carboxyamido)pyrrole-2-aminocarbonyl]pyrrole-2-carboxyamido]propionamidine (Ic, $X_1$ = $X_3$ = -NHCO-, $X_2$ = -CONH-] A solution of XIII ($X_3$ = -NHCO-) (1 g; 2.5 mM) in 20 ml of MeOH, additioned with 2.5 ml of HCl 1M, was hydrogenated in a Brown apparatus at rom temperature over a Pd/C catalyst (10%) (250 mg) until the hydrogen absorption ceased (4-5 hours). The catalyst was filtered off and the resulting filtrate containing the unstable hydrochloride of III ($X_3$ = -NHCO-) was evaporated under vacuum.

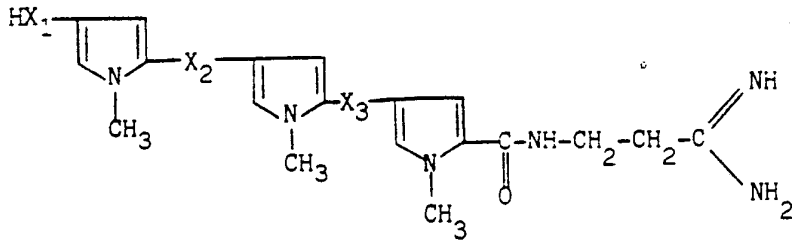
To the crude product, being suspended in EtOH, was added a solution in THF of the chloride obtained from the acid II ($X_1$ = -NHCO-) and 5 mM of diisopropylethylamine. After 30 minutes ethyl acetate was added to completely precipitate the product. 850 mg were obtained (65% yield)

(Ic, $X_1$ = $X_3$ = -NHCO- , $X_2$ = -CONH-)

| | | |
|---|---|---|
| $^1$H-NMR DMSO-$d_6$ δ : | 2.58 (t,2H) | 7.65 (d,1H) |
| | 3.53 (q,2H) | 6.95-7.55 (bd,2H) |
| | 3.85 (s,6H) | 8.65-8,98 (bd,4H) |
| | 3.92 (s,3H) | 8.45 (t,1H) |
| | 5.94 (d,1H) | 9.42 (bs,1H) |
| | 7.05 (d, 1H) | 10.28 (bs,1H) |
| | 7.25 (d,1H) | |
| | 7.52 (m,2H) | |

C L A I M S

1. Polyaminopyrrolecarboxamido derivatives of general formula (I)



(I)

and pharmaceutically acceptable salts thereof, wherein $X_1$, $X_2$ and $X_3$, same or different, represent -CONH- or -NHCO- group, the case wherein $X_1 = X_2 = X_3$ = -CONH- being excluded.

2. Compounds of general formula (I) according to claim 1, represented by:

3-[1-methyl-4-[1-methyl-4-[1-methyl-4-(formylamino)pyrrole-2-carboxamido]pyrrole-2-aminocarbonyl]pyrrole-2-carboxamido]propionamidine (Ia) [I, $X_1 = X_2$ = -CONH-, $X_3$ = -NHCO-]

3-[1-methyl-4-[1-methyl-4-[1-methyl-4-(carboxamido)-pyrrole-2-carboxamido]pyrrole-2-carboxamido] pyrrole-2-carboxamido]propionamidine (Ib) [I, $X_1$ = -NHCO-, $X_2 = X_3$ = -CONH-]

3-[1-methyl-4-[1-methyl-4-[1-methyl-4-(carboxamide)-pyrrole-2-carboxamido]pyrrole-2-aminocarbonyl]pyrrole-2-carboxamido]propionamidine (Ic) [I, $X_1 = X_3$ = -NHCO-, $X_2$ = -CONH-]

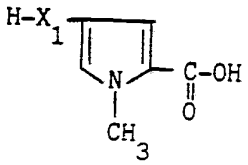
3-[1-methyl-4-[1-methyl-4-[1-methyl-4-(formylamino)-pyrrole-2-aminocarbonyl] pyrrole-2-carboxamido] pyrrole-2-carboxamido]propionamidine (Id) [I, $X_1 = X_3$ = -CONH-, $X_2$ = -NHCO-]

3-[1-methyl-4-[1-methyl-4-[1-methyl-4-(carbocamide)-pyrrole-2-

aminocarbonyl] pyrrole-2-carboxamido] pyrrole-2-carboxamido]propionamidine (Ie) [I, $X_1 = X_2 =$ -NHCO-, $X_3 =$ -CONH-] 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-(formylamino)-pyrrole-2-aminocarbonyl] pyrrole-2-aminocarbonyl] pyrrole-2-carboxamido]propionamidine (If) [I, $X_1 =$ -CONH-, $X_2 = X_3 =$ --NHCO-] 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-(carboxamide)-pyrrole-2-aminocarbonyl] pyrrole-2-aminocarbonyl] pyrrole-2-carboxamido]prionamidine (Ig) [I, $X_1 = X_2 = X_3 =$ -NHCO-]

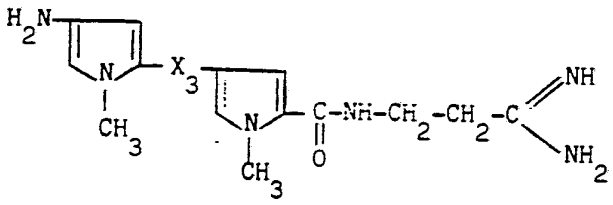
3. A process for the preparation of compounds of formula (I) as defined in claims 1 and 2 wherein:

A) compound of formula (II)



(II)

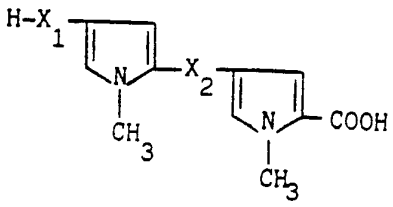
wherein $X_1$ is defined as above, or a reactive derivative thereof, is reacted with a compound of formula (III)



(III)

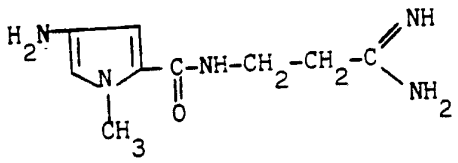
wherein $X_3$ is defined as above, thus obtaining the compounds represented by formulas from (Ia) to (Ic) as defined in claim 2; or

B) a compound of formula (IV)



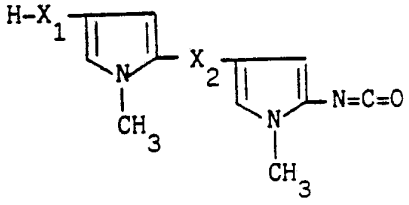
(IV)

9 wherein $X_1$ and $X_2$ are defined as above, or a reactive derivative
10 thereof, is reacted with a compound of formula (V)



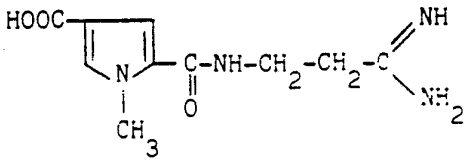
(V)

11 thus obtaining the compounds of formulas (Id) and (Ie) as defined in
12 claim 2; or
13 C) a compound of formula (VI)



(VI)

14 wherein $X_1$ and $X_2$ are defined as above, or a reactive precursor
15 thereof, is reacted with a compound of formula (VII)



(VII)

thus obtaining the compounds of the formulas (If) and (Ig) as defined in claim 2.

4. The compound of formula (II) wherein $X_1$ is -NHCO-.

5. The compound of formula (III) wherein $X_3$ is - NHCO -.

6. The compound of formula (IV) wherein $X_1$ is -CONH- and $X_2$ is either -NHCO- or -CONH- or $X_1$ is -NHCO- and $X_2$ is either -CONH- or -NHCO-.

7. The compound of formula (VI) wherein $X_1$ and $X_2$ are indipendently either -CONH- or -NHCO-.

8. The compound of formula (VIII) wherein $X_1$ and $X_2$ are indipendently either -CONH- and -NHCO-.

9. The compound of formula (XIII) wherein $X_3$ is -NHCO-.

10. The compound of formula (XIV) wherein $X_3$ is -NHCO-.

11. The compound of formula (XV) wherein $X_3$ is -NHCO-.

12. The compound of formula (XVII).

13. The compound of formula (XX) wherein $X_1$ is either -CONH- or -NHCO-.

14. The compound of formula (XXI) wherein $X_1$ is either -CONH- or -NHCO-.

15. The compound of formula (XXII) wherein $X_1$ is either -CONH- or -NHCO-.

16. The compound of formula (XXIII) wherein $X_3$ is either -NHCO- or -CONH-.

17. The compound of formula (XXV) wherein R is a protecting group of carboxylic group.

18. The compound of formula (XXVI) wherein R is a protecting group of a carboxylic group.

19. The compound of formula (XXVII) wherein R is a protecting group of a carboxylic group.

20. A process for the preparation of a compound of formula (XIV), as defined in claim 12, wherein

a) a compound of formula (XV), or a reactive derivative thereof, is reacted with a compound of formula (XVI), thus obtaining a compound of formula (XIV) wherein $X_3$ is -NHCO-.

21. A process for the preparation of a compound of formula (XVII) wherein a compound of formula (XVIII) or a reactive precursor thereof of formula (XIX) is reacted with a compound of formula (XI).

22. A process for the preparation of a compound of formula (XX), as defined in claim 13, wherein a compound of formula (XXI) or a reactive precursor thereof of formula (XXII), is reacted with a compound of formula (XI).

23. A process for the preparation of a compound of formula (XXVI), as defined in claim 18, wherein a) a compound of formula (XXVII) as defined in claim 19 or a reactive derivative, is reacted with a compound of formula (XVI).

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

25. A compound of formula (I) according to claim 1 for use as

antiviral and antitumoral agent.

26. The pharmaceutical composition according to claim 24 for use as antiviral and antitumoral agent.

27. The use of a compound of formula (I) according to claim 1 in the preparation of a pharmaceutical composition according to claim 24 having antiviral and antitumoral activity.

28. A method for treatment of viral and tumoral diseases in man and animals, wherein the compounds according to claims 1 and 2 are utilized.