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DIVISION DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No 03-003259

EL EXTRACTO DE LA PRESENTE SOLICITUD DE **PATENTE DE INVENCION**

PCT FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **532**

DE FECHA **30 DE SEPTIEMBRE DE 2003** EL TERMINO HABIL SEÑALADO

POR LA LEY EXPIRA EL **30 DE DICIEMBRE DEL 2003**

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI _____

NO___ **X** _____

Bogotá D.C, SEPTIEMBRE DE 2007

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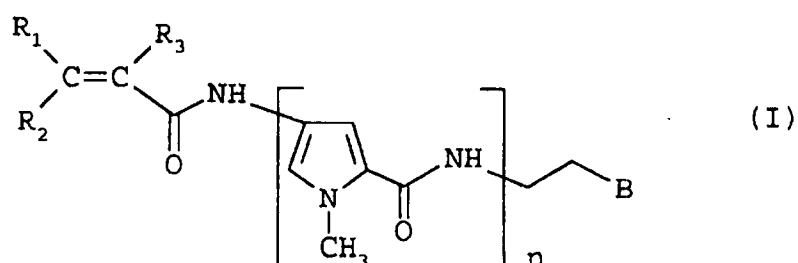
Acryloyl substituted distamycin derivatives of formula (I) wherein n is 2, 3, or 4; R₁ and R₂ are selected, each independently, from: hydrogen, halogen, and C₁-C₄ alkyl; R₃ is hydrogen or halogen; B is selected from: (1), (2), (3), (4), (5), (6) and (7); wherein R₄, R₅, R₆, R₇, and R₈ are, each independently, hydrogen or C₁-C₄ alkyl, with the proviso that at least one of R₄, R₅ and R₆ is C₁-C₄ alkyl; and pharmaceutically acceptable salts thereof. Such compounds are useful as antineoplastic and antiviral agents.

derivatives as defined hereinunder, wherein the distamycin formyl group is substituted by an acryloyl moiety while the amidine group is substituted by different nitrogen-containing end-groups, shows valuable biological properties.

5

Accordingly, the present invention relates to new distamycin derivatives of formula (I) as defined hereinunder, to a process for preparing them, to pharmaceutical compositions containing them and to their use in therapy, particularly as
10 antitumor and antiviral agents.

Therefore, object of the present invention are acryloyl substituted distamycin derivatives of formula:



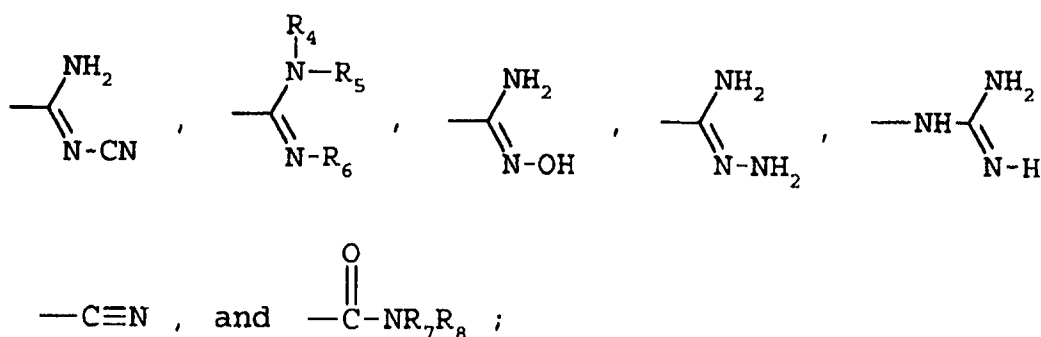
15 wherein:

n is 2, 3 or 4;

R₁ and R₂ are selected, each independently, from: hydrogen, halogen, and C₁-C₄ alkyl;

R₃ is hydrogen or halogen;

20 B is selected from:



wherein R₄, R₅, R₆, R₇, and R₈ are, each independently, hydrogen or C₁-C₄ alkyl, with the proviso that at least one

animal body by therapy.

Furthermore, the present invention provides a method for treating tumors and viral infections in a patient in need of it, which comprises administering to said patient a
5 composition of the invention.

A further object of the present invention is a combined method for treating cancer or for ameliorating the conditions of mammals, including humans, suffering from cancer, said method comprising administering a compound of
10 formula (I), or a pharmaceutically acceptable salt thereof, and an additional antitumor agent, close enough in time and in amounts sufficient to produce a therapeutically useful effect.

15 The present invention also provides combined preparations for simultaneous, separate or sequential use in anti-cancer therapy, comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, and an additional antitumour agent.

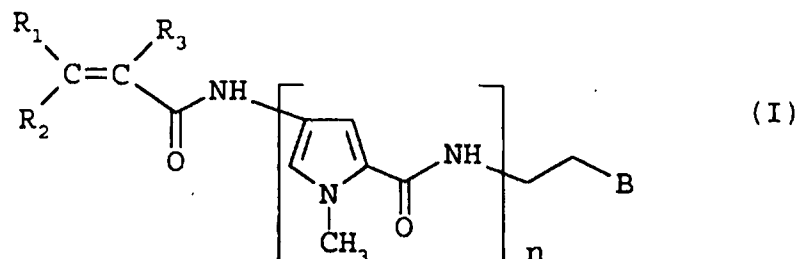
20 The term "antitumor agent" is meant to comprise both a single antitumor drug and "cocktails" i.e. a mixture of such drugs, according to the clinical practice. Examples of antitumor agents that can be formulated with a compound of formula (I), or alternatively, can be administered in a
25 combined method of treatment, include doxorubicin, daunomycin, epirubicin, idarubicin, etoposide, fluoro-uracil, melphalan, cyclo-phosphamide, 4-demethoxy daunorubicin, bleomycin, vinblastin, and mitomycin, or mixtures thereof.

30

The following examples are given to better illustrate the invention, but do not limit the scope of the invention

CLAIMS

1. An acryloyl substituted distamycin derivative of formula:



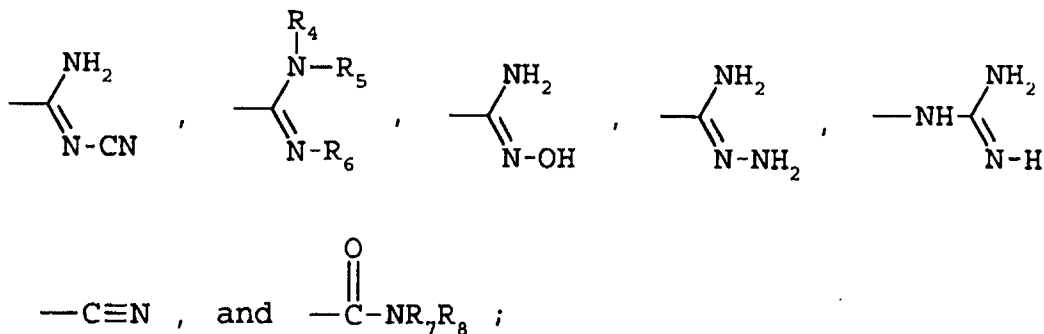
wherein:

n is 2, 3 or 4;

R₁ and R₂ are selected, each independently, from: hydrogen, halogen, and C₁-C₄ alkyl;

10 R₃ is hydrogen or halogen;

B is selected from:



wherein R₄, R₅, R₆, R₇, and R₈ are, each independently, hydrogen or C₁-C₄ alkyl, with the proviso that at least one
 15 of R₄, R₅ and R₆ is C₁-C₄ alkyl;
 or a pharmaceutically acceptable salt thereof.

2. A compound as defined in claim 1, wherein:

n is 3 or 4;

20 R₁ and R₂ are hydrogen;

R₃ is chlorine or bromine;

B is selected from:

compound of formula (I) into a pharmaceutically acceptable salt thereof.

5 5. A compound as defined in any one of claims 1 to 3, for use in a method of treating the human or animal body by therapy.

6. A compound as claimed in claim 5 for use as an antineoplastic agent.

10

7. A compound as claimed in claim 5 for use as an antiviral agent.

15 8. Use of a compound as defined in any one of claims 1 to 3, in the manufacture of a medicament for use in the treatment of cancer.

9. Use of a compound as defined in any one of claims 1 to 3, in the manufacture of a medicament for use in the
20 treatment of viral infection.

10. A pharmaceutical composition, which comprises an effective amount of a compound as defined in any one of claims 1 to 3 as an active principle, in association with
25 one or more pharmaceutically acceptable carriers and/or diluents.



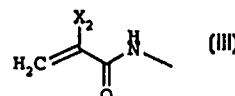
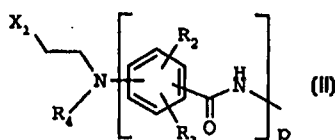
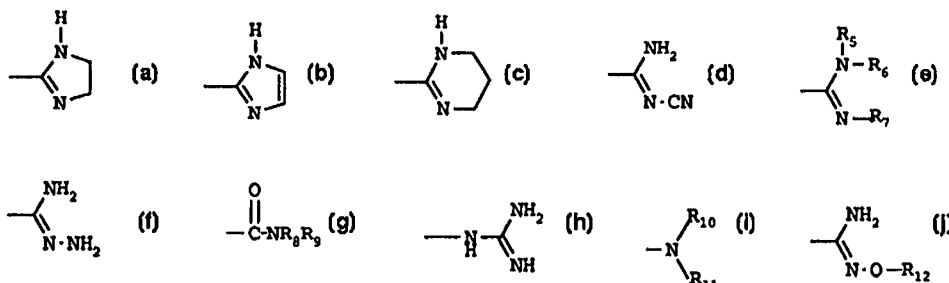
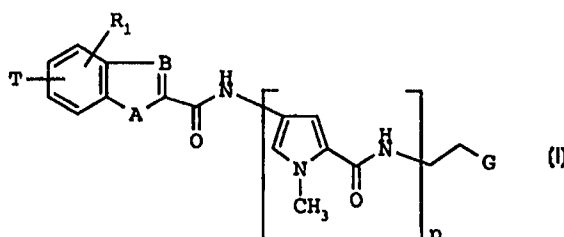
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(54) Title: BENZOHETEROCYCLIC DISTAMYCIN DERIVATIVES, PROCESS FOR PREPARING THEM, AND THEIR USE AS ANTITUMOR AGENTS

(57) Abstract

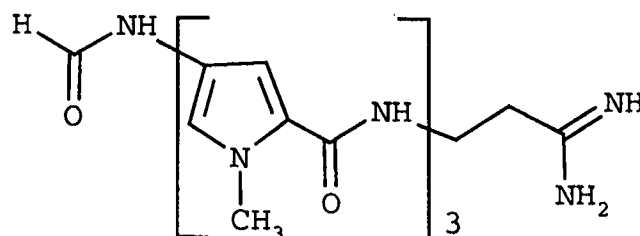
Compounds which are benzoheterocyclic distamycin derivatives of formula (I), wherein n is 2, 3 or 4; A is a heteroatom selected from O and S or a group NR, wherein R is hydrogen or C₁-C₄ alkyl; B is CH or N; R₁ is hydrogen or C₁-C₄ alkyl; G is selected from the group consisting of (a), (b), (c), (d), (e), (f), (g), (h), (i), (j), and -C≡N; wherein R₅, R₆, R₇, R₈, R₉, R₁₀, R₁₁ and R₁₂ are, independently from each other, hydrogen or C₁-C₄ alkyl; T is a group of formula (II) or (III) as defined above, wherein p is 0 or 1; R₂ and R₃ are, independently from each other, hydrogen, C₁-C₄ alkyl optionally substituted by one or more fluorine atoms, or C₁-C₄ alkoxy; R₄ is C₁-C₄ alkyl or C₁-C₃ haloalkyl; X₁ and X₂ are halogen atoms or pharmaceutically acceptable salts thereof; provided that at least one of R₅, R₆ and R₇ is alkyl; are useful as antitumor agents.



BENZOHETEROCYCLIC DISTAMYCIN DERIVATIVES, PROCESS FOR PREPARING THEM, AND THEIR USE AS ANTITUMOR AGENTS.

The present invention relates to new alkylating antitumor agents analogous to Distamycin A, to a process for their preparation, to pharmaceutical compositions containing them and to their use as therapeutic agents.

Distamycin A, whose formula is reported below,



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

Several analogous to distamycin are known in the art.

The international patent application WO 97/28123, in the name of the applicant, describes distamycin derivatives in which the distamycin formyl group is substituted by aromatic moieties bearing alkylating groups and the amidino moiety is replaced with other basic and non-basic nitrogen containing ending groups.

It has now been found that a new class of distamycin derivatives as defined hereinunder, wherein the distamycin formyl group is substituted by benzoheterocyclic rings bearing alkylating groups and the amidino moiety is substituted by different nitrogen-containing ending-groups, shows valuable biological properties.

Therefore, the present invention provides compounds which are distamycin derivatives of formula:

Further object of the present invention are the compounds of formula (I) for use in a method for treating the human or animal body by therapy.

Furthermore, the present invention provides a method for
5 treating tumors in a patient in need of it, which comprises administering to said patient a composition of the invention.

A further object of the present invention is a combined method for treating cancer or for ameliorating the
10 conditions of mammals, including humans, suffering from cancer, said method comprising administering a compound of formula (I), or a pharmaceutically acceptable salt thereof, and an additional antitumor agent, close enough in time and in amounts sufficient to produce a therapeutically useful
15 effect.

The present invention also provides products containing a compound of formula (I), or a pharmaceutically acceptable salt thereof, and an additional antitumour agent as a combined preparation for simultaneous, separate or
20 sequential use in anti-cancer therapy.

The term "antitumor agent" is meant to comprise both a single antitumor drug and "cocktails" i.e. a mixture of such drugs, according to the clinical practice. Examples of antitumor agents that can be formulated with a compound of
25 formula (I), or alternatively, can be administered in a combined method of treatment, include doxorubicin, daunomycin, epirubicin, idarubicin, etoposide, fluoro-uracil, melphalan, cyclophosphamide, 4-demethoxy daunorubicin, bleomycin, vinblastin, and mitomycin, or
30 mixtures thereof.

The following examples are given to better illustrate the present invention, but do not limit the scope of the invention itself.

35 **EXAMPLE 1**

**3-[1-methyl-4[1-methyl-4[1-methyl-4[5(α -
bromoacrylamido)benzofurane-2-carboxamido]pyrrole-2-**

carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N,N'-dimethylamidine hydrochloride (11)

Step I: The intermediate 5- α -bromoacrylamidobenzofurane-2-carboxylic acid

- 5 To a solution of 500 mg of commercial α -bromoacrylic acid in 5 ml of acetonitrile, a solution of 343 mg of N,N-dicyclohexylcarbodiimide in 15 ml of acetonitrile was slowly added. After one hour, the solution obtained after filtration of the precipitate was added to a solution of
- 10 294 mg of 5-amino-2-benzofuranic acid, prepared as reported in Helv.Chim.Acta 31, 75 (1948), and 229 mg of sodium bicarbonate in 20 ml of water. The reaction was stirred at room temperature for one hour, then 2N hydrochloric acid was added until pH=4. The solution was extracted with ethyl
- 15 acetate (3x10 ml), dried over sodium sulfate and evaporated to dryness in vacuo and the crude residue purified by flash chromatography with a methylene chloride/methanol mixture to yield 500 mg of the intermediate as a pale yellow solid.
- 20 By analogous procedure and by using the opportune starting materials the following products can be obtained:
- 5- α -bromoacrylamidobenzothiophene-2-carboxylic acid;
- 5- α -bromoacrylamidoindole-2-carboxylic acid;
- 1-methyl-5- α -bromoacrylamidoindole-2-carboxylic acid;
- 25 5- α -bromoacrylamidoindazole-2-carboxylic acid;
- 1-methyl-5- α -bromoacrylamidoindazole-2-carboxylic acid;
- 5- α -chloroacrylamidoindole-2-carboxylic acid;
- 1-methyl-5- α -chloroacrylamidoindole-2-carboxylic acid.

30 **Step II:** The title compound

- A solution of 250 mg of N-deformyl-distamycin A N,N'-dimethyl dihydrochloride, prepared as reported in WO 97/28123, in 5 ml of dry DMF was cooled to 5°C and added with 0.086 ml of N,N'-diisopropylethylamine. After 10 min,
- 35 180 mg of the intermediate obtained from step I, and 192 mg

of N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide (EDCI) were added. The reaction was stirred at room temperature for 16 hours, then 2N hydrochloric acid was added until pH=4. The solvent was evaporated in vacuo and the crude
5 residue purified by flash chromatography (methylene chloride/methanol:8/2) to yield a yellow oil which was precipitated from methanol/diethyl ether obtaining 200 mg of the title compound as a pale yellow solid.

FAB-MS: m/z , 775(100, [M+H]⁺)

10 PMR (DMSO-d₆) δ :

10.69 (s, 1H), 10.39 (s, 1H), 10.00 (s, 1H), 9.91 (s, 1H),
9.41 (q, J=5.1Hz, 1H), 8.66 (q, J=4.8Hz, 1H), 8.27 (t,
J=5.7Hz, 1H), 8.14 (s, 1H); 7.66 (m, 3H), 7.32 (d, J=1.7
Hz, 1H), 7.24 (d, J=1.7 Hz, 1H), 7.18 (d, J=1.7 Hz, 1H),
15 7.15 (d, J=1.7 Hz, 1H), 7.07 (d, J=1.7 Hz, 1H), 6.93 (d,
J=1.7 Hz, 1H), 6.78 (d, J=3.0 Hz, 1H), 6.31 (d, J=3.0 Hz,
1H), 3.87 (s, 3H), 3.84 (s, 3H), 3.80 (s, 3H), 3.00 (d,
J=4.8Hz, 3H), 2.77 (d, J=5.1Hz, 3H), 2.71 (t, J=6.3Hz, 2H).

20 By analogous procedure and by using the opportune starting materials the following products can be obtained:

3-[1-methyl-4[1-methyl-4[1-methyl-4[5(α-
bromoacrylamido)indole-2-carboxamido]pyrrole-2-
carboxamido]pyrrole-2-carboxamido]pyrrole-2-
25 carboxamido]propioncyanamidine (1);
3-[1-methyl-4[1-methyl-4[1-methyl-4[1-methyl-5(α-
bromoacrylamido)indazole-2-carboxamido]pyrrole-2-
carboxamido]pyrrole-2-carboxamido]pyrrole-2-
carboxamido]propioncyanamidine (2);

30 3-[1-methyl-4[1-methyl-4[1-methyl-4[5(α-
bromoacrylamido)indole-2-carboxamido]pyrrole-2-
carboxamido]pyrrole-2-carboxamido]pyrrole-2-
carboxamido]propion-N-methylamidine (3)

FAB-MS: m/z , 760(100, [M+H]⁺)

35 PMR (DMSO-d₆) δ :

- 11.68 (d, J=1.9Hz, 1H), 10.38 (s, 1H), 10.16 (s, 1H), 10.01 (s, 1H), 9.92 (s, 1H), 9.50 (b.s., 1H), 9.10 (b.s., 1H), 8.55 (b.s., 1H), 8.21 (t, J=5.7Hz, 1H), 7.99 (s, 1H); 7.39 (m, 2H), 7.34 (d, J=1.7 Hz, 1H), 7.28 (d, J=1.9Hz, 1H), 7.25 (d, J=1.7 Hz, 1H), 7.18 (d, J=1.7 Hz, 1H), 7.09 (d, J=1.7 Hz, 1H), 7.07 (d, J=1.7 Hz, 1H), 6.94 (d, J=1.7 Hz, 1H), 6.74 (d, J=3.0 Hz, 1H), 6.26 (d, J=3.0 Hz, 1H), 3.88 (s, 3H), 3.84 (s, 3H), 3.80 (s, 3H), 3.49 (m, 2H), 2.80 (d, J=5.0Hz, 3H), 2.60 (m, 2H);
- 10 3-[1-methyl-4[1-methyl-4[1-methyl-4[1-methyl-5(α-bromoacrylamido)indole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N-methylamidine (4)
FAB-MS: m/z 774(100, [M+H]⁺)
- 15 PMR (DMSO-d₆) δ :
10.44 (s, 1H), 10.23 (s, 1H), 10.00 (s, 1H), 9.93 (s, 1H), 9.54 (b.s., 1H), 9.13 (b.s., 1H), 8.57 (b.s., 1H), 8.22 (t, J=5.8Hz, 1H), 8.04 (d, J=1.7Hz, 1H), 7.56 (d, J=9.0Hz, 1H), 7.46 (dd, J=9.0Hz and 1.7Hz, 1H), 7.33 (d, J=1.7 Hz, 1H),
20 7.25 (d, J=1.7 Hz, 1H), 7.20 (s, 1H), 7.19 (d, J=1.7 Hz, 1H), 7.12 (d, J=1.7 Hz, 1H), 7.07 (d, J=1.7 Hz, 1H), 6.93 (d, J=1.7 Hz, 1H), 6.77 (d, J=3.0 Hz, 1H), 6.28 (d, J=3.0 Hz, 1H), 4.01 (s, 3H), 3.87 (s, 3H), 3.84 (s, 3H), 3.80 (s, 3H), 3.48 (m, 2H), 2.78 (d, J=5.0Hz, 3H), 2.60 (t, J=6.3Hz, 2H);
25 3-[1-methyl-4[1-methyl-4[1-methyl-4[1-methyl-5(α-chloroacrylamido)indole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N-methylamidine (5);
- 30 3-[1-methyl-4[1-methyl-4[1-methyl-4[5(α-bromoacrylamido)benzofurane-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N-methylamidine (6)
FAB-MS: m/z , 761(100, [M+H]⁺)
- 35 PMR (DMSO-d₆) δ :

10.69 (s, 1H), 10.39 (s, 1H), 10.00 (s, 1H), 9.90 (s, 1H),
 9.50 (b.s., 1H), 9.10 (s, 1H), 8.55 (s, 1H), 8.20 (t,
 J=5.7Hz, 1H), 8.14 (s, 1H), 7.65 (m, 3H), 7.32 (d, J=1.7
 Hz, 1H), 7.23 (d, J=1.7 Hz, 1H), 7.17 (d, J=1.7 Hz, 1H),
 5 7.15 (d, J=1.7 Hz, 1H), 7.07 (d, J=1.7 Hz, 1H), 6.93 (d,
 J=1.7 Hz, 1H), 6.78 (d, J=3.0 Hz, 1H), 6.29 (d, J=3.0 Hz,
 1H), 3.87 (s, 3H), 3.84 (s, 3H), 3.80 (s, 3H), 3.49 (m,
 2H), 2.79 (d, J=5.1Hz, 3H), 2.59 (t, J=6.4Hz, 2H);

3-[1-methyl-4[1-methyl-4[1-methyl-4[5(α -
 10 bromoacrylamido)benzothiophene-2-carboxamido]pyrrole-2-
 carboxamido]pyrrole-2-carboxamido]pyrrole-2-
 carboxamido]propion-N-methylamidine (7)

FAB-MS: m/z , 777(100, [M+H]⁺)

PMR (DMSO-d₆) δ :

15 10.67 (s, 1H), 10.46 (s, 1H), 10.00 (s, 1H), 9.92 (s, 1H),
 9.48 (b.s., 1H), 9.09 (s, 1H), 8.54 (s, 1H), 8.35 (d,
 J=2.1Hz, 1H), 8.23 (s, 1H), 8.21 (t, J=5.9Hz, 1H), 7.99 (d,
 J=9.0Hz, 1H), 7.66 (dd, J=9.0 and 2.1Hz, 1H), 7.31 (d,
 J=1.7 Hz, 1H), 7.24 (d, J=1.7 Hz, 1H), 7.18 (d, J=1.7 Hz,
 20 1H), 7.11 (d, J=1.7 Hz, 1H), 7.06 (d, J=1.7 Hz, 1H), 6.93
 (d, J=1.7 Hz, 1H), 6.80 (d, J=3.0 Hz, 1H), 6.34 (d, J=3.0
 Hz, 1H), 3.87 (s, 3H), 3.84 (s, 3H), 3.79 (s, 3H), 3.48 (m,
 2H), 2.78 (d, J=5.1Hz, 3H), 2.58 (t, J=6.4Hz, 2H);

3-[1-methyl-4[1-methyl-4[1-methyl-4[5(α -
 25 bromoacrylamido)indole-2-carboxamido]pyrrole-2-
 carboxamido]pyrrole-2-carboxamido]pyrrole-2-
 carboxamido]propion-N,N'-dimethylamidine (8)

FAB-MS: m/z , 774(100, [M+H]⁺)

PMR (DMSO-d₆) δ :

30 11.68 (d, J=2.0Hz, 1H), 10.39 (s, 1H), 10.15 (s, 1H), 9.99
 (s, 1H), 9.92 (s, 1H), 9.48 (q, J=4.7Hz, 1H), 8.73 (q,
 J=4.7Hz, 1H), 7.99 (s, 1H), 7.34 (d, J=1.7 Hz, 1H), 7.28
 (d, J=2.0Hz, 1H), 7.25 (d, J=1.7 Hz, 1H), 7.19 (d, J=1.7
 Hz, 1H), 7.09 (d, J=1.7 Hz, 1H), 7.07 (d, J=1.7 Hz, 1H),
 35 6.93 (d, J=1.7 Hz, 1H), 6.74 (d, J=3.0 Hz, 1H), 6.26 (d,

J=3.0 Hz, 1H), 3.88 (s, 3H), 3.84 (s, 3H), 3.80 (s, 3H), 3.45 (m, 2H), 3.00 (d, J=4.7Hz, 3H), 2.78 (t, J=4.7Hz, 2H);

3-[1-methyl-4[1-methyl-4[1-methyl-4[5(α -chloroacrylamido)indole-2-carboxamido]pyrrole-2-

5 carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N,N'-dimethylamidine (9);

3-[1-methyl-4[1-methyl-4[1-methyl-4[1-methyl-5(α -bromoacrylamido)indole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-

10 carboxamido]propion-N,N'-dimethylamidine (10)

FAB-MS: m/z , 788(100, [M+H]⁺)

PMR (DMSO-d₆) δ :

10.43 (s, 1H), 10.22 (s, 1H), 10.00 (s, 1H), 9.93 (s, 1H), 9.46 (q, J=4.7Hz, 1H), 8.70 (q, J=5.0Hz, 1H), 8.30 (t, J=5.7Hz, 2H), 8.04 (d, J=1.9Hz, 1H), 7.54 (d, J=9.2Hz, 1H), 7.46 (dd, J=9.2 and 1.9Hz, 1H), 7.20 (s, 1H), 7.33 (d, J=1.7 Hz, 1H), 7.25 (d, J=1.7 Hz, 1H), 7.19 (d, J=1.7 Hz, 1H), 7.12 (d, J=1.7 Hz, 1H), 7.07 (d, J=1.7 Hz, 1H), 6.93 (d, J=1.7 Hz, 1H), 6.76 (d, J=3.0 Hz, 1H), 6.28 (d, J=3.0 Hz, 1H), 4.01 (s, 3H), 3.87 (s, 3H), 3.84 (s, 3H), 3.80 (s, 3H), 3.45 (m, 2H), 3.00 (d, J=4.7Hz, 3H), 2.79 (d, J=5.0Hz, 3H), 2.70 (t, J=6.3Hz, 2H);

3-[1-methyl-4[1-methyl-4[1-methyl-4[5(α -

bromoacrylamido)benzothiophene-2-carboxamido]pyrrole-2-

25 carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N,N'-dimethylamidine (12)

FAB-MS: m/z , 789(100, [M+H]⁺)

PMR (DMSO-d₆) δ :

10.64 (s, 1H), 10.44 (s, 1H), 10.98 (s, 1H), 9.91 (s, 1H), 9.38 (q, J=4.8Hz, 1H), 8.63 (q, J=4.6Hz, 1H), 8.35 (t, J=2.0Hz, 1H), 8.26 (t, J=5.7Hz, 1H), 8.21 (s, 1H), 7.98 (d, J=8.8Hz, 1H), 7.65 (dd, J=8.8 and 2.0Hz, 1H), 7.31 (d, J=1.7 Hz, 1H), 7.24 (d, J=1.7 Hz, 1H), 7.18 (d, J=1.7 Hz, 1H), 7.11 (d, J=1.7 Hz, 1H), 7.07 (d, J=1.7 Hz, 1H), 6.93 (d, J=1.7 Hz, 1H), 6.79 (d, J=3.0 Hz, 1H), 6.33 (d, J=3.0 Hz, 1H), 3.88 (s, 3H), 3.84 (s, 3H), 3.80 (s, 3H), 3.47 (m,

2H), 3.00 (d, J=4.6Hz, 3H), 2.77 (d, J=4.8Hz, 3H), 2.71 (m, 2H);

3-[1-methyl-4[1-methyl-4[1-methyl-4[1-methyl-5(α-bromoacrylamido)indazole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N,N'-dimethylamidine (13);

3-[1-methyl-4[1-methyl-4[1-methyl-4[1-methyl-5(α-bromoacrylamido)indole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidoxime (14);

3-[1-methyl-4[1-methyl-4[1-methyl-4[5(α-bromoacrylamido)indazole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidoxime (15);

3-[1-methyl-4[1-methyl-4[1-methyl-4[5(α-chloroacrylamido)indole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamide (16);

3-[1-methyl-4[1-methyl-4[1-methyl-4[1-methyl-5(α-bromoacrylamido)indole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamide (17);

3-[1-methyl-4[1-methyl-4[1-methyl-4[5(α-bromoacrylamido)benzofurane-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamide (18);

3-[1-methyl-4[1-methyl-4[1-methyl-4[1-methyl-5(α-chloroacrylamido)indazole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamide (19);

3-[1-methyl-4[1-methyl-4[1-methyl-4[5-N,N-bis(2-chloroethyl)aminobenzothiophene-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamide (29);

3-[1-methyl-4[1-methyl-4[1-methyl-4[5-N,N-bis(2-chloroethyl)aminobenzofurane-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propioncyanamidine (24).

5

EXAMPLE 2

3-[1-methyl-4[1-methyl-4[1-methyl-4[1-methyl-5(α -bromoacrylamido)indole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionitrile (23)

10

Step I: The intermediate 3-[1-methyl-4[1-methyl-4[1-methyl-4[1-methyl-5(α -bromoacrylamido)indole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine hydrochloride.

15

A solution of 260 mg of N-deformyldistamycin A dihydrochloride, prepared as reported in J.Med.Chem. 32, 774-778 (1989), in 5 ml of dry dimethylformamide (DMF) was cooled to 5°C and added with 0.086 ml of N,N'-diisopropylethylamine. After 10 min, 180 mg of 5- α -bromoacrylamidoindole-2-carboxylic acid and 190 mg of N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide (EDCI) were added. The reaction was stirred at room temperature for 10 hours, then 2N hydrochloric acid was added up to pH=4. The solvent was removed under reduced pressure and the crude residue purified by flash chromatography (methylene chloride/methanol:8/2) to give 240 mg of the title compound.

25

FAB-MS: m/z 760, (100, [M+H]⁺)

30 PMR (DMSO-d₆) δ :

10.44 (s, 1H), 10.23 (s, 1H), 10.00 (s, 1H), 9.93 (s, 1H), 8.97 (b.s., 2H), 8.60 (b.s., 2H), 8.22 (t, J=5.7 Hz, 1H), 8.05 (d, J=1.8 Hz, 1H), 7.54 (d, J=8.9 Hz, 1H), 7.47 (dd, J=8.9 Hz and J=1.9 Hz, 1H), 7.25 (d, J=1.8 Hz, 1H), 7.21 (s, 1H), 7.19 (d, J=1.8 Hz, 1H), 7.12 (d, J=1.8 Hz, 1H), 7.07 (d, J=1.8 Hz, 1H), 7.05 (d, J=1.8 Hz, 1H), 6.95 (d,

35

J=1.8 Hz, 1H), 6.77 (d, J=3.1 Hz, 1H), 6.29: (d, J=3.1 Hz, 1H), 4.01 (s, 3H), 3.88 (s, 3H), 3.85 (s, 3H), 3.81 (s, 3H), 3.50 (m, 2H), 2.61 (m, 2H).

5 **Step II:** the title compound

To a solution of 150 mg of 3-[1-methyl-4[1-methyl-4[1-methyl-4[1-methyl-5(α -bromoacrylamido)indole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamide hydrochloride, prepared as described in step I as above, in 10 ml DMF were added 25 mg of potassium carbonate and 20 mg of succinic anhydride. The mixture was heated at 60°C for 4 hours. The solvent evaporated under vacuum and the crude residue purified by flash chromatography (methylene chloride/methanol:8/2) to yield 100 mg of the title compound as a yellow powder.

FAB-MS: m/z, 741(8, [M+H]⁺);

PMR(DMSO-d₆) δ :

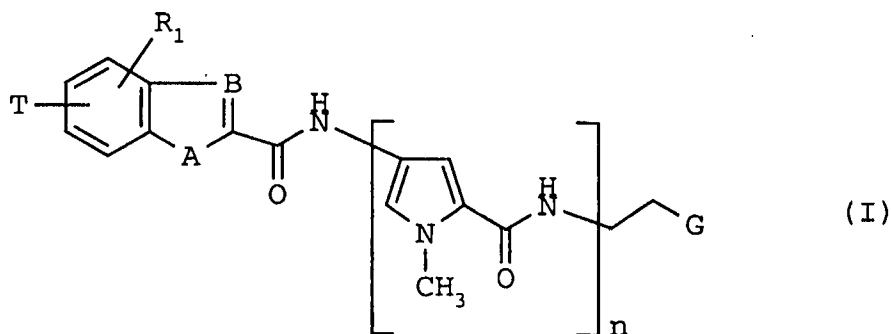
10.44 (s, 1H), 10.22 (s, 1H), 10.00 (s, 1H), 9.93 (s, 1H),
20 8.22 (t, J=5.8Hz, 1H), 8.04 (d, J=1.7Hz, 1H), 7.56 (d, J=9.0Hz, 1H), 7.46 (dd, J=9.0Hz and 1.7Hz, 1H), 7.33 (d, J=1.7 Hz, 1H), 7.25 (d, J=1.7 Hz, 1H), 7.20 (s, 1H), 7.19 (d, J=1.7 Hz, 1H), 7.12 (d, J=1.7 Hz, 1H), 7.07 (d, J=1.7 Hz, 1H), 6.93 (d, J=1.7 Hz, 1H), 6.77 (d, J=3.0 Hz, 1H),
25 6.28 (d, J=3.0 Hz, 1H), 4.01 (s, 3H), 3.87 (s, 3H), 3.84 (s, 3H), 3.80 (s, 3H), 3.40 (m, 2H), 2.72 (t, J=6.4Hz, 2H).

By analogous procedures and by using the opportune starting materials the following products can be obtained:

30 3-[1-methyl-4[1-methyl-4[1-methyl-4[5(α -bromoacrylamido)indole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionitrile (22);
3-[1-methyl-4[1-methyl-4[1-methyl-4[5-N,N-bis(2-
35 chloroethyl)aminoindazole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionitrile (32).

CLAIMS

1. A compound which is a benzoheterocyclic distamycin derivative of formula:



5

wherein:

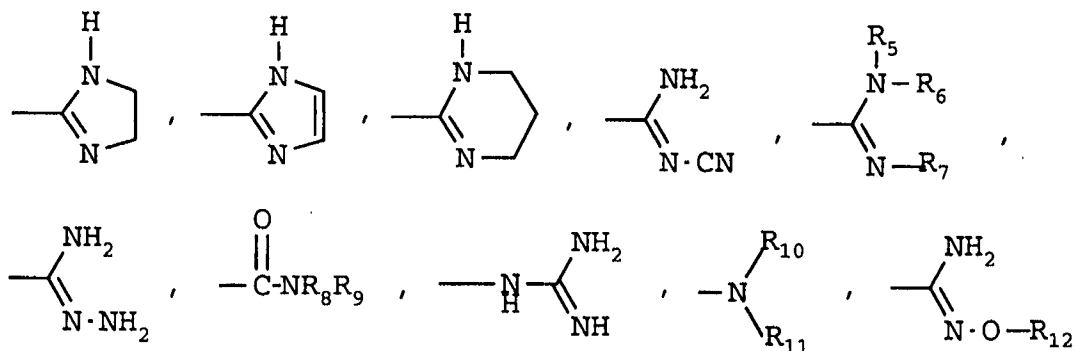
n is 2, 3 or 4;

A is a heteroatom selected from O and S or is a group NR, wherein R is hydrogen or C₁-C₄ alkyl;

10 B is CH or N;

R₁ is hydrogen or C₁-C₄ alkyl;

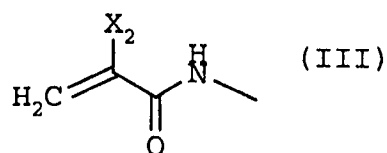
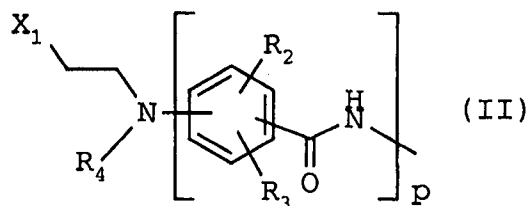
G is selected from the group consisting of:



and $-\text{C}\equiv\text{N}$;

15 wherein R₅, R₆, R₇, R₈, R₉, R₁₀, R₁₁ and R₁₂ are, independently from each other, hydrogen or C₁-C₄ alkyl;

T is a group of formula (II) or (III) as defined below



6. A pharmaceutical composition comprising one or more pharmaceutically acceptable carriers and/or diluents and, as the active principle, a compound as defined in claim 1.

5 7. A compound as defined in claim 1 for use in a method of treating the human or animal body by therapy.

8. A compound as claimed in claim 7 for use as an antitumor agent.

10

9. Use of a compound as defined in claim 1 in the manufacture of a medicament for use as an antitumor agent.