

Description**BACKGROUND OF THE INVENTION****5 Field of the Invention**

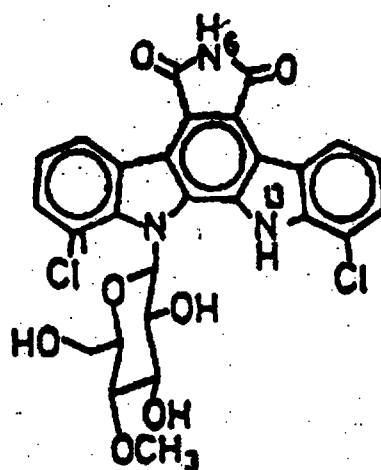
This invention relates to novel compounds having antineoplastic properties, to their production, to a pharmaceutical composition containing an amount of at least one compound according to the invention which is effective to inhibit the growth of tumors in experimental animal systems, and to a method for therapeutically treating an experimental animal by administering an amount of at least one compound according to the invention which is effective to inhibit tumor growth in an experimental animal system.

Background Art

15 U. S. Patents 4,487,925, 4,552,842 and 4 524 145 disclose the anti-tumor agent designated rebeccamycin, the 5'-N-methyl and 5',2'',3'',6''-tetraacetate and the 4'-deschloro derivatives thereof, and a process for producing the same agent by cultivating a rebeccamycin-producing strain of *Nocardia aerocolonigenes*, preferably *Nocardia aerocolonigenes* ATCC 39243, or a rebeccamycin-producing mutant thereof in an aqueous nutrient medium containing assimilable sources of carbon and nitrogen under submerged aerobic conditions until a substantial amount of rebeccamycin is produced.

SUMMARY OF THE INVENTION

This invention comprises analogs of the antitumor agent designated rebeccamycin (Formula I)

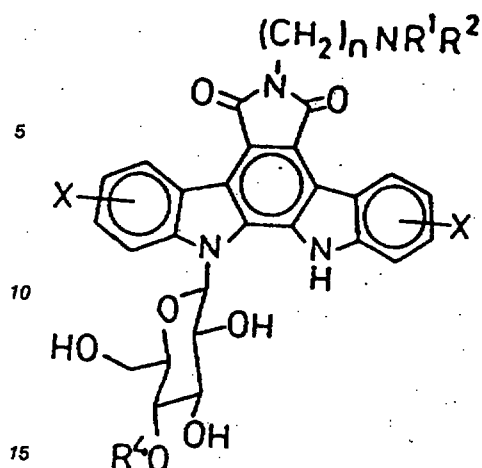


Formula I

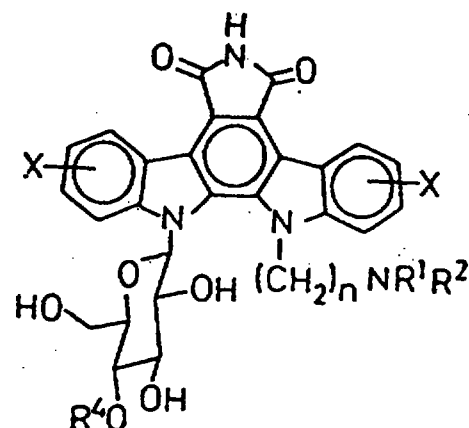
produced by first reacting rebeccamycin with a strong base to obtain a reactive intermediate and then reacting the reactive intermediate with an aminoalkyl halide. By the use of an amount of strong base slightly in excess, for example about 10 % excess, of the molar equivalent amount of rebeccamycin followed by reacting the resulting intermediate with at least one molar equivalent based on rebeccamycin of an aminoalkyl halide as the alkylating agent, there is obtained the corresponding 6-aminoalkylrebeccamycin analog. By the use of an amount of strong base slightly in excess of two-times the molar equivalent amount of rebeccamycin, for example about 20 % excess over two-times the molar equivalent amount of rebeccamycin, and then reacting the resulting intermediate with about one molar equivalent of an aminoalkyl halide as the alkylating agent, there is obtained the corresponding 13-aminoalkylrebeccamycin analog.

DETAILED DESCRIPTION OF THE INVENTION

In one generic aspect, this invention is a compound selected from the group consisting of the compounds having the formulas II and III below



Formula II



Formula III

wherein:

n is an integer from 1 to 6;

R¹ and R², independently, are selected from hydrogen, unsubstituted and substituted C₁-C₆ alkyl, aralkyl having 1 to 3 carbons in the alkyl moiety and unsubstituted phenyl or phenyl substituted with 1 to 3 alkyl, alkoxy, hydroxy, halo, carboxyl, alkoxycarbonyl, and amino and mono- and di-lower-alkylamino groups in the aryl moiety, and aryl selected from unsubstituted phenyl and phenyl substituted with 1 to 3 alkyl, alkoxy, hydroxy, halo, amino, mono- and dialkylamino, nitro, carboxyl, alkoxycarbonyl, and cyano groups provided that both R¹ and R² are not each aryl and, when taken together, R¹ and R² may be selected from -(CH₂)₄- and (CH₂)₂-R³-(CH₂)₂- to form a 5- or 6-membered ring together with the N-atom wherein R³ is selected from CH₂, NH, O and S;

X is selected from H, F, Cl, Br, C₁-C₃ alkyl, OH, carboxyl, alkoxycarbonyl and alkoxy wherein the alkyl moiety is C₁-C₃ alkyl, benzyloxy, amino, mono- and dialkylamino; and

R⁴ is selected from H and CH₃; and pharmaceutically acceptable acid addition and base salts thereof.

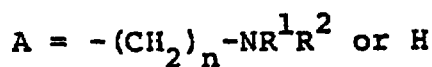
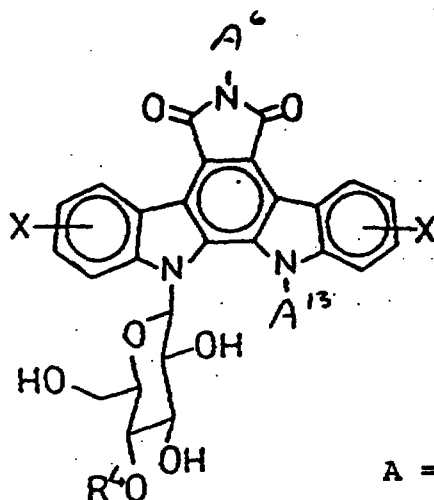
Preferred, compounds according to this invention having one of Formulas II and III above are those wherein n is an integer from 1 to 6, R¹ and R², independently, are selected from unsubstituted and substituted C₁-C₆ alkyl and, when taken together, R¹ and R² may be selected from -(CH₂)₄- and -(CH₂)₂-R³-(CH₂)₂- to form a 5- or 6-membered ring together with the N-atom wherein R³ is selected from CH₂, NH, O and S, and wherein R⁴ is H or CH₃ and X is selected from H, Cl, Br, OH, OCH₃ and OCH₂C₆H₅.

More preferred compounds according to this invention having one of Formulas II and III above are those wherein n is selected from the integers 1, 2 and 3; R¹ and R², independently, are selected from H, C₁-C₃ alkyl, and -(CH₂)₄-; R⁴ is H or CH₃; and X is selected from H, Cl, Br, OH, OCH₃ and OCH₂C₆H₅.

Most preferred compounds according to this invention having one of Formulas II and III above are those wherein n is an integer selected from 2 and 3; X is Cl in each of the 1- and 11-positions of the ring system; R¹ and R² are each C₂H₅; and R⁴ is H or CH₃.

The following Table 1 presents representative combinations of the many groups within the definition of X, n, R¹, R², R³ and R⁴ and many further combinations of such groups will be readily apparent to those skilled in the art. It is to be understood that the aminoalkyl group, A, bearing the groups n, R¹ and R² may be substituted at either or both the 6- and 13-positions (designated A⁶ and A¹³) of the rebeccamycin ring system. Of course, when only one of A⁶ or A¹³ is aminoalkyl, the other is H.

Table 1 - Representative Substituent Groups



	<u>X</u>	<u>n</u>	<u>R¹</u>	<u>R²</u>	<u>R⁴</u>
25	1,11-dichloro	2	ethyl	ethyl	methyl
	1,11-dichloro	3	ethyl	ethyl	methyl
	3,9-diamino	3	methyl	methyl	H
30	2,10-diamino	4	propyl	propyl	H
	3,9-dibenzyloxy	5	i-propyl	H	methyl
	4,8-dichloro	6	ethyl	H	methyl
35	3,9-dichloro	2	phenethyl	H	methyl
	4,8-dihydroxy	3	benzyl	H	methyl
	3,9-dihydroxy	2	$-(CH_2)_4-$		H
	4,8-dimethoxy	3	$-(CH_2)_2-O-(CH_2)_2-$		methyl
40	3,9-dimethoxy	2	$-(CH_2)_2-NH-(CH_2)_2-$		methyl
	4,8-dimethyl	3	$-(CH_2)_5-$		H
	3,9-dimethyl	1	$-(CH_2)_2-S-(CH_2)_2-$		methyl
45	2,10-dimethyl	2	hexyl	H	methyl
	3,9-dihydroxycarbonyl	3	ethyl	ethyl	methyl
	2,10-dibromo	2	$-(CH_2)_4-$		methyl
50	H	3	ethyl	ethyl	H

In other aspects, this invention is a pharmaceutical composition containing at least one of the compounds according to the invention and a method for therapeutically treating a mammalian host, for example, an experimental animal, affected by a malignant tumor by administering at least one of the compounds according to this invention in a tumor growth-inhibiting amount and, usually, by means of administering the compound in the form of the pharmaceutical composition.

By the expression "C₁-C₆ alkyl", more particularly unsubstituted C₁-C₆ alkyl, is meant straight-chain or branched-chain or cyclic alkyl groups having a total of six carbon atoms. Examples of suitable straight-chain

alkyl groups include methyl, ethyl, propyl, butyl, pentyl and hexyl groups. Examples of suitable branched-chain alkyl groups include isopropyl, sec-butyl, t-butyl, 2-methylbutyl, 2-pentyl, 3-pentyl and the like groups. Examples of suitable cyclic alkyl groups include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl groups. The alkyl groups may be substituted, generally with 1 or 2 substituents, with substituents selected from halo, hydroxy, alkoxy, amino, mono- and dialkylamino, nitro, carboxyl, alkoxycarbonyl, and cyano groups. By the expression "aralkyl" is meant benzyl, phenethyl (phenylethyl) and phenylpropyl groups wherein the phenyl moiety may be substituted. By the expression "aryl" is meant phenyl. The aralkyl or aryl group may contain substituted phenyl wherein the substituent may be from 1 to 3 alkyl, hydroxy, alkoxy, halo, amino, mono- and dialkylamino, nitro, carboxyl, alkoxycarbonyl, and cyano groups.

As used herein, the expression "halo" is meant in the conventional sense to include F, Cl, Br, and I.

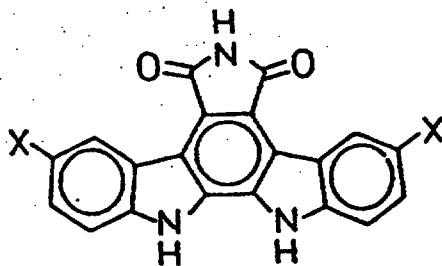
When the expressions alkoxy, alkoxycarbonyl, mono- and dialkylamino are used, these expressions usually are meant to include an alkyl moiety having 1 to 3 carbon atoms.

As mentioned above, R¹ and R² are not each aryl. Also, R¹ and R² generally are not each selected from the sterically larger of the C₁-C₆ alkyl and from aralkyl groups. Preferably, when R¹ and R² are each alkyl, they are each selected from C₁-C₃ alkyl groups.

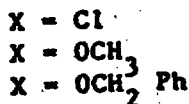
As is mentioned above, rebeccamycin is a known antitumor agent disclosed in U.S. Patents 4,487,525 and 4,552,842. The Chemical Abstracts nomenclature for rebeccamycin is as follows: 5H-Indolo[2,3-a]pyrrolo[3, 4-c] carbazole-5,7 (6H)dione, 1, 11-dichloro-12, 13-dihydro-12-(4-O-methyl-beta-D-glucopyranosyl). However, the name "rebeccamycin" is used throughout for simplicity although the Chemical Abstracts numbering systems is used to identify the various positions in the rebeccamycin ring system.

The starting material for the most preferred compounds according to this invention is rebeccamycin itself. Rebeccamycin, Formula I, may be produced by cultivating a rebeccamycin-producing strain of *Nocardia aerocolonigenes*, preferably a strain having the characteristics of *Nocardia aerocolonigenes* strain C38,383-RK2(ATCC39243) or a mutant thereof under submerged aerobic conditions in an aqueous nutrient medium as is described in U.S. Patents 4,487,925 and 4,552,842.

Derivatives of rebeccamycin having various groups substituted on the rebeccamycin ring system in place of the 1,11-dichloro substituents may be used as starting materials in the place of rebeccamycin to obtain compounds within the broad definition and preferred and more preferred embodiments according to the present invention. For example, didechlororebeccamycin can be produced by subjecting rebeccamycin to hydrogenolysis and the resulting intermediate may be subjected to alkylation using strong base followed by reaction of the intermediate from the strong base treatment with a suitable aminoalkyl halide. Other chromophores of rebeccamycin having various substituents on the rebeccamycin ring system can be produced using methods disclosed by T. Kaneko et al., *Tetrahedron Letters*, 26, 4015 (1985). For example, by using the procedures therein disclosed, compounds having the following formula, IV, were produced:



Formula IV

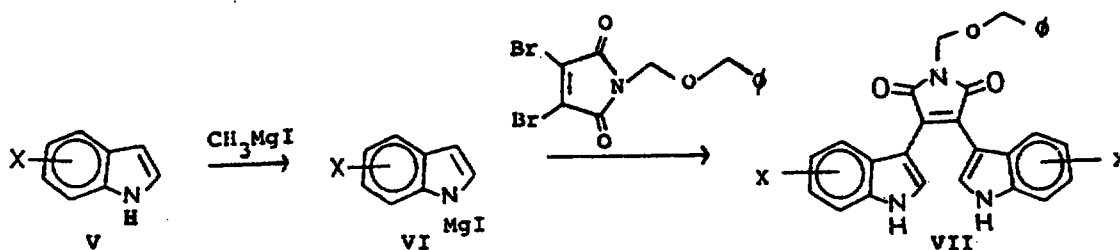


The following more particularly describes a typical synthesis of analogs or chromophores of rebeccamycin having various substituents on the ring system in the place of the Cl groups. Treatment of a substituted indole with methyl magnesium tetrahydrofuran produces a solution of indole Grignard (VI). Two equivalents of this solution and one equivalent of N-benzyloxymethyl 3,4-dibromo-maleimide gives an adduct of formula VII. This can be either photochemically cyclized by irradiation at 300 nm in a benzene solution containing a small amount of I₂ or thermally by refluxing a solution of the adduct in benzene in the

presence of Ag_2O . The intermediate thus prepared (VIII) is then coupled with O-acylated 1-halosugar in the presence of Ag_2O to give N-glycoside IX. A catalytic hydrogenation to remove the N6 protecting group and a base hydrolysis of the sugar O-acyl groups gives the desired product X. Illustrative of the substituted indoles that can be used in this preparation are listed in Table 2.

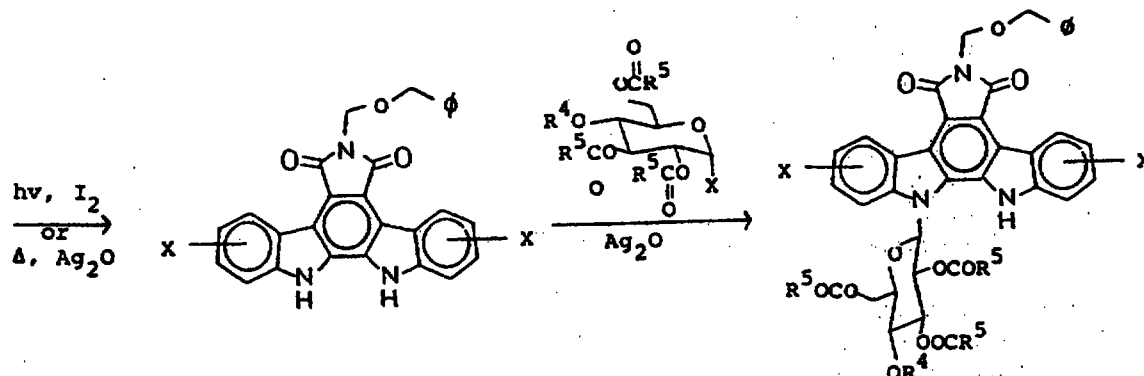
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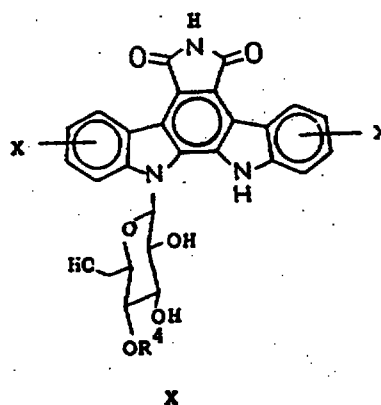


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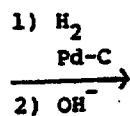
VIII

IX

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X and R^4 are as defined herein
 R^5 , typically, is CH_3

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Table 2 - Starting Indoles

5	5-Aminoindole
	6-Aminoindole
	5-Benzyloxyindole
10	4-Chloroindole
	5-Chloroindole
	4-Hydroxyindole
	5-Hydroxyindole
15	Indole
	4-Methoxyindole
	5-Methoxyindole
20	4-Methylindole
	5-Methylindole
	6-Methylindole
25	Indole-5-carboxylic acid

Glycosidation of any one of the three chromophores represented by Formula IV or a chromophore represented by Formula X by reaction with an appropriate glycosyl halide provides a rebeccamycin derivative. And, reaction of the rebeccamycin derivative first with strong base followed by an aminoalkyl halide provides analogs of rebeccamycin according to this invention having one of Formulas II or III.

Having obtained rebeccamycin or a rebeccamycin derivative or chromophore, this starting material is first dissolved in a suitable inert solvent, for example dimethylformamide (DMF), dimethylsulfoxide (DMSO), tetrahydrofuran (THF) or other anhydrous, aprotic solvent and then reacted with a strong base in an inert atmosphere, for example in an argon or nitrogen atmosphere. Although any strong base that is compatible with the starting material and solvent may be used, for example, KNH_2 or KH or NaNH_2 or NaH or lithium diisopropyl amide (LDA) or lithium hexamethyl disilazide or KOTBu or Grignard reagent such as MeMgBr or NaNH_2 or NaH or equivalent base, NaH may be advantageously employed.

It has been discovered that by using strong base, for example NaH , in an amount slightly in excess of the molar equivalent of the amount of starting material, for example in the range of from about 5% to about 15% and preferably about 10% (9-11%) excess, followed by treatment with at least one molar equivalent based on rebeccamycin starting material of an appropriate aminoalkyl compound, there may be obtained a compound according to the invention having an aminoalkyl substituent on the N-atom in the 6-position of the rebeccamycin ring system.

Further, it has been discovered that by using strong base, for example NaH , in a relatively large excess amount such as an amount slightly in excess of two-times the molar equivalent of the amount starting material, for example, in the range of about 15% to about 25% and preferably about 20% (18-22%) excess, followed by treatment with an appropriate aminoalkyl compound in an amount about the molar equivalent of starting material, there may be obtained a compound according to the invention having an aminoalkyl substituent on the N-atom in the 13-position of the rebeccamycin ring system.

When more than two equivalents of base are used, a dianion at N6 and N13 is formed. Since the N13 anion is more reactive than the N6 anion, a N13 aminoalkyl derivative is obtained when only one equivalent of aminoalkyl halide is used. When two equivalents of aminoalkyl halide is used, the N6,N13-diaminoalkyl derivative may be obtained.

Following the reaction of the starting material with a strong base, the resulting reactive intermediate is reacted *in situ* with an appropriate reactive aminoalkyl compound by adding the aminoalkyl compound to the mixture of starting material and strong base and intermediate reaction product thereof in inert solvent. Any aminoalkyl compound that is compatible with the starting material and product and solvent may be

used, for example an aminoalkyl halide or sulfonate and the like, represented by the formula $L-(CH_2)_n-NR^1R^2$ wherein n , R^1 and R^2 are as defined above and L is a leaving group such as halide or methanesulfonate or p-toluenesulfonate. Generally an aminoalkyl halide such as, for example, diethylaminoethyl chloride and diethylaminopropyl chloride, may be advantageously employed.

Generally, the reaction of strong base with starting material may be carried-out advantageously at about room temperature, that is, at about 18°C to about 22°C. The mixture of starting material and strong base, generally, may be stirred for a period of a few minutes to several hours; however, the reaction is usually complete in about 20-30 minutes.

Then, there is added to the stirred mixture of starting material and strong base and resulting reactive intermediate reaction product thereof in inert solvent the appropriate aminoalkyl compound and the resulting mixture may be stirred at room temperature for about 20-24 hours or at about 4°C for a shorter period of time, for example, six hours until the reaction of the reactive intermediate with aminoalkyl compound is complete.

The compounds of Formulas II and III according to this invention may be provided as pharmaceutically acceptable acid addition and base salts provided that the anion or cation thereof did not contribute significantly to the toxicity of the salt and that the salts are compatible with the standard and conventional pharmaceutical carriers and other conventional adjuvants and excipients customarily employed in producing pharmaceutical compositions adapted for oral or parenteral administration. The acid addition salts are formed by conventional techniques involving reaction of compounds of Formulas II and III with a mineral acid or organic carboxylic and sulfonic acids. Examples of suitable mineral acids include hydrochloric acid, phosphoric acid, and the like. Examples of suitable organic acids include acetic acid, citric acid, maleic acid, succinic acid, benzoic acid, tartaric acid, ascorbic acid, methanesulfonic acid, p-toluenesulfonic acid, and the like.

The base salts are formed by conventional techniques involving reaction of the compounds of Formulas II and III with alkali (Na, K) and alkalkine earth (Ca, Zn, Ba, Mg, and Mn) metal bases, more preferably with alkali metal bases, and by reaction with amines. Suitable bases include the hydroxide, carbonate or bicarbonate salts of the metals mentioned above such as, for example, sodium and potassium hydroxides, sodium and potassium carbonates, and sodium and potassium bicarbonates and the corresponding calcium and zinc salts. Additional suitable bases include ammonium salts those formed by reaction of compounds of formulas II and III with triethylamine, dibenzylamine, N, N'-dibenzylethylenediamine, procaine, and equivalent amines.

The pharmaceutical carrier may be solid or liquid to provide solid or liquid compositions. Solid form compositions suitable for oral administration include powders, tablets, capsules, caplets, dispersible granules, and cachets. Suitable solid carriers include at least one carrier substance which may function only as a carrier or may in addition serve a further function such as a diluent, flavoring agent, solubilizer, lubricant, suspending agent, binder, tablet disintegrating agent, encapsulating agent and the like. Inert solid carriers include, to name but a few, magnesium carbonate and stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, cellulosic materials, and the like. The compounds according to the invention may be provided as sterile soluble compounds or compositions, including solutions and suspensions and emulsions, thereof which can be dissolved in sterile water or other liquid medium for oral administration or for parenteral administration. Examples of liquid carriers suitable for oral administration include water, alcohol, polypropylene glycol, polyethylene glycol and mixtures of two or more of the above. Examples of liquid carriers suitable for parenteral use include water-for-injection, physiological saline, and other suitable sterile injection media. Suitable buffers for use with the liquid carrier to provide, generally, a suitable buffered isotonic solution include trisodium orthophosphate, sodium bicarbonate, sodium citrate, N-methylglucamine, L(+)-lysine, and L(+)-arginine to name but a few representative buffering agents.

The pharmaceutical composition will contain an amount of active component, that is, compound of Formula II or III or mixture thereof, which may be varied or adjusted widely depending upon the particular application, the form, the potency of the particular compound used, and the desired concentration of compound in the composition. Generally, the amount of active component will range between about 0.5-90% by weight based on total weight of composition.

In therapeutic use for treating a mammalian host, for example an experimental animal host, affected by a malignant tumor, the compounds of this invention will be administered in an amount effective to inhibit the growth of the tumor, that is, a tumor growth-inhibiting amount of dosage. Generally, the tumor growth-inhibiting amount will be in the range of about 0.1 to about 15 mg/kg of animal body weight/day. It is to be understood that the actual preferred dosage of compound will vary widely depending upon the requirements of the animal being treated, the particular animal host and situs and disease being treated, the composition being used, and the route of administration. Many factors that modify the action of the anti-neoplastic agent

will be taken into account by one skilled in the art to which this invention pertains including, for example, age, body weight and sex of the animal host; diet; time of administration; rate of excretion; condition of the host; severity of the disease; and the like. Administration may be carried out simultaneously or periodically within the maximum tolerated dose. Optimal administration (or application) rates for a given set of conditions may be readily ascertained by those skilled in the art using conventional dosage determination tests.

The following examples are presented to illustrate but a few representative embodiments of this invention and are not to be construed as limiting in scope. All parts and percentages are by weight and all temperatures are in degrees Celsius unless otherwise indicated.

- 10 Rebeccamycin analogs according to this invention were tested for antitumor activity against the transplanted mouse leukemia P-388 according to the procedures of Geran et al. reported in Cancer Chemother. Rpts., 3, 1-103 (1972). Prolongation of survival of leukemic mice was observed at several dosage levels ranging from 6 mg/kg body wt/day to 100 mg/kg body wt./day. Results of the tests are shown in the accompanying Table 3. The standard, comparison agent is selected from olivomycin and mitomycin
- 15 C. These results illustrate that the rebeccamycin analogs according to the invention possess useful antineoplastic activity.

Example 1. 6-(2-Diethylaminoethyl)rebeccamycin

- 20 DMF (100 mL) was added under argon to a mixture of rebeccamycin (990 mg, 1.74 mmol) and NaH (46 mg, 1.91 mmol). After 20 minutes of stirring at room temperature, 2-diethylaminoethyl chloride (524 mg, 3.86 mmol) was added.

The resulting mixture was stirred for 24 h. and the reaction was then quenched by addition of 1% aq HCl solution. The reaction mixture was basified by addition of saturated NaHCO₃ solution and extracted with

- 25 EtOAc. The organic layer was collected and washed with brine and dried over Na₂SO₄. The residue obtained by evaporation of the solvent was chromatographed on silica gel (elution with EtOAc) to give 770 mg (66%) of the title compound: mp >250°C; NMR (DMSO-d₆) δ 10.68 (s, 1H), 9.26 (d, 1H, J = 7.8 Hz); 9.08 (d, 1H, J = 7.9 Hz), 7.73 (d, 1H, J = 8.9 Hz), 7.70 (d, 1H, J = 8.9 Hz), 7.45 (t, 2H, J = 7.8 Hz), 6.94 (d, 1H, J = 9.1 Hz), 5.43 (d, 1H, J = 5.6 Hz), 5.31 (bs, 1H), 5.03 (d, 1H, J = 5.7 Hz), 3.95 (s, 2H), 3.82 (m, 2H), 3.70 - 3.48 (m, 7H), 2.72 (m, 2H), 2.53 (m, 4H), 0.94 (t, 6H, J = 7.0 Hz); IR (KBr) 3343, 1692, 1381, 1070, 760 cm⁻¹; FABMS 669 (M+1), 493, 217 m/e.

Example 2. 6-(2-Diethylaminoethyl)rebeccamycin hydrochloride

- 35 To a solution of 6-(2-diethylaminoethyl)rebeccamycin (770 mg, 1.15 mmol) in 30 mL of THF at 0°C was added one equivalent of 5.6M ethanolic HCl solution. After stirring 3 h at 0°C the resulting precipitate was collected by filtration and washed with diethyl ether to give 728 mg (90%) of the title compound: mp >250°C; NMR (DMSO-d₆) δ 10.7 (s, 1H), 10.16 (s, 1H), 9.23 (d, 1H, J = 8.1 Hz), 9.05 (d, 1H, J = 8.0 Hz), 7.74 (d, 1H, J = 8.5), 7.72 (d, 1H, J = 9.3 Hz), 7.46 (t, 2H, J = 8.1 Hz), 6.94 (d, 1H, J = 9.1 Hz), 5.47 (bs, 1H), 5.36 (bs, 1H), 5.08 (bd, 1H, J = 3.8 Hz), 4.11 (t, 2H, J = 6.3 Hz), 3.97 (bs, 1H), 3.85 (d, 1H, J = 9.5 Hz), 3.66 - 3.57 (m, 7H), 3.49 - 3.20 (m, 7H), 1.26 (t, 6H, J = 7.0 Hz); IR (KBr) 3336, 1699, 1416, 1381, 1084, 760 cm⁻¹; FABMS 669 (M+1), 635, 493 m/e.

45 Example 3. 6-(3-Diethylaminopropyl)rebeccamycin

- DMF (20mL) was added under argon to a mixture of rebeccamycin (162 mg, 0.28 mmol) and NaH (7.5 mg, 0.31 mmol). To this solution was added 110 mg (0.78 mmol) of 3-diethylaminopropyl chloride. The resulting solution was stirred and warmed to 40°C for 6 h. A workup similar to Example 1 gave 55 mg (28%) of the
- 50 title compound: NMR (DMSO-d₆) δ 9.28 (d, 1H, J = 7.8 Hz), 9.10 (d, 1H, J = 8.1 Hz), 7.73 (d, 1H, J = 9.4 Hz), 7.70 (d, 1H, J = 9.4 Hz), 7.45 (d, 1H, J = 7.8 Hz), 6.94 (d, 1H, J = 9.1 Hz), 5.42 (bd, 1H, J = 5.8 Hz), 5.31 (bs, 1H), 5.03 (bs, 1H), 3.95 (bs, 2H), 3.82 - 3.59 (m, 9H), 2.44 (m, 6H), 1.81 (m, 2H), 0.90 (t, 6H, J = 7.0 Hz); IR (KBr), 3328, 1691, 1376, 1052, 755 cm⁻¹; MS 682 (M), 653, 403, 393 m/e.

55 Example 4. 6-(3-Diethylaminopropyl)rebeccamycin hydrochloride

Treatment of the product from Example 3 with ethanolic HCl in a similar manner as Example 2 gave the title compound in 89% yield: mp >250°C; NMR (DMSO-d₆) δ 10.70 (s, 1H), 9.81 (bs, 1H), 9.26 (d, 1H, J = 7.1

H_z), 9.09 (d, 1H, J = 8.0 Hz), 7.73 (d, 1H, J = 11.4 Hz), 7.72 (d, 1H, J = 11.0 Hz), 7.43 (t, 2H, J = 7.9 Hz), 6.94 (d, 1H, J = 9.2 Hz), 5.46 (bs, 1H), 5.34 (bs, 1H), 5.06 (bs, 1H), 3.95 (bs, 2H), 3.83 (m, 2H), 3.66 - 3.54 (m, 5H), 3.20 (m, 2H), 3.10 (m, 4H), 2.12 (m, 2H), 1.18 (t, 6H, J = 7.2 Hz); IR (KBr) 3343, 1692, 1452, 1070, 760 cm⁻¹; FABMS 683, (M + 1), 507, 406 m/e.

Example 5. 13-(3-Dethylaminopropyl)rebeccamycin

DMF (25 mL) was added under argon to a mixture of rebeccamycin (188 mg, 0.33 mmol) and NaH (17 mg 0.73 mmol). After a few minutes of stirring at room temperature, 3-diethylaminopropyl chloride (54 mg, 0.36 mmol) was added and the resulting solution was stirred at room temperature for 22 h. The reaction was quenched by addition of 10% HCl solution in water. Saturated NaHCO₃ solution was added to basify the solution and the product was extracted with EtOAc. The organic layer was collected and washed with brine and dried over MgSO₄. The residue obtained after evaporation of the solvent was chromatographed on neutral alumina (10% MeOH-acetone) to give 76 mg (34%) of the title compound: mp 203-204°C; NMR (DMSO-d₆) δ 10.67 (s, 1H), 9.28 (d, 1H, J = 8.1 Hz), 9.10 (d, 1H, J = 8.1 Hz), 7.73 (d, 1H, J = 10.9 Hz), 7.71 (d, 1H, J = 11.6 Hz), 7.45 (t, 2H, J = 8.1 Hz), 6.94 (d, 1H, J = 9.0 Hz), 5.43 (d, 1H, J = 5.8 Hz), 5.32 (t, 1H, J = 5.2 Hz), 5.03 (d, 1H, J = 5.5 Hz), 3.96 (m, 2H), 3.85-3.79 (m, 3H), 3.91-3.53 (m, 5H), 2.71 (m, 4H) 1.95 (m, 2H), 1.13 (m, 6H); IR (KBr) 3343, 1696, 1388, 1085, 760 cm⁻¹; MS 683 (M + 1), 654, 506 m/e.

TABLE 3

EFFECT OF REBECCAMYCIN ANALOGS ON P-388 LEUKEMIA				
Compound	Dose, IP mg/kg/inj	Median Survival Time (MST) Days	% T/C	Avg. wt. change, gm day 4
Olivomycin	0.8	17.0	162	-2.4
	0.4	13.5	129	-2.6
Ex. 1	100	13.0	124	-2.0
	50	17.5	167	-2.2
	25	14.0	133	-0.5
Mitomycin C	4.8	19.0	211	-2.0
	3.2	22.0	244	-1.5
Ex. 2	8.0	12.0	133	-0.4
	6.0	12.5	139	-0.0
Ex. 4	8.0	12.5	139	-0.9
	6.0	13.0	144	0.1

Claims

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

1. A compound having the formula

Hz), 9.09 (d, 1H, J = 8.0 Hz), 7.73 (d, 1H, J = 11.4 Hz), 7.72 (d, 1H, J = 11.0 Hz), 7.43 (t, 2H, J = 7.9 Hz), 6.94 (d, 1H, J = 9.2 Hz), 5.46 (bs, 1H), 5.34 (bs, 1H), 5.06 (bs, 1H), 3.95 (bs, 2H), 3.83 (m, 2H), 3.66 - 3.54 (m, 5H), 3.20 (m, 2H), 3.10 (m, 4H), 2.12 (m, 2H), 1.18 (t, 6H, J = 7.2 Hz); IR (KBr) 3343, 1692, 1452, 1070, 760 cm^{-1} ; FABMS 683, (M+1), 507, 406 m/e.

Example 5. 13-(3-Dethylaminopropyl)rebeccamycin

DMF (25 mL) was added under argon to a mixture of rebeccamycin (188 mg, 0.33 mmol) and NaH (17 mg 0.73 mmol). After a few minutes of stirring at room temperature, 3-diethylaminopropyl chloride (54 mg, 0.36 mmol) was added and the resulting solution was stirred at room temperature for 22 h. The reaction was quenched by addition of 10% HCl solution in water. Saturated NaHCO_3 solution was added to basify the solution and the product was extracted with EtOAc. The organic layer was collected and washed with brine and dried over MgSO_4 . The residue obtained after evaporation of the solvent was chromatographed on neutral alumina (10% MeOH-acetone) to give 76 mg (34%) of the title compound: mp 203-204°C; NMR (DMSO-d_6) δ 10.67 (s, 1H), 9.28 (d, 1H, J = 8.1 Hz), 9.10 (d, 1H, J = 8.1 Hz), 7.73 (d, 1H, J = 10.9 Hz), 7.71 (d, 1H, J = 11.6 Hz), 7.45 (t, 2H, J = 8.1 Hz), 6.94 (d, 1H, J = 9.0 Hz), 5.43 (d, 1H, J = 5.8 Hz), 5.32 (t, 1H, J = 5.2 Hz), 5.03 (d, 1H, J = 5.5 Hz), 3.96 (m, 2H), 3.85-3.79 (m, 3H), 3.91-3.53 (m, 5H), 2.71 (m, 4H) 1.95 (m, 2H), 1.13 (m, 6H); IR (KBr) 3343, 1696, 1388, 1085, 760 cm^{-1} ; MS 683 (M+1), 654, 506 m/e.

TABLE 3

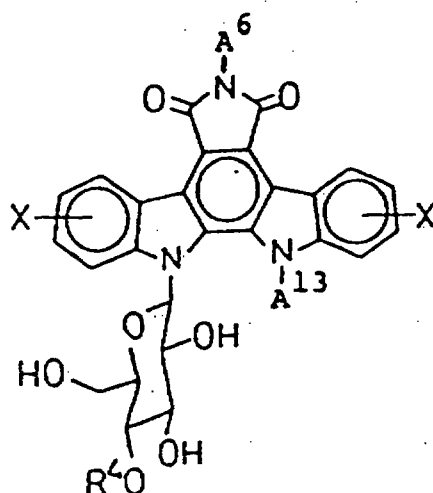
EFFECT OF REBECCAMYCIN ANALOGS ON P-388 LEUKEMIA				
Compound	Dose, IP mg/kg/inj	Median Survival Time (MST) Days	% T/C	Avg. wt. change, gm day 4
Olivomycin	0.8	17.0	162	-2.4
	0.4	13.5	129	-2.6
Ex. 1	100	13.0	124	-2.0
	50	17.5	167	-2.2
	25	14.0	133	-0.5
Mitomycin C	4.8	19.0	211	-2.0
	3.2	22.0	244	-1.5
Ex. 2	8.0	12.0	133	-0.4
	6.0	12.5	139	-0.0
Ex. 4	8.0	12.5	139	-0.9
	6.0	13.0	144	0.1

Claims

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

1. A compound having the formula





I

wherein:

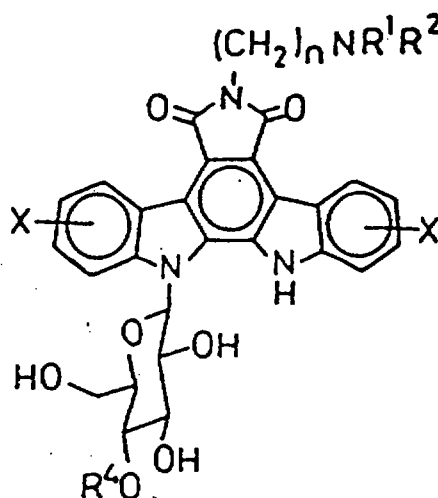
A^6 and A^{13} are selected from H and $-(CH_2)_nNR^1R^2$ and at least one of A^6 and A^{13} is $-(CH_2)_n-NR^1R^2$; n is an integer from 1 to 6;

R^1 and R^2 , independently, are selected from hydrogen, unsubstituted and substituted C_1 - C_6 alkyl, aralkyl having 1 to 3 carbons in the alkyl moiety and unsubstituted phenyl or phenyl substituted with 1 to 3 alkyl, alkoxy, hydroxy, halo, carboxyl, alkoxycarbonyl, and amino and mono- and di-lower-alkylamino groups in the aryl moiety, and aryl selected from unsubstituted phenyl and phenyl substituted with 1 to 3 alkyl, alkoxy, hydroxy, halo, amino, mono- and dialkylamino, nitro, carboxyl, alkoxycarbonyl, and cyano groups provided that both R^1 and R^2 are not each aryl and, when taken together, R^1 and R^2 may be selected from $-(CH_2)_4$ - and $(CH_2)_2-R^3-(CH_2)_2$ - to form a 5- or 6-membered ring together with the N-atom wherein R^3 is selected from CH_2 , NH, O and S;

X is selected from H, F, Cl, Br, C_1 - C_3 alkyl, OH, carboxyl, alkoxycarbonyl and alkoxy wherein the alkyl moiety is C_1 - C_3 alkyl, benzyloxy, amino, and mono- and dialkylamino; and

R^4 is selected from H and CH_3 ; and pharmaceutically acceptable acid addition and base salts thereof.

2. A compound according to Claim 1 having the formula



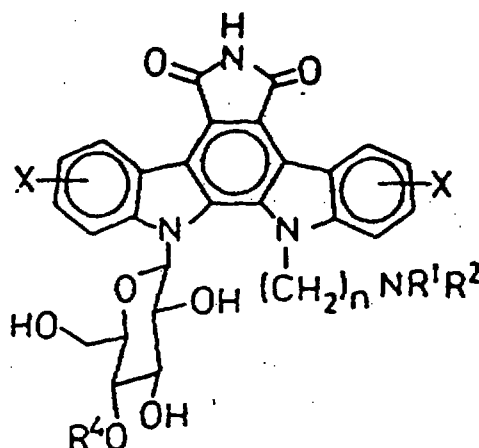
II

wherein:



R^1 , R^2 , X and R^4 are as defined in claim 1; and pharmaceutically acceptable acid addition and base salts thereof.

3. A compound according to Claim 2 wherein X is selected from H, Cl, Br, OH, OCH_3 and $OCH_2C_6H_5$.
4. A compound according to Claim 3 wherein n is selected from the integers 1, 2, and 3 and R^1 and R^2 , independently, are selected from H, C_1 - C_3 alkyl, and $-(CH_2)_4-$.
5. A compound according to Claim 4 wherein X is Cl in each of the 1- and 11-positions.
6. A compound according to Claim 5 wherein n is an integer selected from 2 and 3; and R^1 and R^2 are each C_2H_5 .
7. The compound of claim 6 having formula II wherein X is Cl in each of the 1- and 11-positions, R^4 is methyl, n is 2, and R^1 and R^2 are each C_2H_5 and the pharmaceutically acceptable acid addition salts thereof, in particular the hydrochloride.
8. A compound having the formula



III

wherein:

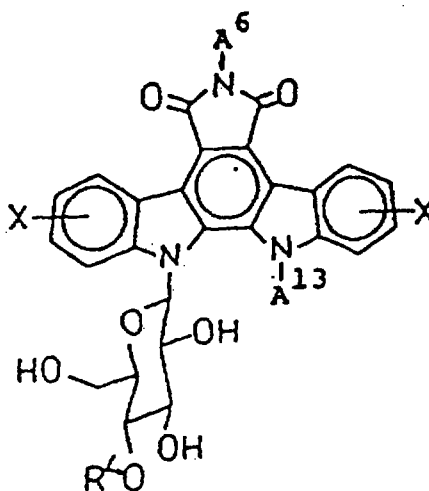
n, R^1 , R^2 , R^4 and X are as defined in claim 1; and pharmaceutically acceptable acid addition and base salts thereof.

9. A compound according to Claim 8 wherein R^4 is CH_3 and X is selected from Cl, Br, OH, OCH_3 and $OCH_2C_6H_5$ in each of the 1- and 11-positions of the ring system.
10. A compound according to Claim 9 wherein n is selected from the integers 1, 2, and 3 and R^1 and R^2 , independently, are selected from H, C_1 - C_3 alkyl, and $-(CH_2)_4-$.
11. A compound according to Claim 10 wherein X is Cl in each of the 1- and 11-positions.
12. A compound according to Claim 11 wherein n is an integer selected from 2 and 3; and R^1 and R^2 are each C_2H_5 .
13. A pharmaceutical composition comprising a tumor growth-inhibiting amount of at least one compound of anyone of claims 1 to 12 or a pharmaceutically acceptable acid addition or base salt thereof, and a pharmaceutically acceptable carrier.
14. The compounds of anyone of claims 1 to 12 for use in therapy.
15. The use of the compounds of anyone of claims 1 to 12 for preparing a pharmaceutical composition for



therapeutically treating a mammalian host affected by a malignant tumor.

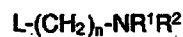
16. A process for producing a compound according to Claims 1 to 12 having the formula



wherein A^6 , A^{13} , X and R^4 are as defined in claims 1 to 12, comprising the steps of:

(a) reacting rebeccamycin or a derivative thereof, dissolved in a suitable inert solvent and held in an inert atmosphere, with an amount of strong base effective to obtain a reactive intermediate selected from (i) a rebeccamycin anion having the negative charge at the 6-position (ii) a rebeccamycin anion having the negative charge at the 13-position, and (iii) a rebeccamycin dianion having negative charges at both the 6- and 13-positions;

(b) reacting the reactive intermediate from step (a) with an aminoalkyl compound represented by the formula

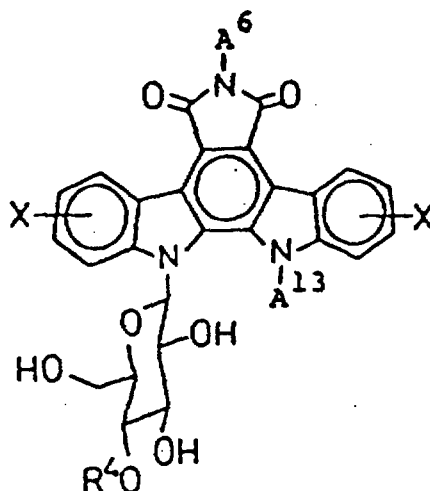


wherein L is a chemical leaving group and n, R^1 and R^2 are as defined hereinabove; and

(c) recovering the resulting aminoalkylated derivative of rebeccamycin from the mixture from step (b).

Claims for the following Contracting State : GR

1. A compound having the formula



I



wherein:

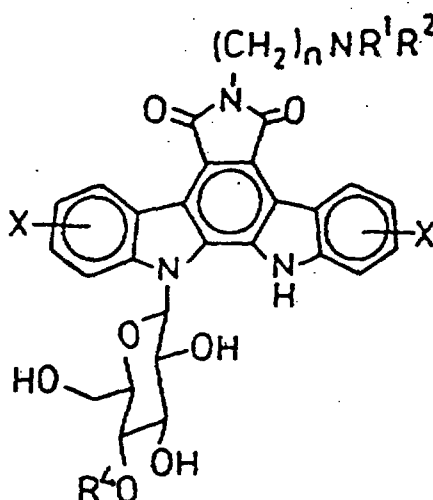
A⁶ and A¹³ are selected from H and $-(CH_2)_nNR^1R^2$ and at least one of A⁶ and A¹³ is $-(CH_2)_n-NR^1R^2$; n is an integer from 1 to 6;

R¹ and R², independently, are selected from hydrogen, unsubstituted and substituted C₁-C₆ alkyl, aralkyl having 1 to 3 carbons in the alkyl moiety and unsubstituted phenyl or phenyl substituted with 1 to 3 alkyl, alkoxy, hydroxy, halo, carboxyl, alkoxycarbonyl, and amino and mono- and di-lower-alkylamino groups in the aryl moiety, and aryl selected from unsubstituted phenyl and phenyl substituted with 1 to 3 alkyl, alkoxy, hydroxy, halo, amino, mono- and dialkylamino, nitro, carboxyl, alkoxycarbonyl, and cyano groups provided that both R¹ and R² are not each aryl and, when taken together, R¹ and R² may be selected from $-(CH_2)_4-$ and $(CH_2)_2-R^3-(CH_2)_2-$ to form a 5- or 6-membered ring together with the N-atom wherein R³ is selected from CH₂, NH, O and S;

X is selected from H, F, Cl, Br, C₁-C₃ alkyl, OH, carboxyl, alkoxycarbonyl and alkoxy wherein the alkyl moiety is C₁-C₃ alkyl, benzyloxy, amino, and mono- and dialkylamino; and

R⁴ is selected from H and CH₃; and pharmaceutically acceptable acid addition and base salts thereof.

2. A compound according to Claim 1 having the formula



II

wherein:

R¹, R², X and R⁴ are as defined in claim 1; and pharmaceutically acceptable acid addition and base salts thereof.

3. A compound according to Claim 2 wherein X is selected from H, Cl, Br, OH, OCH₃ and OCH₂C₆H₅.

4. A compound according to Claim 3 wherein n is selected from the integers 1, 2, and 3 and R¹ and R², independently, are selected from H, C₁-C₃ alkyl, and $-(CH_2)_4-$.

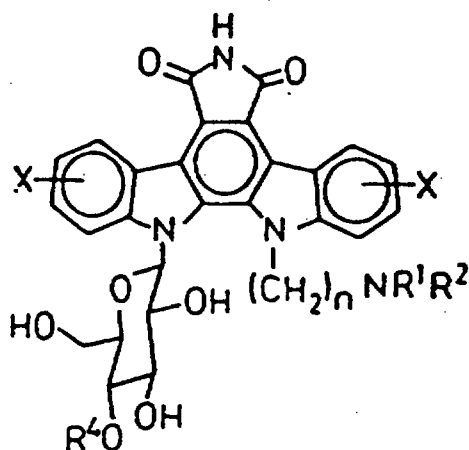
5. A compound according to Claim 4 wherein X is Cl in each of the 1- and 11-positions.

6. A compound according to Claim 5 wherein n is an integer selected from 2 and 3; and R¹ and R² are each C₂H₅.

7. The compound of claim 6 having formula II wherein X is Cl in each of the 1- and 11-positions, R⁴ is methyl, n is 2, and R¹ and R² are each C₂H₅ and the pharmaceutically acceptable acid addition salts thereof, in particular the hydrochloride.

8. A compound having the formula





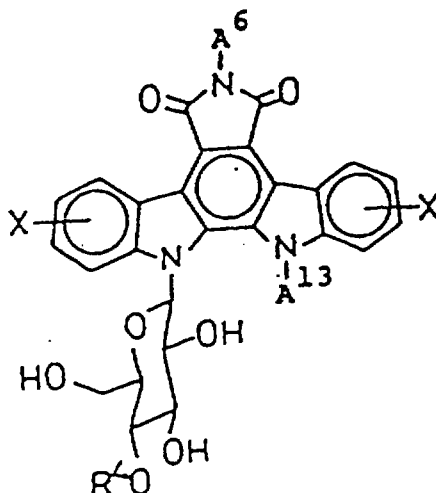
III

wherein:

n , R^1 , R^2 , R^4 and X are as defined in claim 1; and pharmaceutically acceptable acid addition and base salts thereof.

9. A compound according to Claim 8 wherein R^4 is CH_3 and X is selected from Cl , Br , OH , OCH_3 and $OCH_2C_6H_5$ in each of the 1- and 11-positions of the ring system.
10. A compound according to Claim 9 wherein n is selected from the integers 1, 2, and 3 and R^1 and R^2 , independently, are selected from H , C_1 - C_3 alkyl, and $-(CH_2)_4-$.
11. A compound according to Claim 10 wherein X is Cl in each of the 1- and 11-positions.
12. A compound according to Claim 11 wherein n is an integer selected from 2 and 3; and R^1 and R^2 are each C_2H_5 .
13. A process for preparing a pharmaceutical composition which comprises incorporating at least one compound of anyone of claims 1 to 12 or a pharmaceutically acceptable acid addition or base salt thereof, into a pharmaceutically acceptable carrier.
14. The compounds of anyone of claims 1 to 12 for use in therapy.
15. The use of the compounds of anyone of claims 1 to 12 for preparing a pharmaceutical composition for therapeutically treating a mammalian host affected by a malignant tumor.
16. A process for producing a compound according to Claims 1 to 12 having the formula

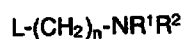




wherein A^6 , A^{13} , X and R^4 are as defined in claims 1 to 12, comprising the steps of:

(a) reacting rebeccamycin or a derivative thereof, dissolved in a suitable inert solvent and held in an inert atmosphere, with an amount of strong base effective to obtain a reactive intermediate selected from (i) a rebeccamycin anion having the negative charge at the 6-position (ii) a rebeccamycin anion having the negative charge at the 13-position, and (iii) a rebeccamycin dianion having negative charges at both the 6- and 13-positions;

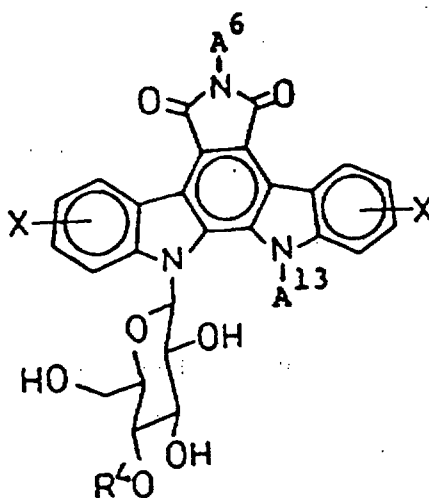
(b) reacting the reactive intermediate from step (a) with an aminoalkyl compound represented by the formula



wherein L is a chemical leaving group and n, R^1 and R^2 are as defined hereinabove; and
(c) recovering the resulting aminoalkylated derivative of rebeccamycin from the mixture from step (b).

Claims for the following Contracting State : ES

1. A process for preparing a compound having the formula



I

wherein:

A^6 and A^{13} are selected from H and $-(CH_2)_nNR^1R^2$ and at least one of A and A^{13} is $-(CH_2)_nNR^1R^2$;
n is an integer from 1 to 6;




 * C I M S *

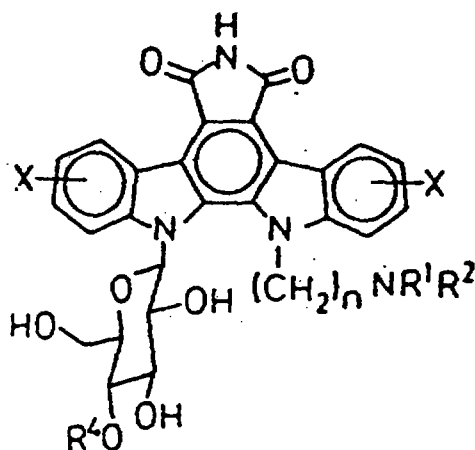
4. A process according to Claim 3 wherein n is selected from the integers 1, 2, and 3 and R^1 and R^2 , independently, are selected from H, C_1 - C_3 alkyl, and $-(CH_2)_4-$.

5. A process according to Claim 4 wherein X is Cl in each of the 1- and 11-positions.

6. A process according to Claim 5 wherein n is an integer selected from 2 and 3; and R^1 and R^2 are each C_2H_5 .

7. The process of claim 6 wherein the compounds obtained are those having formula II wherein X is Cl in each of the 1- and 11-positions, R^4 is methyl, n is 2, and R^1 and R^2 are each C_2H_5 or the pharmaceutically acceptable acid addition salts thereof, in particular the hydrochloride.

8. A process according to claim 1 wherein the compounds obtained are those having the formula



III

wherein:

n , R^1 , R^2 , R^4 and X are as defined in claim 1; or pharmaceutically acceptable acid addition and base salts thereof.

9. A process according to Claim 8 wherein R^4 is CH_3 and X is selected from Cl, Br, OH, OCH_3 and $OCH_2C_6H_5$ in each of the 1- and 11-positions of the ring system.

10. A process according to Claim 9 wherein n is selected from the integers 1, 2, and 3 and R^1 and R^2 , independently, are selected from H, C_1 - C_3 alkyl, and $-(CH_2)_4-$.

11. A process according to Claim 10 wherein X is Cl in each of the 1- and 11-positions.

12. A process according to Claim 11 wherein n is an integer selected from 2 and 3; and R^1 and R^2 are each C_2H_5 .

13. A process for preparing a pharmaceutical composition which comprises incorporating at least one compound as defined in anyone of claims 1 to 12 or a pharmaceutically acceptable acid addition or base salt thereof, into a pharmaceutically acceptable carrier.

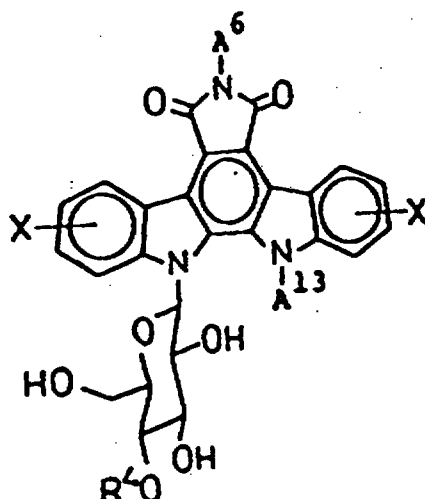
14. The use of the compounds as defined in anyone of claims 1 to 12 for preparing a pharmaceutical composition for therapeutically treating a mammalian host affected by a malignant tumor.

Patentansprüche

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

1. Verbindungen der Formel





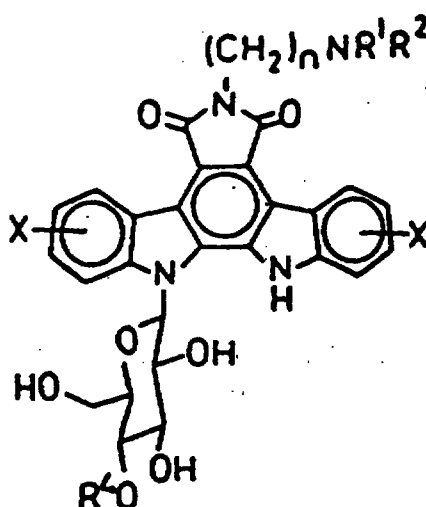
I

worin A^6 und A^{13} ausgewählt sind unter H und $-(CH_2)_nNR^1R^2$ und mindestens einer der Reste A^6 und A^{13} für $-(CH_2)_n-NR^1R^2$ steht, n eine ganze Zahl von 1 bis 6 ist;

R^1 und R^2 , unabhängig voneinander, ausgewählt sind unter Wasserstoff, unsubstituiertem und substituiertem C_1 - C_6 -Alkyl, Aralkyl mit 1 bis 3 Kohlenstoffen im Alkylrest und unsubstituiertem Phenyl oder Phenyl substituiert mit 1 bis 3 Alkyl, Alkoxy, Hydroxy, Halogen, Carboxyl, Alkoxycarbonyl und Amino und Mono- und Diniedrigalkylamino im Arylteil, und Aryl ausgewählt unter unsubstituiertem Phenyl und Phenyl, substituiert mit 1 bis 3 Alkyl, Alkoxy, Hydroxy, Halogen, Amino, Mono- und Dialkylamino, Nitro, Carboxyl, Alkoxycarbonyl und Cyano, vorausgesetzt, daß die beiden Reste R^1 und R^2 nicht jeweils Aryl sind, und R^1 und R^2 zusammengekommen unter $-(CH_2)_4-$ und unter $(CH_2)_2-R^3(CH_2)_2$ ausgewählt werden können, um zusammen mit dem N-Atom einen 5- oder 6-gliedrigen Ring zu bilden, wobei R^3 ausgewählt ist unter CH_2 , NH, O und S;

X ausgewählt ist unter H, F, Cl, Br, C_1 - C_3 -Alkyl, OH, Carboxy, Alkoxycarbonyl und Alkoxy, worin der Alkylrest für C_1 - C_3 -Alkyl steht; Benzyloxy, Amino und Mono- und Dialkylamino; und R^4 ausgewählt ist unter H und CH_3 ; und die pharmazeutisch akzeptablen Säureadditions- und Basensalze davon.

2. Verbindungen gemäß Anspruch 1 der Formel



II

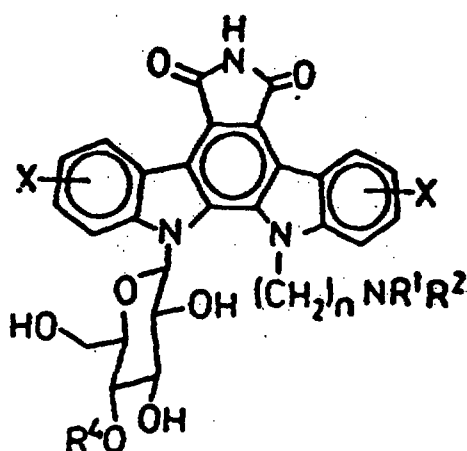
worin:

R^1 , R^2 , X und R^4 wie in Anspruch 1 definiert sind und die pharmazeutisch akzeptablen Säureadditions-



und Basensalze davon.

3. Verbindungen gemäß Anspruch 2, worin X unter H, Cl, Br, OH, OCH₃ und OCH₂C₆H₅ ausgewählt ist.
- 5 ☐ Verbindungen gemäß Anspruch 3, worin n unter den ganzen Zahlen 1, 2 und 3 ausgewählt ist und R¹ und R² unabhängig voneinander, ausgewählt sind unter H, C₁-C₃-Alkyl und -(CH₂)₄-.
5. Verbindungen gemäß Anspruch 4, worin X sowohl in 1- als auch in 11-Position für Cl steht.
- 10 6. Verbindungen gemäß Anspruch 5, worin n eine ganze Zahl, ausgewählt unter 2 und 3, ist; und R¹ und R² beide C₂H₅ sind.
7. Verbindung gemäß Anspruch 6 der Formel II, worin X sowohl in 1- als auch in 11-Position für Cl steht, R⁴ für Methyl steht, n für 2 steht und R¹ und R² beide C₂H₅ sind, und pharmazeutisch akzeptable Säureadditionssalze davon, insbesondere das Hydrochlorid.
- 15 8. Verbindungen der Formel



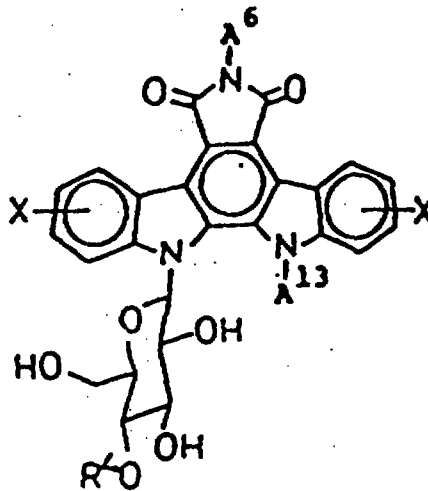
III

- 35 worin :
n, R¹, R², R⁴ und X wie in Anspruch 1 definiert sind und die pharmazeutisch akzeptablen Säureadditions- und Basensalze davon.
- 40 9. Verbindungen gemäß Anspruch 8, worin R⁴ für CH₃ steht und X ausgewählt ist unter Cl, Br, OH, OCH₃ und OCH₂C₆H₅ in jeder der 1- und 11-Positionen des Ringsystems.
10. Verbindungen gemäß Anspruch 9, worin n ausgewählt ist unter den ganzen Zahlen 1, 2 und 3 und R¹ und R² unabhängig voneinander unter H, C₁-C₃-Alkyl und -(CH₂)₄- ausgewählt sind.
- 45 11. Verbindungen gemäß Anspruch 10, worin X sowohl in 1- als auch in 11-Position für Cl steht.
12. Verbindungen gemäß Anspruch 11, worin n eine ganze Zahl ist, ausgewählt unter 2 und 3, und R¹ und R² beide C₂H₅ sind.
- 50 13. Pharmazeutische Zusammensetzung, die eine das Wachstum eines Tumors inhibierende Menge mindestens einer Verbindung nach einem der Ansprüche 1 bis 12 oder eines pharmazeutisch akzeptablen Säureadditions- oder dem Basensalzes davon und einen pharmazeutisch akzeptablen Träger umfaßt.
- 55 14. Verbindungen nach einem der Ansprüche 1 bis 12 zur Anwendung in der Therapie.
15. Verwendung der Verbindungen nach einem der Ansprüche 1 bis 12 zur Herstellung einer pharmazeutischen Zusammensetzung für die therapeutische Behandlung eines Säugetierwirtes, der von einem



malignen Tumor befallen ist.

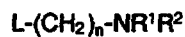
16. Verfahren zur Herstellung einer Verbindung gemäß den Ansprüchen 1 bis 12 der Formel



worin A^6 , A^{13} , X und R^4 wie in den Ansprüchen 1 bis 12 definiert sind, das folgende Schritte umfaßt:

(a) Umsetzung von Rebeccamycin oder einem Derivat davon, gelöst in einem geeigneten inerten Lösungsmittel und in einer inerten Atmosphäre gehalten, mit einer Menge einer starken Base, die zur Erreichung einer reaktiven Zwischenstufe wirksam ist, die ausgewählt ist unter (i) einem Rebeccamycin-Anion, mit der negativen Ladung in 6-Position, (ii) einem Rebeccamycin-Anion mit der negativen Ladung in 13-Position und (iii) einem Rebeccamycin-Dianion mit negativen Ladungen in 6-Position und 13-Position;

(b) Umsetzung der reaktiven Zwischenstufe aus Schritt (a) mit einer Aminoalkyl-Verbindung der Formel



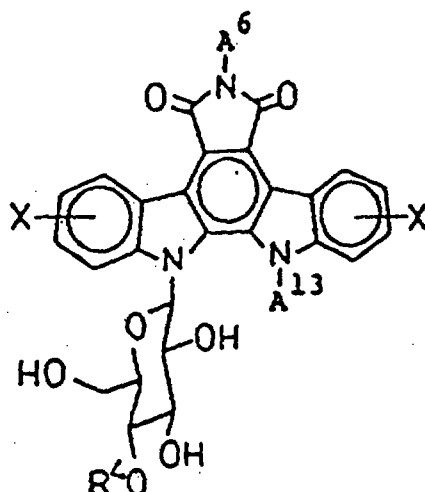
worin L eine chemische Abgangsgruppe ist und n, R^1 und R^2 wie oben definiert sind und

(c) die Gewinnung des sich ergebenden aminoalkylierten Derivates von Rebeccamycin aus der Mischung aus Schritt (b).

Patentansprüche für folgenden Vertragsstaat : GR

1. Verbindungen der Formel





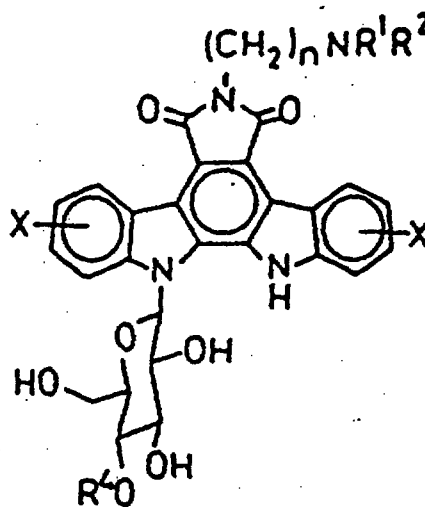
I

worin A^6 und A^{13} ausgewählt sind unter H und $-(CH_2)_nNR^1R^2$ und mindestens einer der Reste A^6 und A^{13} für $-(CH_2)_n-NR^1R^2$ steht, n eine ganze Zahl von 1 bis 6 ist;

R^1 und R^2 , unabhängig voneinander, ausgewählt sind unter Wasserstoff, unsubstituiertem und substituiertem C_1 - C_6 -Alkyl, Aralkyl mit 1 bis 3 Kohlenstoffen im Alkylrest und unsubstituiertem Phenyl oder Phenyl substituiert mit 1 bis 3 Alkyl, Alkoxy, Hydroxy, Halogen, Carboxyl, Alkoxycarbonyl und Amino und Mono- und Diniedrigalkylamino im Arylteil, und Aryl ausgewählt unter unsubstituiertem Phenyl und Phenyl, substituiert mit 1 bis 3 Alkyl, Alkoxy, Hydroxy, Halogen, Amino, Mono- und Dialkylamino, Nitro, Carboxyl, Alkoxycarbonyl und Cyano, vorausgesetzt, daß die beiden Reste R^1 und R^2 nicht jeweils Aryl sind, und R^1 und R^2 zusammengekommen unter $-(CH_2)_4-$ und unter $(CH_2)_2-R^3(CH_2)_2$ ausgewählt werden können, um zusammen mit dem N-Atom einen 5- oder 6-gliedrigen Ring zu bilden, wobei R^3 ausgewählt ist unter CH_2 , NH, O und S;

X ausgewählt ist unter H, F, Cl, Br, C_1 - C_3 -Alkyl, OH, Carboxy, Alkoxycarbonyl und Alkoxy, worin der Alkylrest für C_1 - C_3 -Alkyl steht, Benzyl, Amino und Mono- und Dialkylamino; und R^4 ausgewählt ist unter H und CH_3 ; und die pharmazeutisch akzeptablen Säureadditions- und Basensalze davon.

2. Verbindungen gemäß Anspruch 1 der Formel



II

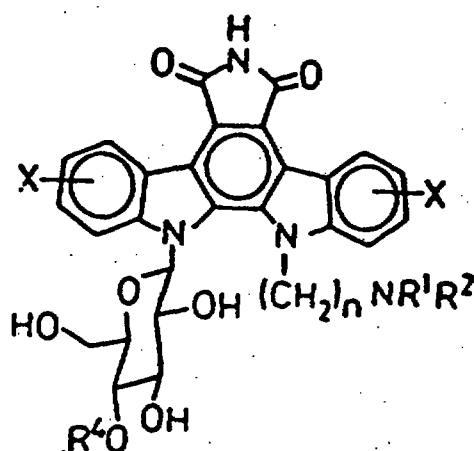
worin:

R^1 , R^2 , X und R^4 wie in Anspruch 1 definiert sind und die pharmazeutisch akzeptablen Säureadditions-



und Basensalze davon.

3. Verbindungen gemäß Anspruch 2, worin X unter H, Cl, Br, OH, OCH₃ und OCH₂C₆H₅ ausgewählt ist.
- 5 4. Verbindungen gemäß Anspruch 3, worin n unter den ganzen Zahlen 1, 2 und 3 ausgewählt ist und R¹ und R² unabhängig voneinander, ausgewählt sind unter H, C₁-C₃-Alkyl und -(CH₂)₄-.
5. Verbindungen gemäß Anspruch 4, worin X sowohl in 1- als auch in 11-Position für Cl steht.
- 10 6. Verbindungen gemäß Anspruch 5, worin n eine ganze Zahl, ausgewählt unter 2 und 3, ist; und R¹ und R² beide C₂H₅ sind.
7. Verbindung gemäß Anspruch 6 der Formel II, worin X sowohl in 1- als auch in 11-Position für Cl steht, R⁴ für Methyl steht, n für 2 steht und R¹ und R² beide C₂H₅ sind, und pharmazeutisch akzeptable Säureadditionssalze davon, insbesondere das Hydrochlorid.
- 15 8. Verbindungen der Formel

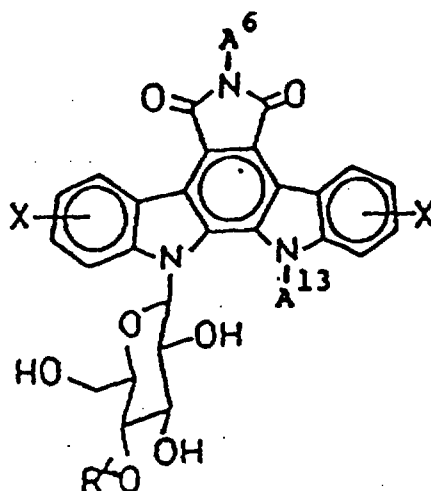


III

- 35 worin :
n, R¹, R², R⁴ und X wie in Anspruch 1 definiert sind und die pharmazeutisch akzeptablen Säureadditions- und Basensalze davon.
- 40 9. Verbindungen gemäß Anspruch 8, worin R⁴ für CH₃ steht und X ausgewählt ist unter Cl, Br, OH, OCH₃ und OCH₂C₆H₅ in jeder der 1- und 11-Positionen des Ringsystems.
10. Verbindungen gemäß Anspruch 9, worin n ausgewählt ist unter den ganzen Zahlen 1, 2 und 3 und R¹ und R² unabhängig voneinander unter H, C₁-C₃-Alkyl und -(CH₂)₄- ausgewählt sind.
- 45 11. Verbindungen gemäß Anspruch 10, worin X sowohl in 1- als auch in 11-Position für Cl steht.
12. Verbindungen gemäß Anspruch 11, worin n eine ganze Zahl ist, ausgewählt unter 2 und 3, und R¹ und R² beide C₂H₅ sind.
- 50 13. Verfahren zur Herstellung einer pharmazeutischen Zusammensetzung, wobei man wenigstens eine Verbindung nach einem der Ansprüche 1 bis 12 oder ein pharmazeutisch akzeptables Säureadditions- oder Basensalz davon einem pharmazeutisch akzeptablen Träger einverleiht.
14. Verbindungen nach einem der Ansprüche 1 bis 12 zur Anwendung in der Therapie.
- 55 15. Verwendung der Verbindungen nach einem der Ansprüche 1 bis 12 zur Herstellung einer pharmazeutischen Zusammensetzung für die therapeutische Behandlung eines Säugetierwirtes, der von einem malignen Tumor befallen ist.

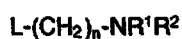


16. Verfahren zur Herstellung einer Verbindung gemäß den Ansprüchen 1 bis 12 der Formel



worin A^6 , A^{13} , X und R^4 wie in den Ansprüchen 1 bis 12 definiert sind, das folgende Schritte umfaßt:

- (a) Umsetzung von Rebeccamycin oder einem Derivat davon, gelöst in einem geeigneten inerten Lösungsmittel und in einer inerten Atmosphäre gehalten, mit einer Menge einer starken Base, die zur Erreichung einer reaktiven Zwischenstufe wirksam ist, die ausgewählt ist unter (i) einem Rebeccamycin-Anion, mit der negativen Ladung in 6-Position, (ii) einem Rebeccamycin-Anion mit der negativen Ladung in 13-Position und (iii) einem Rebeccamycin-Dianion mit negativen Ladungen in 6-Position und 13-Position;
- (b) Umsetzung der reaktiven Zwischenstufe aus Schritt (a) mit einer Aminoalkyl-Verbindung der Formel

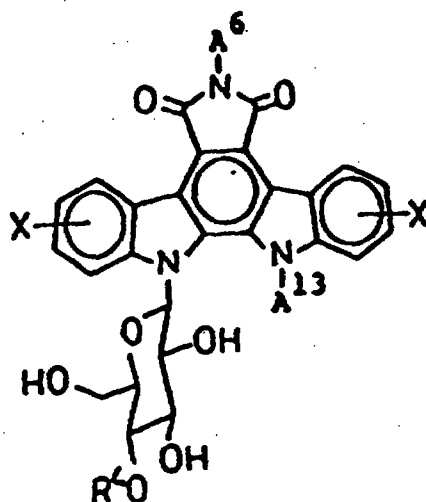


worin L eine chemische Abgangsgruppe ist und n , R^1 und R^2 wie oben definiert sind und

- (c) die Gewinnung des sich ergebenden aminoalkylierten Derivates von Rebeccamycin aus der Mischung aus Schritt (b).

Patentansprüche für folgenden Vertragsstaat : ES

1. Verfahren zur Herstellung der Verbindungen der Formel



I



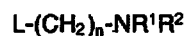
worin A^6 und A^{13} ausgewählt sind unter H und $-(CH_2)_nNR^1R^2$ und mindestens einer der Reste A^6 und A^{13} für $-(CH_2)_n-NR^1R^2$ steht, n eine ganze Zahl von 1 bis 6 ist;

R^1 und R^2 , unabhängig voneinander, ausgewählt sind unter Wasserstoff, unsubstituiertem und substituiertem C_1 - C_6 -Alkyl, Aryl mit 1 bis 3 Kohlenstoffen im Alkylrest und unsubstituiertem Phenyl oder Phenyl substituiert mit 1 bis 3 Alkyl, Alkoxy, Hydroxy, Halogen, Carboxyl, Alkoxy-carbonyl und Amino und Mono- und Diniedrigalkylamino im Arylteil, und Aryl ausgewählt unter unsubstituiertem Phenyl und Phenyl, substituiert mit 1 bis 3 Alkyl, Alkoxy, Hydroxy, Halogen, Amino, Mono- und Dialkylamino, Nitro, Carboxyl, Alkoxy-carbonyl und Cyano, vorausgesetzt, daß die beiden Reste R^1 und R^2 nicht jeweils Aryl sind, und R^1 und R^2 zusammengekommen unter $-(CH_2)_4$ - und unter $(CH_2)_2-R^3(CH_2)_2$ ausgewählt werden können, um zusammen mit den N-Atom einen 5- oder 6-gliedrigen Ring zu bilden, wobei R^3 ausgewählt ist unter CH_2 , NH, O und S;

X ausgewählt ist unter H, F, Cl, Br, C_1 - C_3 -Alkyl, OH, Carboxy, Alkoxy-carbonyl und Alkoxy, worin der Alkylrest für C_1 - C_3 -Alkyl steht, Benzoyloxy, Amino und Mono- und Dialkylamino steht; und R^4 ausgewählt ist unter H und CH_3 ; und die pharmazeutisch akzeptablen Säureadditions- und Basensalze davon, das folgende Schritte umfaßt:

(a) Umsetzung von Rebeccamycin oder einem Derivat davon, gelöst in einem geeigneten interen Lösungsmittel und in einer inerten Atmosphäre gehalten, mit einer Menge einer starken Base, die zur Erreichung einer reaktiven Zwischenstufe wirksam ist, die ausgewählt ist unter (i) einem Rebeccamycin-Anion, mit der negativen Ladung in 6-Position, (ii) einem Rebeccamycin-Anion mit der negativen Ladung in 13-Position und (iii) einem Rebeccamycin-Dianion mit negativen Ladungen in 6-Position und 13-Position;

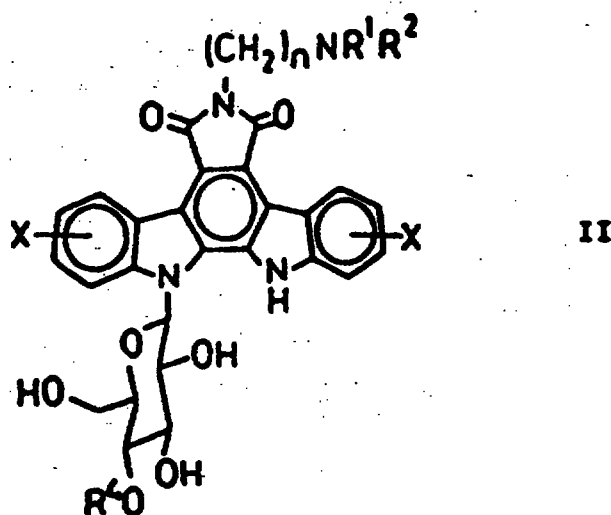
(b) Umsetzung der reaktiven Zwischenstufe aus Schritt (a) mit einer Aminoalkyl-Verbindung der Formel



worin L eine chemische Abgangsgruppe ist und n, R^1 und R^2 , wie oben definiert sind und

(c) die Gewinnung des sich ergebenden aminoalkylierten Derivates von Rebeccamycin aus der Mischung aus Schritt (b).

2. Verfahren nach Anspruch 1, worin die erhaltenen Verbindungen diejenigen der Formel



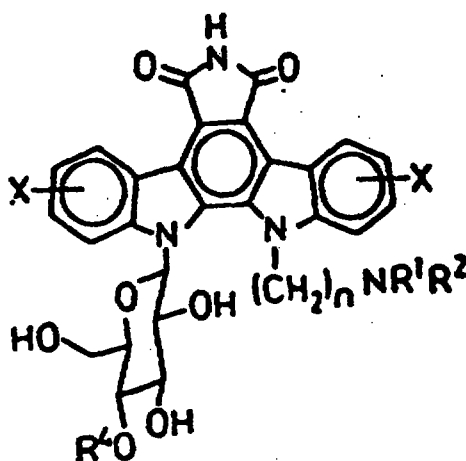
sind, worin:

R^1 , R^2 , X und R^4 wie in Anspruch 1 definiert sind oder die pharmazeutisch akzeptable Säureadditions- und Basensalze davon.

3. Verfahren nach Anspruch 2, worin X unter H, Cl, Br, OH, OCH_3 und $OCH_2C_6H_5$ ausgewählt ist.



4. Verfahren nach Anspruch 3, worin n unter den ganzen Zahlen 1, 2 und 3 ausgewählt ist und R^1 und R^2 unabhängig voneinander, ausgewählt sind unter H, C_1 - C_3 -Alkyl und $-(CH_2)_4-$.
5. Verfahren nach Anspruch 4, worin X sowohl in 1- als auch in 11-Position für Cl steht.
6. Verfahren nach Anspruch 5, worin n eine ganze Zahl, ausgewählt unter 2 und 3, ist; und R^1 und R^2 beide C_2H_5 sind.
7. Verfahren nach Anspruch 6 worin die erhaltenen Verbindungen diejenigen der Formel II, worin X sowohl in 1-als auch in 11-Position für Cl steht, R^4 für Methyl steht, n für 2 steht und R^1 und R^2 beide C_2H_5 sind, und oder die pharmazeutisch akzeptablen Säureadditionssalze davon, insbesondere das Hydrochlorid, sind.
8. Verfahren nach Anspruch 1, worin die erhaltenen Verbindungen diejenigen der Formel



worin

n , R^1 , R^2 , R^4 und X wie in Anspruch 1 definiert sind oder die pharmazeutisch akzeptablen Säureadditions- und Basensalze davon sind.

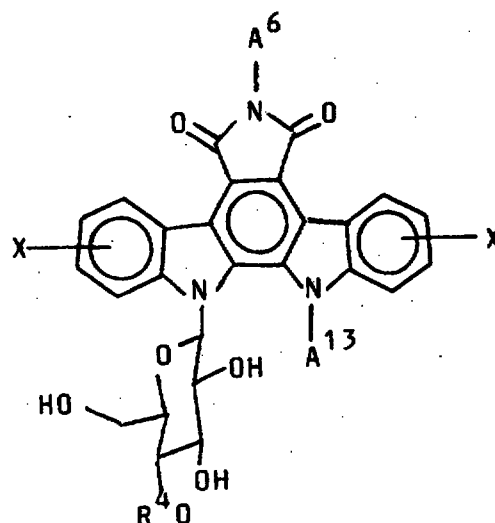
9. Verfahren nach Anspruch 8, worin R^4 für CH_3 steht und X ausgewählt ist unter Cl, Br, OH, OCH_3 und $OCH_2C_6H_5$ in jeder der 1- und 11-Positionen des Ringsystems.
10. Verfahren nach Anspruch 9, worin n ausgewählt ist unter den ganzen Zahlen 1, 2 und 3 und R^1 und R^2 unabhängig voneinander unter H, C_1 - C_3 -Alkyl und $-(CH_2)_4-$ ausgewählt sind.
11. Verfahren nach Anspruch 10, worin X sowohl in 1- als auch in 11-Position für Cl steht.
12. Verfahren nach Anspruch 11, worin n eine ganze Zahl ist, ausgewählt unter 2 und 3, und R^1 und R^2 beide C_2H_5 sind.
13. Verfahren zur Herstellung einer pharmazeutischen Zusammensetzung, wobei man wenigstens eine Verbindung wie in einem der Ansprüche 1 bis 12 definiert oder ein pharmazeutisch akzeptables Säureadditions- oder Basensalz davon einem pharmazeutisch akzeptablen Träger einverleibt.
14. Verwendung der Verbindungen wie in einem der Ansprüche 1 bis 12 definiert zur Herstellung einer pharmazeutischen Zusammensetzung zur therapeutischen Behandlung eines von einem malignen Tumor befallenen Säugetierwirts.

Revendications

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



1. Composé ayant pour formule



où :

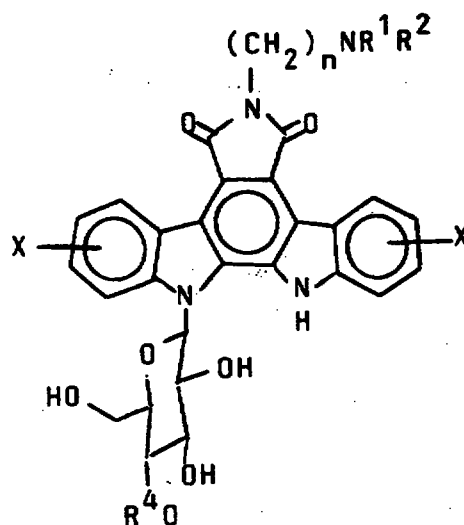
A^6 et A^{13} sont choisis parmi H et $-(CH_2)_nNR^1R^2$ et au moins un de A^6 et A^{13} est $-(CH_2)_n-NR^1R^2$;
 n est un nombre entier de 1 à 6 ;

R^1 et R^2 , indépendamment, sont choisis parmi hydrogène, alkyle C_1-C_6 non substitué et substitué, aralkyle ayant 1 à 3 carbones dans le fragment alkyle et phényle non substitué ou phényle substitué par 1 à 3 groupes alkyle, alcoxy, hydroxy, halo, carboxyle, alcoxycarbonyle et amino et mono- et dialkylamino inférieur, dans le fragment aryle, et aryle choisi parmi phényle non substitué et phényle substitué par 1 à 3 groupes alkyle, alcoxy, hydroxy, halo, amino, mono- et dialkylamino, nitro, carboxyle, alcoxycarbonyle et cyano, à condition que R^1 et R^2 ne soient pas tous deux aryle et, lorsqu'ils sont pris ensemble, R^1 et R^2 peuvent être choisis parmi $-(CH_2)_4-$ et $(CH_2)_2-R^3-(CH_2)_2-$ pour former un noyau à 5 ou 6 membres avec l'atome N où R^3 est choisi parmi CH_2 , NH , O et S ;

X est choisi parmi H, F, Cl, Br, alkyle C_1-C_3 , OH, carboxyle, alcoxycarbonyle et alcoxy où le fragment alkyle est alkyle C_1-C_3 , benzyloxy, amino et mono- et dialkylamino ; et

R^4 est choisi parmi H et CH_3 ; et leurs sels d'addition d'acide et sels de base acceptables en pharmacie.

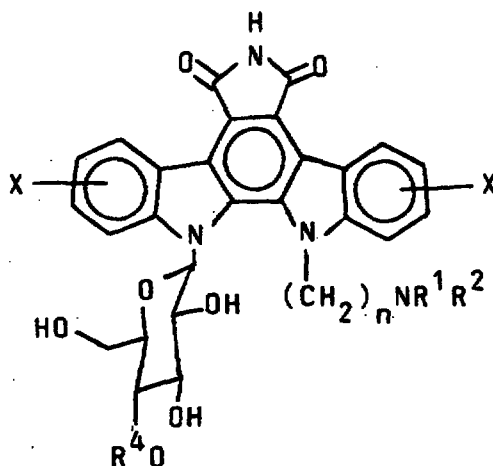
2. Composé selon la revendication 1 ayant pour formule



où

R^1 , R^2 , X et R^4 sont tels que définis à la revendication 1 ; et leurs sels d'addition d'acide et de base acceptables en pharmacie.

3. Composé selon la revendication 2, où X est choisi parmi H, Cl, Br, OH, OCH_3 et $OCH_2C_6H_5$.
4. Composé selon la revendication 3, où n est choisi parmi les nombres entiers 1, 2 et 3 et R^1 et R^2 , indépendamment, sont choisis parmi H, alkyle C_1-C_3 et $-(CH_2)_4-$.
5. Composé selon la revendication 4, où X est Cl à chacune des positions 1 et 11.
6. Composé selon la revendication 5, où n est un nombre entier choisi parmi 2 et 3, et chacun de R^1 et R^2 est C_2H_5 .
7. Composé de la revendication 6 ayant la formule II où X est Cl à chacune des positions 1 et 11, R^4 est méthyle, n est 2 et chacun de R^1 et R^2 est C_2H_5 et leurs sels d'addition d'acide acceptables en pharmacie, en particulier le chlorhydrate.
8. Composé ayant pour formule



III

où

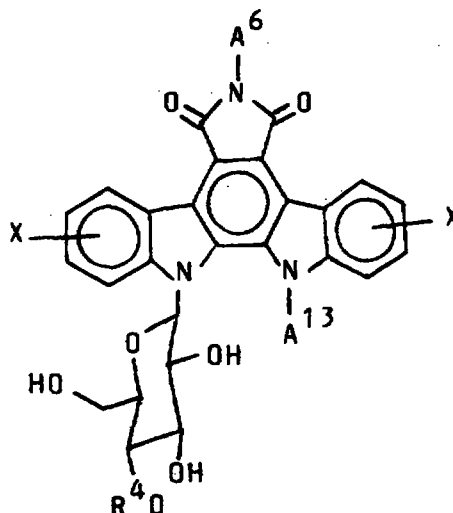
n, R^1 , R^2 , R^4 et X sont tels que définis à la revendication 1 ; et leurs sels d'addition d'acide et sels de base acceptables en pharmacie.

9. Composé selon la revendication 8, où R^4 est CH_3 et X est choisi parmi Cl, Br, OH, OCH_3 et $OCH_2C_6H_5$ à chacune des positions 1 et 11 du système du noyau.
10. Composé selon la revendication 9, où n est choisi parmi les nombres entiers 1, 2 et 3 et R^1 et R^2 , indépendamment, sont choisis parmi H, alkyle C_1-C_3 et $-(CH_2)_4-$.
11. Composé selon la revendication 10, où X est Cl dans chacune des positions 1 et 11.
12. Composé selon la revendication 11, où n est un nombre entier choisi parmi 2 et 3 ; et R^1 et R^2 sont chacun C_2H_5 .
13. Composition pharmaceutique comprenant une quantité inhibant la croissance d'une tumeur d'au moins un composé selon l'une quelconque des revendications 1 à 12 ou bien son sel d'addition d'acide ou sel de base acceptable en pharmacie, ainsi qu'un support acceptable en pharmacie.
14. Composés selon l'une quelconque des revendications 1 à 12 pour une utilisation en thérapie.



15. Utilisation des composés selon l'une quelconque des revendications 1 à 12 pour préparer une composition pharmaceutique pour le traitement thérapeutique d'un hôte mammifère affecté d'une tumeur maligne.

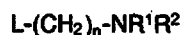
5 16. Procédé de production d'un composé selon les revendications 1 à 12 ayant pour formule



où A^6 , A^{13} , X et R^4 sont tels que définis aux revendications 1 à 12, comprenant les étapes de :

(a) faire réagir la rébeccamycine ou son dérivé, dissoute dans un solvant inerte approprié et maintenue dans une atmosphère inerte, avec une quantité d'une base forte efficace pour obtenir un intermédiaire réactif choisi parmi (i) un anion de rébeccamycine ayant la charge négative à la position 6, (ii) un anion de rébeccamycine ayant la charge négative à la position 13 et (iii) un dianion de rébeccamycine ayant des charges négatives aux deux positions 6 et 13 ;

(b) faire réagir l'intermédiaire réactif de l'étape (a) avec un composé d'aminoalkyle représenté par la formule



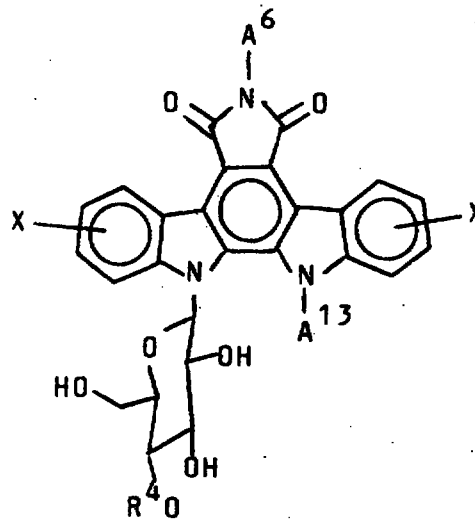
où L est un groupe chimique partant et n, R^1 et R^2 sont tels que définis ci-dessus ; et

(c) récupérer le dérivé aminoalkylé résultant de rébeccamycine du mélange de l'étape (b).

40 Revendications pour l'Etat contractant suivant : GR

1. Composé ayant pour formule





I

où :

A^6 et A^{13} sont choisis parmi H et $-(CH_2)_nNR^1R^2$ et au moins un de A^6 et A^3 est $-(CH_2)_n-NR^1R^2$;
 n est un nombre entier de 1 à 6 ;

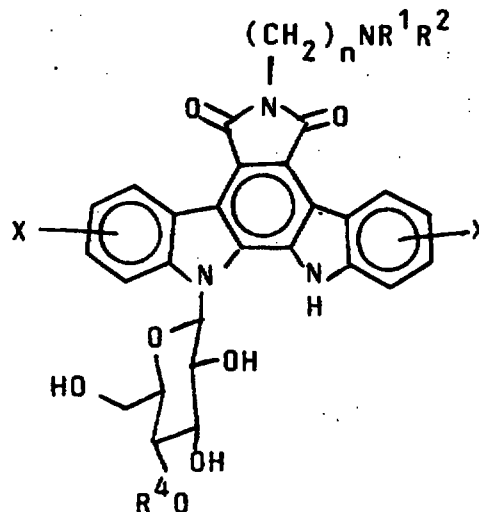
R^1 et R^2 , indépendamment, sont choisis parmi hydrogène, alkyle C_1-C_6 non substitué et substitué, aralkyle ayant 1 à 3 carbones dans le fragment alkyle et phényle non substitué ou phényle substitué par 1 à 3 groupes alkyle, alcoxy, hydroxy, halo, carboxyle, alcoxycarbonyle et amino et mono- et dialkylamino inférieur, dans le fragment aryle, et aryle choisi parmi phényle non substitué et phényle substitué par 1 à 3 groupes alkyle, alcoxy, hydroxy, halo, amino, mono- et dialkylamino, nitro, carboxyle, alcoxycarbonyle et cyano, à condition que R^1 et R^2 ne soient pas tous deux aryle et, lorsqu'ils sont pris ensemble, R^1 et R^2 peuvent être choisis parmi $-(CH_2)_4-$ et $(CH_2)_2-R^3-(CH_2)_2-$ pour former un noyau à 5 ou 6 membres avec l'atome N où R^3 est choisi parmi CH_2 , NH, O et S ;

X est choisi parmi H, F, Cl, Br, alkyle C_1-C_3 , OH, carboxyle, alcoxycarbonyle et alcoxy où le fragment alkyle est alkyle C_1-C_3 , benzyloxy, amino et mono- et dialkylamino ; et

R^4 est choisi parmi H et CH_3 ; et

leurs sels d'addition d'acide et sels de base acceptables en pharmacie.

2. Composé selon la revendication 1 ayant pour formule



II

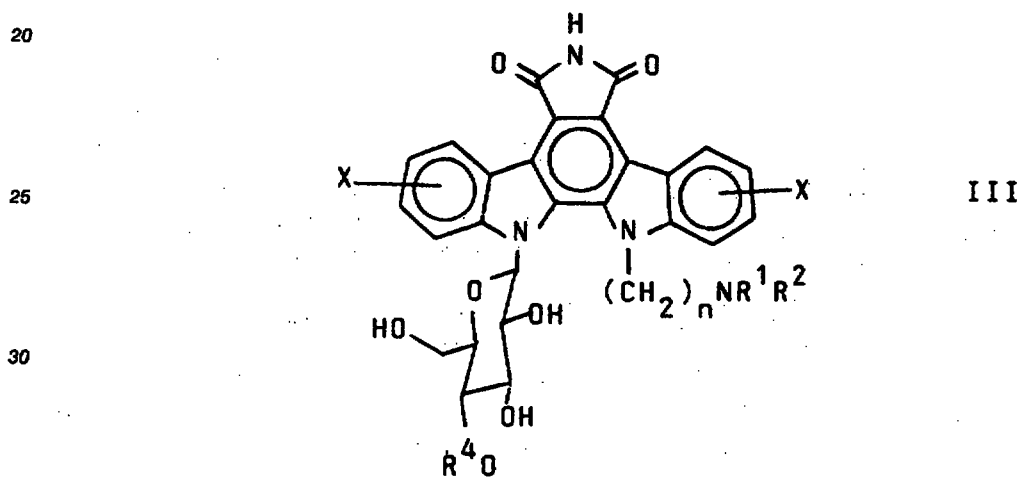
où

R^1 , R^2 , X et R^4 sont tels que définis à la revendication 1 ; et leurs sels d'addition d'acide et de base



acceptables en pharmacie.

3. Composé selon la revendication 2, où X est choisi parmi H, Cl, Br, OH, OCH₃ et OCH₂C₆H₅.
- 5 4. Composé selon la revendication 3, où n est choisi parmi les nombres entiers 1, 2 et 3 et R¹ et R², indépendamment, sont choisis parmi H, alkyle C₁-C₃ et -(CH₂)₄-.
5. Composé selon la revendication 4, où X est Cl à chacune des positions 1 et 11.
- 10 6. Composé selon la revendication 5, où n est un nombre entier choisi parmi 2 et 3, et chacun de R¹ et R² est C₂H₅.
7. Composé de la revendication 6 ayant la formule II où X est Cl à chacune des positions 1 et 11, R⁴ est méthyle, n est 2 et chacun de R¹ et R² est C₂H₅ et leurs sels d'addition d'acide acceptables en pharmacie, en particulier le chlorhydrate.
- 15 8. Composé ayant pour formule



où

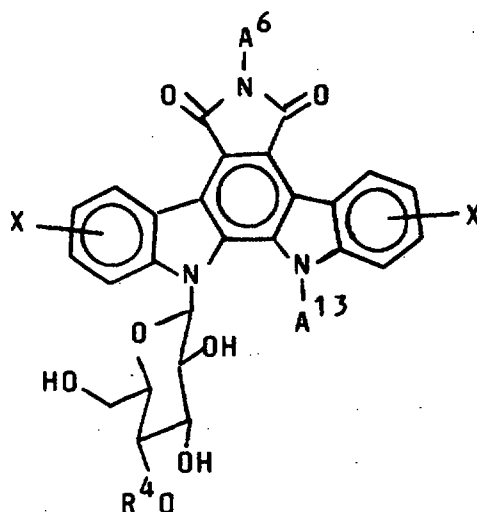
n, R¹, R², R⁴ et X sont tels que définis à la revendication 1 ; et leurs sels d'addition d'acide et sels de base acceptables en pharmacie.

- 40 9. Composé selon la revendication 8, où R⁴ est CH₃ et X est choisi parmi Cl, Br, OH, OCH₃ et OCH₂C₆H₅ à chacune des positions 1 et 11 du système du noyau.
10. Composé selon la revendication 9, où n est choisi parmi les nombres entiers 1, 2 et 3 et R¹ et R², indépendamment, sont choisis parmi H, alkyle C₁-C₃ et -(CH₂)₄-.
- 45 11. Composé selon la revendication 10, où X est Cl dans chacune des positions 1 et 11
12. Composé selon la revendication 11, où n est un nombre entier choisi parmi 2 et 3 ; et R¹ et R² sont chacun C₂H₅.
- 50 13. Procédé de préparation d'une composition pharmaceutique qui comprend l'incorporation d'au moins un composé selon l'une quelconque des revendications 1 à 12 ou son sel d'addition d'acide ou sel de base acceptable en pharmacie, dans un support acceptable en pharmacie.
- 55 14. Composés selon l'une quelconque des revendications 1 à 12 pour une utilisation en thérapie.
15. Utilisation des composés selon l'une quelconque des revendications 1 à 12 pour préparer une composition pharmaceutique pour le traitement thérapeutique d'un hôte mammifère affecté d'une



tumeur maligne.

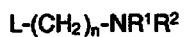
16. Procédé de production d'un composé selon les revendications 1 à 12 ayant pour formule



où A^6 , A^{13} , X et R^4 sont tels que définis aux revendications 1 à 12, comprenant les étapes de :

(a) faire réagir la rébeccamycine ou son dérivé, dissoute dans un solvant inerte approprié et maintenue dans une atmosphère inerte, avec une quantité d'une base forte efficace pour obtenir un intermédiaire réactif choisi parmi (i) un anion de rébeccamycine ayant la charge négative à la position 6, (ii) un anion de rébeccamycine ayant la charge négative à la position 13 et (iii) un dianion de rébeccamycine ayant des charges négatives aux deux positions 6 et 13 ;

(b) faire réagir l'intermédiaire réactif de l'étape (a) avec un composé d'aminoalkyle représenté par la formule

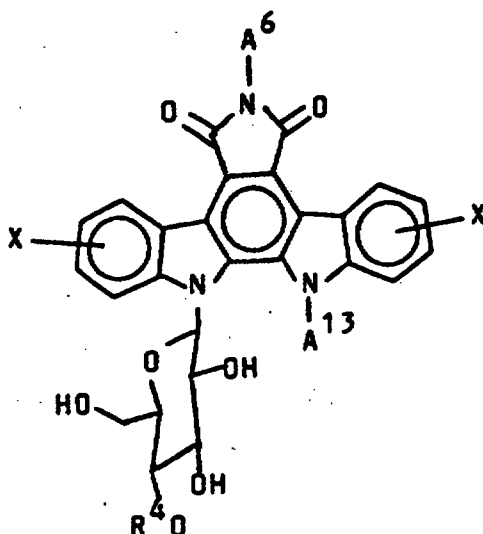


où L est un groupe chimique partant et n, R^1 et R^2 sont tels que définis ci-dessus ; et

(c) récupérer le dérivé aminoalkylé résultant de rébeccamycine du mélange de l'étape (b).

Revendications pour l'Etat contractant suivant : ES

1. Procédé pour la préparation d'un composé ayant la formule



I



où :

A⁶ et A¹³ sont choisis parmi H et $-(CH_2)_nNR^1R^2$ et au moins un de A⁶ et A¹³ est $-(CH_2)_n-NR^1R^2$;
n est un nombre entier de 1 à 6 ;

R¹ et R², indépendamment, sont choisis parmi hydrogène, alkyle C₁-C₆ non substitué et substitué, aralkyle ayant 1 à 3 carbones dans le fragment alkyle et phényle non substitué ou phényle substitué par 1 à 3 groupes alkyle, alcoxy, hydroxy, halo, carboxyle, alcoxycarbonyle et amino et mono- et dialkylamino inférieur, dans le fragment aryle, et aryle choisi parmi phényle non substitué et phényle substitué par 1 à 3 groupes alkyle, alcoxy, hydroxy, halo, amino, mono- et dialkylamino, nitro, carboxyle, alcoxycarbonyle et cyano, à condition que R¹ et R² ne soient pas tous deux aryle et, lorsqu'ils sont pris ensemble, R¹ et R² peuvent être choisis parmi $-(CH_2)_4-$ et $(CH_2)_2-R^3-(CH_2)_2-$ pour former un noyau à 5 ou 6 membres avec l'atome N où R³ est choisi parmi CH₂, NH, O et S ;

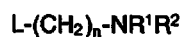
X est choisi parmi H, F, Cl, Br, alkyle C₁-C₃, OH, carboxyle, alcoxycarbonyle et alcoxy où le fragment alkyle est alkyle C₁-C₃, benzyloxy, amino et mono- et dialkylamino ; et

R⁴ est choisi parmi H et CH₃ ; et

leurs sels d'addition d'acide et sels de base acceptables en pharmacie, comprenant les étapes de :

(a) faire réagir la rébeccamycine ou son dérivé, dissoute dans un solvant inerte approprié et maintenue dans une atmosphère inerte, avec une quantité d'une base forte efficace pour obtenir un intermédiaire réactif choisi parmi (i) un anion de rébeccamycine ayant la charge négative à la position 6, (ii) un anion de rébeccamycine ayant la charge négative à la position 13 et (iii) un dianion de rébeccamycine ayant des charges négatives aux deux positions 6 et 13 ;

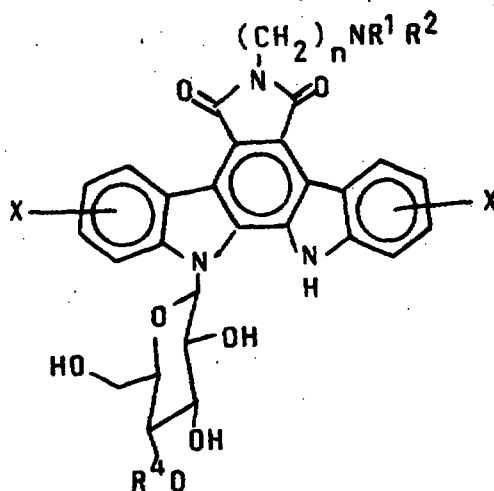
(b) faire réagir l'intermédiaire réactif de l'étape (a) avec un composé d'aminoalkyle représenté par la formule



où L est un groupe chimique partant et n, R¹ et R² sont tels que définis ci-dessus ; et

(c) récupérer le dérivé aminoalkylé résultant de rébeccamycine du mélange de l'étape (b).

2. Procédé selon la revendication 1 où les composés obtenus sont ceux ayant la formule



II

où

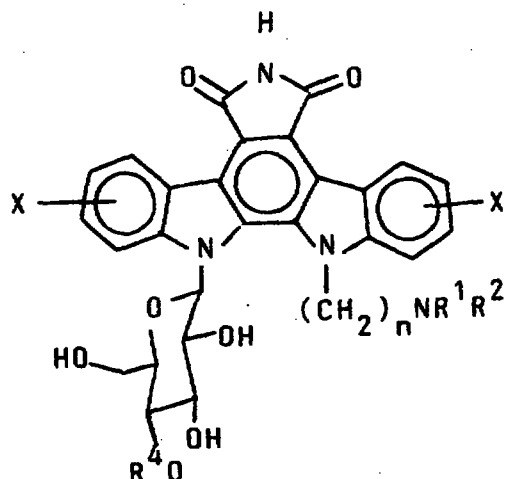
R¹, R², X et R⁴ sont tels que définis à la revendication 1 ; ou leurs sels d'addition d'acide et de base acceptables en pharmacie.

3. Procédé selon la revendication 2, où X est choisi parmi H, Cl, Br, OH, OCH₃ et OCH₂C₆H₅.

4. Procédé selon la revendication 3, où n est choisi parmi les nombres entiers 1, 2 et 3 et R¹ et R², indépendamment, sont choisis parmi H, alkyle C₁-C₃ et $-(CH_2)_4-$.



5. Procédé selon la revendication 4, où X est Cl à chacune des positions 1 et 11.
6. Procédé selon la revendication 5, où n est un nombre entier choisi parmi 2 et 3, et chacun de R¹ et R² est C₂H₅.
7. Procédé selon la revendication 6, où les composés obtenus sont ceux ayant la formule II où X est Cl dans chacune des positions 1 et 11, R⁴ est méthyle, n est 2 et chacun de R¹ et R² est C₂H₅ ou les sels d'addition d'acide acceptables en pharmacie, en particulier le chlorhydrate.
8. Procédé selon la revendication 1, où les composés obtenus sont ceux ayant la formule



III

- où
- n, R¹, R², R⁴ et X sont tels que définis à la revendication 1 ; ou leurs sels d'addition d'acide et sels de base acceptables en pharmacie.
9. Procédé selon la revendication 8, où R⁴ est CH₃ et X est choisi parmi Cl, Br, OH, OCH₃ et OCH₂C₆H₅ à chacune des positions 1 et 11 du système du noyau.
10. Procédé selon la revendication 9, où n est choisi parmi les nombres entiers 1, 2 et 3 et R¹ et R², indépendamment, sont choisis parmi H, alkyle C₁-C₃ et -(CH₂)₄-.
11. Procédé selon la revendication 10, où X est Cl dans chacune des positions 1 et 11.
12. Procédé selon la revendication 11, où n est un nombre entier choisi parmi 2 et 3 ; et R¹ et R² sont chacun C₂H₅.
13. Procédé pour la préparation d'une composition pharmaceutique qui comprend l'incorporation d'au moins un composé selon l'une quelconque des revendications 1 à 12 ou son sel d'addition d'acide ou sel de base acceptable en pharmacie dans un support acceptable en pharmacie.
14. Utilisation des composés selon l'une quelconque des revendications 1 à 12 pour la préparation d'une composition pharmaceutique pour le traitement thérapeutique d'un hôte mammifère affecté d'une tumeur maligne.

