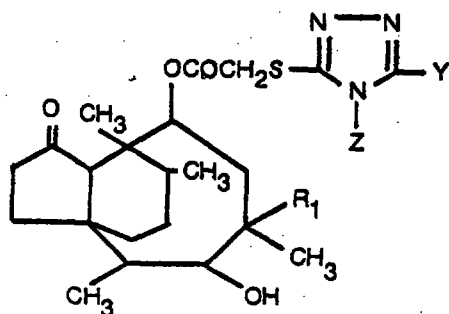


This invention provides compounds of formula I



in which

R_1 is ethyl or vinyl;

Y is hydrogen, amino, trifluoromethyl, C_1-C_4 -alkyl, pyridyl or $-N(R_3)(R_4)$;

Z is hydrogen, C_1-C_4 -alkylsulphonyl, amino, formyl, $-N(R_3)(R_4)$, $-S(CH_2)_n N(R_3)(R_4)$ or $CX.NHR_6$;

R_3 and R_4 are the same or different and each is hydrogen, C_1-C_4 -hydroxyalkyl, C_1-C_4 -dihydroxyalkyl, unsubstituted or substituted C_1-C_4 -alkanoyl, C_1-C_4 -alkylsulphonyl or C_1-C_4 -alkyl or together with the nitrogen atom stand for a piperazinyl radical which may be substituted on the second nitrogen atom by C_1-C_4 -alkyl, C_1-C_4 -hydroxyalkyl or C_1-C_4 -dihydroxyalkyl;

R_6 is C_1-C_4 -alkyl or C_1-C_4 -alkoxy-carbonyl;

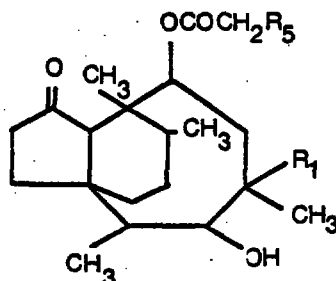
n is 2 to 5; and

x is oxygen or sulphur;

and acid addition and quaternary ammonium salts thereof.

Egger et. al. J. Antibiotics, v. XXIV, No. 9, pp. 923—27 describe antimicrobial pleuromutilin derivatives having a side chain and bearing i.a. saturated heterocyclic groups attached via a heteroatom to said side chain. There is no disclosure of compounds of the present invention.

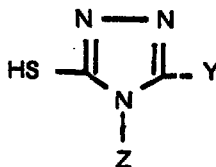
The invention also provides a process for the production of compounds of formula I, characterised by reacting a compound of formula II,



in which

R_1 is as defined above, and

R_5 is chlorine, bromine or $-OSO_2R_7$, in which R_7 is alkyl or aryl, with a compound of formula III,



in which Y and Z are as defined above.

The process is suitably carried out in the presence of an alkali metal lower alkoxide, for example sodium ethoxide or methoxide. This is preferably produced *in situ*. Conveniently, the compound of formula III may be dissolved in a solution of sodium in a water-free lower alcohol, e.g. methanol or ethanol. A solution of the compound of formula II in an inert organic solvent, e.g. an aliphatic ketone,

(10)

such as methyl ethyl ketone or acetone, is then conveniently added. The process is suitably effected at a temperature from room temperature to the reflux temperature of the reaction mixture, in particular from 22° to 55°C. The reaction time may typically vary from 2 to 12 hours.

The resulting compounds of formula I may be isolated and purified using conventional techniques. Where required, free base forms thereof may be converted into salt forms, in particular into acid addition salt and quaternary ammonium salt forms, in conventional manner, and *vice versa*.

The compounds of formula I are indicated for use as chemotherapeutic agents, in particular as antimicrobial agents, as indicated, e.g. by their inhibiting effect against various bacterial strains, e.g. *Staph. aureus*, *Staph. epidermis*, *Strept. pyogenes*, *Strept. aranson*, *Strept. pneumoniae*, *Strept. faecalis*, *Strept. viridans*, *Corynebact. pyogenes*, *Sarcina lutea*, *Klebsiella pneumoniae*, and *Haemophilus influenzae*, *in vitro* in the series dilution test at a concentration, for example, of 0.01 to 25 µg/ml, and in *in vivo* tests in mice. The compounds also show an inhibiting effect against various mycoplasma, e.g. *M. hominis*, *M. arthritis*, *M. pneumoniae*, and urea plasma urealyticum, and chlamydia, *in vitro* in the series dilution test at concentrations of, for example, 0.008 to 2.5 µg/ml.

The compounds also show an inhibiting effect against various obligatory anaerobes, e.g. *Bacteroides fragilis*, *Bacteroides melaninogenicus*, *Sphaerophorus necrophorus*, *Clostridium perfringens*, etc., *in vitro* in the series dilution test at concentrations of for example 0.1 to 4 µg/ml, and *in vivo* in mice at a dosage of for example 50 to 200 mg/kg of animal body weight, p.o. or s.c.

The compounds are therefore indicated for use as anti microbial agents, in particular as antibacterially active antibiotics and for treatment of infections caused by obligatory anaerobes.

For the above-mentioned uses, an indicated suitable daily dosage is from about 1 to 3 g, suitably administered in divided dosages of from two to four times daily, or in retard form.

The compounds alone or in admixture with a tetracyclin may be administered orally or parenterally in such forms as tablets, capsules, powders, granulates, and injectable or infusion preparations, e.g. solutions or suspensions. The compounds may also be employed in the form of creams or tinctures. For veterinary purposes, the compounds may also be administered as food or drink additives.

It has also been found that mixtures of the compounds of formula I with a tetracyclin show a synergistic antibacterial effect against strains with R-factor coded tetracyclin resistance. This indicated for example by determination of the minimum inhibition concentration of the mixture and the individual components in the series dilution test, and by evaluating the results by the method of Löwe (isobole diagram), *Die Antibiotika*, Volume 1, part 1, 65ff, 1962. Conventional tetracyclines, e.g. chlorotetracyclin, oxytetracyclin, demethyltetracyclin, tetracyclin dioxycyclin, monocyclin, metacyclin, and rolitetracyclin, may be employed in such mixtures. The quantity of the compound of formula I in such mixtures is suitably 10 to 90%, preferably 20 to 35%, in particular 25%, while the quantity of the tetracyclin is suitably from 90 to 10%, preferably 80 to 65%, particularly 75% (these percentages being by weight).

The mixtures are particularly indicated in treating infections of the gastrointestinal tract and other local infections of the organ.

The compounds of formula I, when used alone or in admixture with a tetracyclin, may be employed in free base form or in the form of chemotherapeutically acceptable acid addition or quaternary ammonium salts. These salt forms have the same order of activity as the free base forms.

Suitable acid addition salt forms include the hydrochloride, hydrogen, fumarate, fumarate and naphthalene-1,5-sulphonate.

The compounds (or mixtures thereof with a tetracycline) may be admixed with a chemotherapeutically acceptable diluent or carrier and, optionally other conventional excipients for the production of galenic forms. Suitable excipients include sweeteners, aromas, colouring agents, preserving agents, e.g. ethyl-*o*-hydroxybenzoate, fillers or carriers, e.g. diluents, such as calcium carbonate, disintegrating agents, e.g. starch or alginic acid, binding agents, e.g. starch, gelatine or acacia, and lubricating agents, e.g. magnesium stearate, stearic acid or talc. Oral liquid forms may contain conventional suspending agents, e.g. methylcellulose, tragacanth or sodium alginate. Suitable wetting agents include lecithin, polyoxyethane stearate and polyoxyethylene sorbitan monooleate. For the production of capsules, suitable diluents include calcium carbonate, calcium phosphate and kaolin.

The preferred compound of formula I is that of Example I, hereinafter.

The following Examples illustrate the invention. All temperatures are in degrees Centigrade.

Example 1

19,20-Dihydro-14-O-[(3-amino-1,2,4-triazol-5-yl)thioacetyl]mutilin

2.3 g of sodium are taken up in 500 ml of absolute ethanol. After formation of the sodium ethoxide, 11.6 g of 3-amino-5-mercapto-1,2,4-triazole are added to the solution.

The mixture is allowed to react for 3 hours at 25°C and is then mixed with a solution of 53.5 g of 19,20-dihydro-22-O-tosyl-pleuromutilin in 200 ml of ethylmethylketone. The homogenous reaction mixture is held for 12 hours at 25° and then poured onto water and extracted 3 times with 500 ml of ethyl acetate. The purified ethyl acetate extract is shaken with water, dried over Na₂SO₄ and evaporated.



in vacuo. The crude product is chromatographed over silica gel (eluant: ethyl acetate) to obtain the heading compound, m.p. 213—215° (isopropanol/H₂O).

NMR (DMSO): 5.76 (broad, 2H, NH₂); 5.52 (d, 1H, H₁₄, J_{H₁₄H₁₃} = 8 Hz); 3.76 (s, 2H, S—CH₂—CO); 3.35 (m, 1H, H₁₁).

5 IR (KBr): 2600—3600 (broad), 1720, 1635, 1280 cm⁻¹.

The compounds of the following Examples may be produced in manner analogous to that of Example 1, using appropriate starting materials in approximately equivalent amounts.

Example 2

10 14-O-[(3-Amino-1,2,4-triazol-5-yl)thioacetyl]-mutilin

NMR (CDCl₃): 5.68 (d, 1H, H₁₄, J_{H₁₄H₁₃} = 8 Hz); 3.34 (d, 1H, H₁₁, J_{H₁₁H₁₀} = 6 Hz); 3.7 (s, 2H, S—CH₂—CO); 5.26—4.95 (m, 4H, NH₂ + 2H₂₀); 6.5—6.16 (m, 1H, H₁₉).

IR (KBr): 3300 (broad), 1720, 1625, 1575, 1270 cm⁻¹.

Example 3

15 14-O-[(4-Methylsulfonyl-5-amino-1,2,4-triazol-3-yl)-thioacetyl]mutilin

NMR (CDCl₃): 5.9 (s, 2H, NH₂); 5.76 (di, 1H, H₁₄, J_{H₁₄H₁₃} = 8 Hz); 3.81 (s, 2H, S—CH₂—CO); 3.3 (s, 3H, CH₃SO₂—); 3.4 (m, 1H, H₁₁).

20 IR (KBr): 3400 (broad), 1720, 1625, 1265, 1275, 1180 cm⁻¹.

Example 4

14-O-[(4-Amino-1,2,4-triazol-3-yl)thioacetyl]mutilin

25 NMR (CDCl₃): 8.26 (s, 1H, Triazol-H); 5.7 (d, 1H, H₁₄, J_{H₁₄H₁₃} = 8 Hz); 5.08 (s, 2H, NH₂), AB-System (v_A = 3.86, v_B = 3.75, J_{AB} = 16.2 Hz, S—CH₂—O); 3.34 (dd, 1H, H₁₁, J = 6.3 Hz, J = 10.2 Hz).

IR (KBr): 3400 (broad), 1720 cm⁻¹.

Example 5

30 14-O-[(3-(4-Pyridyl)-1,2,4-triazol-5-yl)thioacetyl]-mutilinhydrochlorid

NMR (DMSO): 8.95 (d, 2H, Pyridin-H, J = 6.3 Hz); 8.36 (d, 2H-Pyridin-H, J = 6.3 Hz); 5.55 (d, 1H, H₁₄, J_{H₁₄H₁₃} = 8 Hz); 4.16 (s, 2H, S—CH₂—CO); 3.4 (d, 1H, H₁₁, J_{H₁₀H₁₁} = 6.3 Hz).

IR (KBr): 3600—2500 (broad), 1725, 1635 cm⁻¹.

Example 6

35 14-O-[(4-Amino-3-trifluoromethyl-1,2,4-triazol-5-yl)-thioacetyl]mutilin

NMR (CDCl₃): 5.74 (d, 1H, H₁₄, J_{H₁₄H₁₃} = 8 Hz); 5.18 (s, 2H, NH₂); 3.9 (s, 2H, S—CH₂CO); 3.38 (1H, H₁₁).

IR (KBr): 3400 (broad), 1720, 1190, 1150 cm⁻¹.

Example 7

40 14-O-[(4-Amino-3-methyl-1,2,4-triazol-5-yl)thioacetyl]mutilin

NMR (CDCl₃): 5.72 (d, 1H, H₁₄, J_{H₁₄H₁₃} = 8 Hz); 4.97 (s, 2H, NH₂); AB-System (v_A = 3.84, v_B = 3.69, J_{AB} = 16.2 Hz, S—CH₂—CO); 3.38 (dd, H₁₁, J = 6.3 Hz, J = 10.2 Hz).

45 IR (KBr): 3400 (broad), 1725 cm⁻¹.

Example 8

14-O-[(3-Methyl-4-acetamido-1,2,4-triazol-5-yl)-thioacetyl]mutilin

50 NMR (CDCl₃): 5.7 (d, 1H, H₁₄, J_{H₁₄H₁₃} = 8 Hz); 3.8 (s, 2H, S—CH₂—CO); 3.38 (m, 1H, H₁₁); 2.33 (s, 3H, CH₃CO—N); 2.26 (s, 3H, Triazol-CH₃).

IR (KBr): 3400 (broad), 1720, 750 cm⁻¹.

Example 9

14-O-[(3-(Methoxysulfonylethylcarboxamido)-1,2,4-triazol-5-yl)thioacetyl]mutilin

55 NMR (CDCl₃): 5.72 (d, 1H, H₁₄, J_{H₁₄H₁₃} = 8 Hz); 3.82 (s, 2H, S—CH₂—CO); 3.34 (m, 1H, H₁₁); s, 14 (s, 3H, —O—CH₃).

IR (KBr): 3400 (broad), 1720, 1625, 1550, 1305, 1110, 730 cm⁻¹.

Example 10

60 14-O-[(1-Ethylaminocarbonyl-3-amino-1,2,4-triazol-5-yl)thioacetyl]mutilin

NMR (CDCl₃)/D₂O 10:1): 5.74 (d, 1H, H₁₄, J_{H₁₄H₁₃} = 8 Hz); 3.75 (s, 2H, S—CH₂—CO); 3—38 (q, 2H, CH₃—CH₂—N); 3.4 (m, 1H, H₁₁); 1.26 (t, 3H, CH₃—CH₂—N).

IR (KBr): 3540, 3430, 3310, 1710, 1630, 1300 cm⁻¹.

65 m.p. 230—232°.

Example 11

14-O-[(3-Amino-4-formyl-1,2,4-triazol-5-yl)thioacetyl]mutilin

NMR (CDCl₃): 8.52 (s, 1H, Formyl-H); 5.74 (d, 1H, H₁₄, J_{H₁₄H₁₃} = 8 Hz); 3.82 (s, 2H, S—CH₂CO); 3.36 (m, 1H, H₁₁).IR (KBr): 3600—2800 (broad), 1725, 1585, 1290 cm⁻¹.

Example 12

14-O-[(3-Amino-1-(carbethoxythiocarbonyl)-1,2,4-triazol-5-yl)thioacetyl]mutilin

NMR (CDCl₃): 7.74 (b, 2H, NH₂); 5.81 (d, 1H, H₁₄, J_{H₁₄H₁₃} = 8 Hz); 4.37 (q, 2H, O—CH₂CH₃); 3.83 (s, 2H, S—CH₂—CO); 3.4 (d, 1H, H₁₁, J_{H₁₁H₁₀} = 6.3 Hz); 1.38 (t, 3H, O—CH₂CH₃).IR (KBr): 3300 (broad), 1770, 1725, 1635, 1465, 1185 cm⁻¹.

Example 13

14-O-[(3-Amino-4-(ethylaminothiocarbonyl)-1,2,4-triazol-5-yl)thioacetyl]mutilin

NMR (CDCl₃): 8.56 (m, 1H, NH); 7.4 (b, 2H, NH₂); 5.76 (d, 1H, H₁₄, J_{H₁₄H₁₃} = 8 Hz); 3.78 (s, 2H, S—CH₂—CO); 3.68 (m, 2H, N—CH₂—CH₃); 3.38 (dd, 1H, H₁₁, J=6.3 Hz, J=10.2 Hz); 1.33 (t, 3H, N—CH₂—CH₃).IR (KBr): 3340 (broad), 1720, 1630, 1290 cm⁻¹.

Example 14

14-O-[(4-Bis-(methylsulfonylamino)-1,2,4-triazol-3-yl)mutilin

NMR (CDCl₃): 8.28 (s, 1H, Triazol-H); 5.72 (d, 1H, H₁₄, J_{H₁₄H₁₃} = 8 Hz); AB-System (v_A=4.18, v_B=4.02, J_{AB}=16.2 Hz, S—CH₂—CO); 3.6 (s, 3H, CH₃SO₂—); 3.58 (s, 3H, CH₃SO₂—); 3.34 (m, 1H, H₁₁).IR (KBr): 3450 (broad), 1720, 1380, 1160 cm⁻¹.

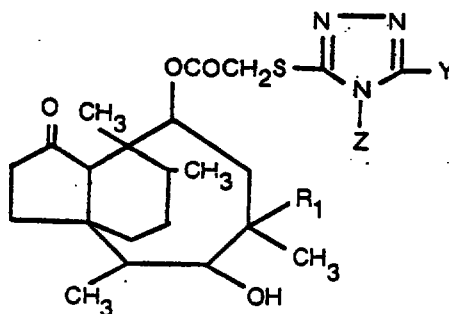
Example 15

14-O-[(3-(2-Pyridyl)-1,2,4-triazol-5-yl)thioacetyl]mutilin

NMR (CDCl₃): 8.82 (d, 1H, Pyridin-H, J=5 Hz); 8.24 (d, 1H, Pyridin-H, J=10 Hz); 7.9 (m, 1H, Pyridin-H); 7.45 (m, 1H, Pyridin-H); 5.78 (d, 1H, H₁₄, J_{H₁₄H₁₃} = 8 Hz); 4.0 (s, 2H, S—CH₂—CO); 3.4 (m, 1H, H₁₁).IR (KBr): 3500—2800 (broad), 1720, 1450, 1280 cm⁻¹.UV (CH₃CH): 232 nm (Σ = 12400), 282 (8170).

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

1. A compound of formula I,



in which

R₁ is ethyl or vinyl;Y is hydrogen, amino, trifluoromethyl, C₁—C₄-alkyl, pyridyl or —N(R₃)(R₄);Z is hydrogen, C₁—C₄-alkylsulphonyl, amino, formyl, —N(R₃)(R₄), —S(CH₂)_nN(R₃)(R₄) or CX.NHR₅;R₃ and R₄ are the same or different and each is hydrogen, C₁—C₄-hydroxyalkyl, C₁—C₄-dihydroxyalkyl, unsubstituted or substituted C₁—C₄-alkanoyl, C₁—C₄-alkylsulphonyl or C₁—C₄-alkyl or together with the nitrogen atom stand for a piperazinyl radical which may be substituted on the second nitrogen atom by C₁—C₄-alkyl, C₁—C₄-hydroxyalkyl or C₁—C₄-dihydroxyalkyl;R₅ is C₁—C₄-alkyl or C₁—C₄-alkoxy-carbonyl;

n is 2 to 5; and

x is oxygen or sulphur;

and acid addition and quaternary ammonium salts thereof.

2. 19,20-Dihydro-14-O-[3-amino-1,2,4-triazole-5-yl]-thioacetyl]mutilin and acid addition and quaternary ammonium salts thereof.



Example 11

14-O-[(3-Amino-4-formyl-1,2,4-triazol-5-yl)thioacetyl]mutilin

NMR (CDCl₃): 8.52 (s, 1H, Formyl-H); 5.74 (d, 1H, H₁₄, J_{H₁₄H₁₃} = 8 Hz); 3.82 (s, 2H, S—CH₂CO); 3.36 (m, 1H, H₁₁).IR (KBr): 3600—2800 (broad), 1725, 1585, 1290 cm⁻¹.

Example 12

14-O-[(3-Amino-1-(carbethoxythiocarbamyl)-1,2,4-triazol-5-yl)thioacetyl]mutilin

NMR (CDCl₃): 7.74 (b, 2H, NH₂); 5.81 (d, 1H, H₁₄, J_{H₁₄H₁₃} = 8 Hz); 4.37 (q, 2H, O—CH₂CH₃); 3.83 (s, 2H, S—CH₂—CO); 3.4 (d, 1H, H₁₁, J_{H₁₁H₁₀} = 6.3 Hz); 1.38 (t, 3H, O—CH₂CH₃).IR (KBr): 3300 (broad), 1770, 1725, 1635, 1465, 1185 cm⁻¹.

Example 13

14-O-[(3-Amino-4-(Ethylaminothiocarbonyl)-1,2,4-triazol-5-yl)thioacetyl]mutilin

NMR (CDCl₃): 8.56 (m, 1H, NH); 7.4 (b, 2H, NH₂); 5.76 (d, 1H, H₁₄, J_{H₁₄H₁₃} = 8 Hz); 3.78 (s, 2H, S—CH₂—CO); 3.68 (m, 2H, N—CH₂—CH₃); 3.38 (dd, 1H, H₁₁, J = 6.3 Hz, J = 10.2 Hz); 1.33 (t, 3H, N—CH₂—CH₃).IR (KBr): 3340 (broad), 1720, 1630, 1290 cm⁻¹.

Example 14

14-O-[(4-Bis-(methylsulfonylamino)-1,2,4-triazol-3-yl)mutilin

NMR (CDCl₃): 8.28 (s, 1H, Triazol-H); 5.72 (d, 1H, H₁₄, J_{H₁₄H₁₃} = 8 Hz); AB-System (ν_A = 4.18, ν_B = 4.02, J_{AB} = 16.2 Hz, S—CH₂—CO); 3.6 (s, 3H, CH₃SO₂—); 3.58 (s, 3H, CH₃SO₂—); 3.34 (m, 1H, H₁₁).IR (KBr): 3450 (broad), 1720, 1380, 1160 cm⁻¹.

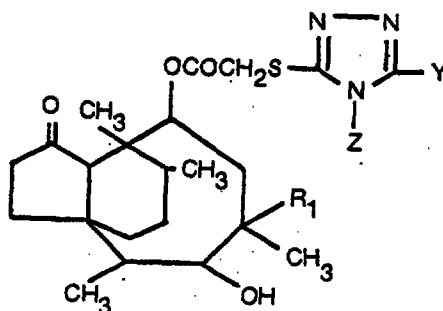
Example 15

14-O-[(3-(2-Pyridyl)-1,2,4-triazol-5-yl)thioacetyl]mutilin

NMR (CDCl₃): 8.82 (d, 1H, Pyridin-H, J = 5 Hz); 8.24 (d, 1H, Pyridin-H, J = 10 Hz); 7.9 (m, 1H, Pyridin-H); 7.45 (m, 1H, Pyridin-H); 5.78 (d, 1H, H₁₄, J_{H₁₄H₁₃} = 8 Hz); 4.0 (s, 2H, S—CH₂—CO); 3.4 (m, 1H, H₁₁).IR (KBr): 3500—2800 (broad), 1720, 1450, 1280 cm⁻¹.UV (CH₃CH): 232 nm (Σ = 12400), 282 (8170).

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

1. A compound of formula I,



in which

R₁ is ethyl or vinyl;Y is hydrogen, amino, trifluoromethyl, C₁—C₄-alkyl, pyridyl or —N(R₃)(R₄);Z is hydrogen, C₁—C₄-alkylsulphonyl, amino, formyl, —N(R₃)(R₄), —S(CH₂)_nN(R₃)(R₄) or CX.NHR₆;R₃ and R₄ are the same or different and each is hydrogen, C₁—C₄-hydroxyalkyl, C₁—C₄-dihydroxyalkyl, unsubstituted or substituted C₁—C₄-alkanoyl, C₁—C₄-alkylsulphonyl or C₁—C₄-alkyl or together with the nitrogen atom stand for a piperazinyl radical which may be substituted on the second nitrogen atom by C₁—C₄-alkyl, C₁—C₄-hydroxyalkyl or C₁—C₄-dihydroxyalkyl;R₆ is C₁—C₄-alkyl or C₁—C₄-alkoxy-carbonyl;

n is 2 to 5; and

x is oxygen or sulphur;

and acid addition and quaternary ammonium salts thereof.

2. 19,20-Dihydro-14-O-[3-amino-1,2,4-triazole-5-yl]-thioacetyl]mutilin and acid addition and

quaternary ammonium salts thereof.



(B)

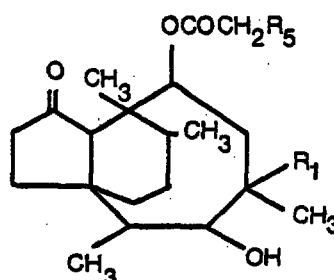
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3. A chemotherapeutic composition comprising a compound of formula I as claimed in Claim 1 or 2, in free base form or in the form of a chemotherapeutically acceptable acid addition or quaternary ammonium salt, together with a chemotherapeutically acceptable diluent or carrier.

4. A compound of Formula I as claimed in Claim 1 or 2, in free base form or in the form of a chemotherapeutically acceptable acid addition or quaternary ammonium salt for use as a chemotherapeutic agent.

5. A compound of Formula I as claimed in Claim 1 or 2, in free base form or in the form of a chemotherapeutically acceptable acid addition or quaternary ammonium salt, for use as an antibacterially active antibiotic and for the treatment of infections caused by obligatory anaerobes.

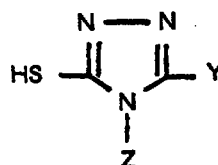
6. A process for the production of a compound of Formula I, stated in Claim 1, or an acid addition or quaternary ammonium salt thereof, which comprises reacting a compound of Formula II,



II

in which

R_1 is as defined in Claim 1 and
 R_5 is chlorine, bromine or $-\text{OSO}_2\text{R}_7$, in which R_7 is alkyl or aryl,
 with a compound of formula III,



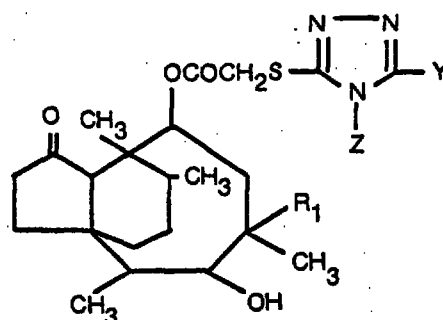
III

in which

Y and Z are as defined in Claim 1, and, if desired, converting a compound of Formula I thus obtained into an acid addition or quaternary ammonium salt thereof or vice versa.

Claims for the Contracting State: AT

1. A process for the production of a compound of formula I



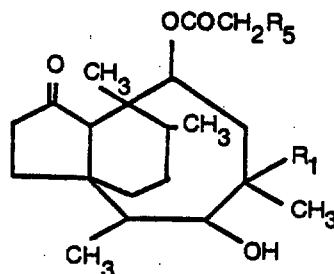
in which

R_1 is ethyl or vinyl;
 Y is hydrogen, amino, trifluoromethyl, C_1-C_4 -alkyl, pyridyl or $-\text{N}(\text{R}_3)(\text{R}_4)$;
 Z is hydrogen, C_1-C_4 -alkylsulphonyl, amino, formyl, $-\text{N}(\text{R}_3)(\text{R}_4)$, $-\text{S}(\text{CH}_2)_n\text{N}(\text{R}_3)(\text{R}_4)$ or CX.NHR_6 ;
 R_3 and R_4 are the same or different and each is hydrogen, C_1-C_4 -hydroxyalkyl, C_1-C_4 -dihydroxyalkyl, unsubstituted or substituted C_1-C_4 -alkanoyl, C_1-C_4 -alkylsulphonyl or C_1-C_4 -alkyl or together with the nitrogen atom stand for a piperazinyl radical which may be substituted on the second nitrogen atom by C_1-C_4 -alkyl, C_1-C_4 -hydroxyalkyl or C_1-C_4 -dihydroxyalkyl;



14

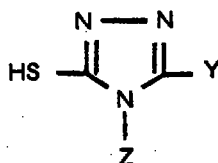
R_5 is C_1-C_4 -alkyl or C_1-C_4 -alkoxy-carbonyl;
 n is 2 to 5; and
 x is oxygen or sulphur;
 or an acid addition or quaternary ammonium salt thereof, which comprises reacting a compound of
 formula II,



II

in which

R_1 is as defined above, and
 R_5 is chlorine, bromine or $-OSO_2R_7$, in which R_7 is alkyl or aryl,
 with a compound of formula III,



III

in which

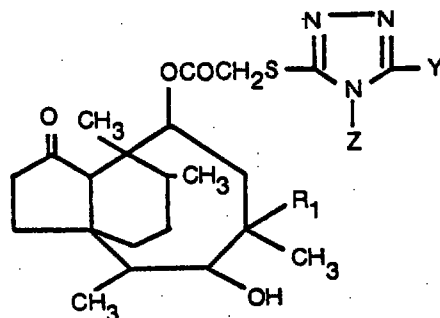
Y and Z are as defined above, and, if desired, converting a compound of formula I thus obtained into an acid addition or quaternary ammonium salt thereof or vice versa.

2. A process as claimed in Claim 1 wherein the compound thus obtained is 19,20-Dihydro-14-O-[3-amino-1,2,4-triazole-5-yl]-thioacetyl]-mutilin or an acid addition or quaternary ammonium salt thereof.

3. A compound of formula I according to Claim 1 or an acid addition or quaternary ammonium salt thereof wherever prepared by a process as claimed in Claim 1.

4. A chemotherapeutic composition comprising a compound of formula I according to Claim 3, in free base form or in the form of a chemotherapeutically acceptable acid addition or quaternary ammonium salt, together with a chemotherapeutically acceptable diluent or carrier.

5. A process for preparing a chemotherapeutic composition which comprises admixing a compound of formula I



I

in which

R_1 is ethyl or vinyl;

Y is hydrogen, amino, trifluoromethyl, C_1-C_4 -alkyl, pyridyl or $-N(R_3)(R_4)$;

Z is hydrogen, C_1-C_4 -alkylsulphonyl, amino, formyl, $-N(R_3)(R_4)$, $-S(CH_2)_nN(R_3)(R_4)$ or $CX.NHR_6$;

R_3 and R_4 are the same or different and each is hydrogen, C_1-C_4 -hydroxyalkyl, C_1-C_4 -dihydroxyalkyl, unsubstituted or substituted C_1-C_4 -alkenyl, C_1-C_4 -alkylsulphonyl or C_1-C_4 -alkyl or together with the nitrogen atom stand for a piperazinyl radical which may be substituted on the second nitrogen atom by C_1-C_4 -alkyl, C_1-C_4 -hydroxyalkyl or C_1-C_4 -dihydroxyalkyl;



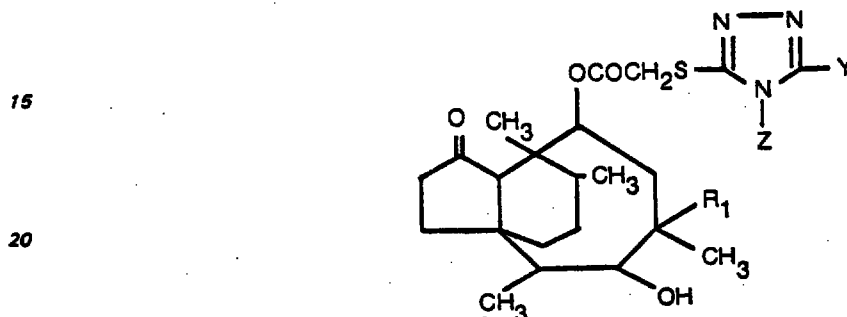
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R_6 is C_1 - C_4 -alkyl or C_1 - C_4 -alkoxy-carbonyl;
n is 2 to 5; and
x is oxygen or sulphur;
in free base form or in the form of a chemotherapeutically acceptable acid addition or quaternary ammonium salt, together with a chemotherapeutically acceptable diluent or carrier.

Patentansprüche für die Vertragsstaaten: BE CH DE FR GB IT LU NL SE

10 1. Eine Verbindung der Formel I



25 worin

R_1 Ethyl oder Vinyl;
Y Wasserstoff, Amino, Trifluormethyl, C_{1-4} -Alkyl, Pyridyl oder $-N(R_3)(R_4)$
Z Wasserstoff, C_{1-4} -Alkylsulfonyl, Amino, Formyl, $-N(R_3)(R_4)$, $-S(CH_2)_n-$, $-N(R_3)(R_4)$ oder $CX.NHR_6$; bedeuten,
30 R_3 und R_4 gleich oder verschieden sind und jeweils für Wasserstoff, C_{1-4} -Hydroxyalkyl, C_{1-4} -Dihydroxyalkyl, unsubstituiertes oder substituiertes C_{1-4} -Alkanoyl, C_{1-4} -Alkylsulfonyl oder C_{1-4} -Alkyl stehen, oder zusammen mit dem Stickstoffatom für einen Piperazinrest stehen der am zweiten Stickstoffatom durch C_{1-4} -Alkyl, C_{1-4} -Hydroxyalkyl oder C_{1-4} -Dihydroxyalkyl substituiert sein kann;
35 R_6 C_{1-4} -Alkyl oder C_{1-4} -Alkoxy-Carbonyl;
n 2 bis 5; und
X Sauerstoff oder Schwefel sind,
und deren Säureadditions- und quaternäre Ammoniumsalze.

2. 19,20-Dihydro-14-O-[3-amino-1,2,4-triazol-5-yl]-thioacetyl]-mutilin und Säureadditions- und quaternäre Ammoniumsalze derselben.

40 3. Eine chemoetherapeutische Zusammensetzung enthaltend eine Verbindung der Formel I wie im Anspruch 1 oder 2 beansprucht, in Form der freien Base oder in Form eines chemotherapeutisch annehmbaren Säureadditions- oder quaternären Ammoniumsalzes, zusammen mit einem chemotherapeutisch annehmbaren Verdünnungsmittel oder Träger.

45 4. Eine Verbindung der Formel I wie im Anspruch 1 oder 2 beansprucht, in Form der freien Base oder in Form eines chemotherapeutisch annehmbaren Säureadditions- oder quaternären Ammoniumsalzes, zur Verwendung als chemotherapeutisches Mittel.

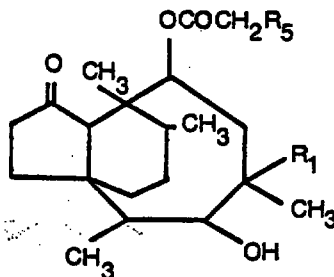
50 5. Eine Verbindung der Formel I wie im Anspruch 1 oder 2 beansprucht, in Form der freien Base oder in Form eines chemotherapeutisch annehmbaren Säureadditions- oder quaternären Ammoniumsalzes, zur Verwendung als anti-bakteriell wirksames Antibiotikum oder zur Behandlung von durch obligate Anaerobier verursachten Infektionen.

6. Verfahren zur Herstellung einer Verbindung der Formel I wie im Anspruch 1 dargelegt oder eines Säureadditions- oder quaternären Ammoniumsalzes derselben, bestehend aus Umsetzung einer Verbindung der Formel II

55

60

65 worin

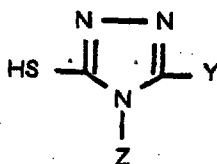




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R_1 wie oben definiert ist und
 R_5 Chlor, Brom oder OSO_2R_7 bedeutet wobei R_7 für Alkyl oder Aryl steht
mit einer Verbindung der Formel III



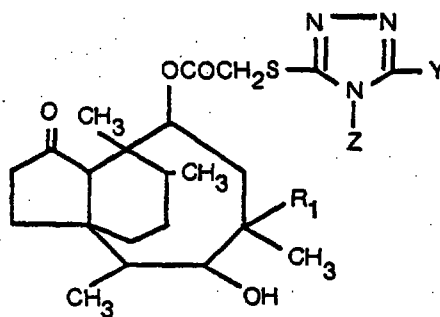
III

worin

Y und Z wie oben definiert sind,
und, gewünschtenfalls Umwandlung einer so erhaltenen Verbindung der Formel I in ein Säure-
additions- oder quaternäres Ammoniumsalz derselben oder umgekehrt.

Patentansprüche für den Vertragsstaat: AT

1. Ein Verfahren zur Herstellung einer Verbindung der Formel I



worin

R_1 Ethyl oder Vinyl;

Y Wasserstoff, Amino, Trifluormethyl, C_{1-4} -Alkyl, Pyridyl oder $-\text{N}(\text{R}_3)(\text{R}_4)$

Z Wasserstoff, C_{1-4} -Alkylsulfonyl, Amino, Formyl, $-\text{N}(\text{R}_3)(\text{R}_4)$, $-\text{S}(\text{CH}_2)_n-$, $-\text{N}(\text{R}_3)(\text{R}_4)$ oder

CX.NHR_6 ; bedeuten,

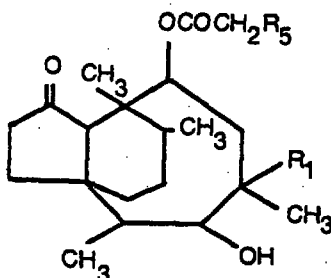
R_3 und R_4 gleich oder verschieden sind und jeweils für Wasserstoff, C_{1-4} -Hydroxyalkyl, C_{1-4} -
Dihydroxyalkyl, unsubstituiertes oder substituiertes C_{1-4} -Alkanoyl, C_{1-4} -Alkylsulfonyl oder C_{1-4} -Alkyl
stehen, oder zusammen mit dem Stickstoffatom für einen Piperazinrest stehen der am zweiten Stick-
stoffatom durch C_{1-4} -Alkyl, C_{1-4} -Hydroxyalkyl oder C_{1-4} -Dihydroxyalkyl substituiert sein kann;

R_6 C_{1-4} -Alkyl oder C_{1-4} -Alkoxy-Carbonyl;

n 2 bis 5; und

X Sauerstoff oder Schwefel sind,

oder eines Säureadditions- oder quaternäre Ammoniumsalzes derselben bestehen aus Umsetzung einer
Verbindung der Formel II



II

worin

R_1 wie oben definiert ist und

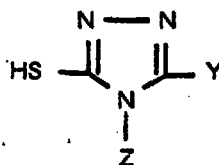
R_5 Chlor, Brom oder OSO_2R_7 bedeutet wobei R_7 für Alkyl oder Aryl steht

mit einer Verbindung der Formel III



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III (17)



worin

Y und Z wie oben definiert sind,

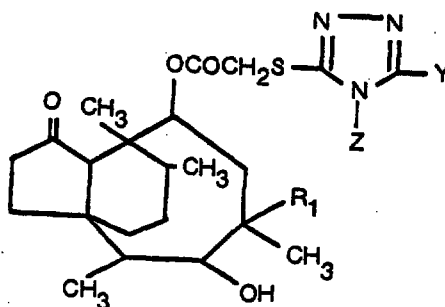
und, gewünschtenfalls Umwandlung einer so erhaltenen Verbindung der Formel I in ein Säureadditions- oder quaternäres Ammoniumsalz derselben oder umgekehrt.

2. Verfahren wie im Anspruch 1 beansprucht worin die so erhaltene Verbindung 19,20-Dihydro-14-O-[3-amino-1,2,4-triazol-5-yl]-thioacetylmutilin oder ein Säureadditions- oder quaternäres Ammoniumsalz derselben ist.

3. Eine Verbindung der Formel I gemäss Anspruch 1 oder ein Säureadditions- oder ein quaternäres Ammoniumsalz derselben falls nach einem Verfahren wie im Anspruch 1 beansprucht hergestellt.

4. Chemotherapeutische Zusammensetzung enthaltend eine Verbindung der Formel I gemäss Anspruch 3, in Form des freien Base oder in Form eines chemotherapeutisch annehmbaren Säureadditions- oder quaternären Ammoniumsalzen zusammen mit einem chemotherapeutisch annehmbaren Verdünnungsmittel oder Träger.

5. Ein Verfahren zur Herstellung einer chemotherapeutischen Zusammensetzung welches darin besteht, dass man eine Verbindung der Formel I



worin

R₁ Ethyl oder Vinyl;

Y Wasserstoff, Amino, Trifluormethyl, C₁₋₄-Alkyl, Pyridyl oder —N(R₃)(R₄)

Z Wasserstoff, C₁₋₄-Alkylsulfonyl, Amino, Formyl, —N(R₃)(R₄), —S(CH₂)_n—, —N(R₃)(R₄) oder CX.NHR₆; bedeuten,

R₃ und R₄ gleich oder verschieden sind und jeweils für Wasserstoff, C₁₋₄-Hydroxyalkyl, C₁₋₄-Dihydroxyalkyl, unsubstituiertes oder substituiertes C₁₋₄-Alkanoyl, C₁₋₄-Alkylsulfonyl oder C₁₋₄-Alkyl stehen, oder zusammen mit dem Stickstoffatom für einen Piperazinrest stehen der am zweiten Stickstoffatom durch C₁₋₄-Alkyl, C₁₋₄-Hydroxyalkyl oder C₁₋₄-Dihydroxyalkyl substituiert sein kann;

R₆ C₁₋₄-Alkyl oder C₁₋₄-Alkoxy-Carbonyl;

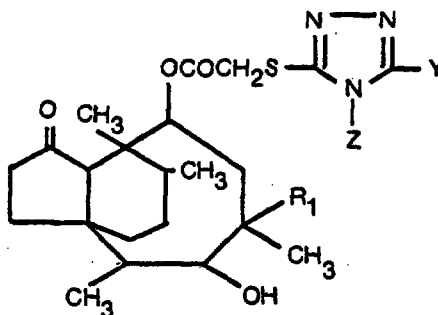
n 2 bis 5; und

X Sauerstoff oder Schwefel sind,

in Form der freien Base oder in Form eines chemotherapeutisch annehmbaren Säureadditions- oder quaternären Ammoniumsalzes zusammen mit einem chemotherapeutisch annehmbaren Verdünnungsmittel oder Träger vermischt.

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

1. Un composé de formule I



dans laquelle



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R_1 est éthyle ou vinyle;

Y est hydrogène, amino, trifluorométhyle, C_1-C_4 -alkyle, pyridyle ou $-N(R_3)(R_4)$;

Z est hydrogène, C_1-C_4 -alkylsulfonyl, amino, formyle, $-N(R_3)(R_4)$, $-S(CH_2)_nN(R_3)(R_4)$ ou

$CX.NHR_6$;

R_3 et R_4 sont identiques ou différents et chacun est hydrogène, C_1-C_4 -hydroxyalkyle, C_1-C_4 -dihydroxyalkyle, C_1-C_4 -alcanoyl non substitué ou substitué, C_1-C_4 -alkylsulfonyl ou C_1-C_4 -alkyle ou ensemble avec l'atome d'azote représentent un radical pipérazinyle qui peut être substitué sur le second atome d'azote par C_1-C_4 -alkyle, C_1-C_4 -hydroxyalkyle ou C_1-C_4 -dihydroxyalkyle;

R_6 est C_1-C_4 -alkyle ou C_1-C_4 -alcoxy-carbonyl,

n est 2 à 5; et

x est l'oxygène ou le soufre;

et ses sels d'addition d'acide et d'ammonium quaternaire.

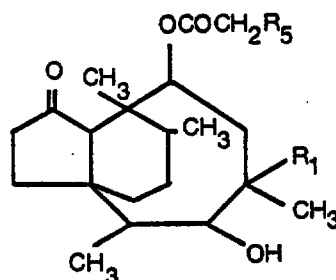
2. 19,20-dihydro-14-O-[3-amino-1,2,4-triazole-5-yl]-thioacétyl)-mutiline et ses sels d'addition d'acide et d'ammonium quaternaire.

3. Une composition chimiothérapeutique comprenant un composé de formule I tel que revendiqué à la revendication 1 ou 2, sous forme de base libre ou sous la forme d'un sel d'addition d'acide ou d'ammonium quaternaire chimiothérapeutiquement acceptable, en association avec un diluant ou véhicule chimiothérapeutiquement acceptable.

4. Un composé de formule I tel que revendiqué à la revendication 1 ou 2, sous forme de base libre ou sous la forme d'un sel d'addition d'acide ou d'ammonium quaternaire chimiothérapeutiquement acceptable, pour l'utilisation comme agent chimiothérapeutique.

5. Un composé de formule I tel que revendiqué à la revendication 1 ou 2, sous forme de base libre ou sous la forme d'un sel d'addition d'acide ou d'ammonium quaternaire chimiothérapeutiquement acceptable, pour l'utilisation comme antibiotique à activité antibactérienne et pour le traitement des infections provoquées par des anaérobies obligatoires.

6. Un procédé de préparation d'un composé de formule I, indiqué à la revendication 1, ou d'un sel d'addition d'acide ou d'ammonium quaternaire de ce composé, qui comprend la réaction d'un composé de formule II



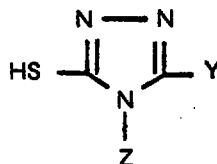
II

dans laquelle

R_1 est tel que défini à la revendication 1 et

R_5 est le chlore, le brome ou $-OSO_2R_7$, dans lequel R_7 est alkyle ou aryle,

avec un composé de formule III



III

dans laquelle

Y et Z sont tels que définis à la revendication 1,

et, si désiré, la transformation d'un composé de formule I ainsi obtenu en un sel d'addition d'acide ou d'ammonium quaternaire de ce composé, ou vice versa.

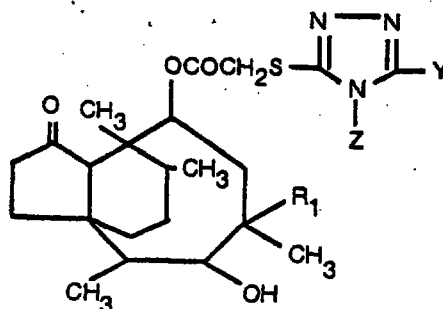


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Revendications pour l'Etat contractant: AT

1. Un procédé de préparation d'un composé de formule I



dans laquelle

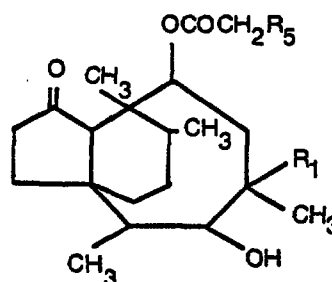
 R_1 est éthyle ou vinyle;Y est hydrogène, amino, trifluorométhyle, C_1-C_4 -alkyle, pyridyle ou $-N(R_3)(R_4)$;Z est hydrogène, C_1-C_4 -alkylsulfonyl, amino, formyle, $-N(R_3)(R_4)$, $-S(CH_2)_nN(R_3)(R_4)$ ou $CX.NHR_n$; R_3 et R_4 sont identiques et différents et chacun est hydrogène, C_1-C_4 -hydroxyalkyle, C_1-C_4 -dihydroxyalkyle, C_1-C_4 -alcanoyl non substitué ou substitué, C_1-C_4 -alkylsulfonyl ou C_1-C_4 -alkyle ou ensemble avec l'atome d'azote représentent un radical pipérazinyle qui peut être substitué sur le second atome d'azote par C_1-C_4 -alkyle, C_1-C_4 -hydroxyalkyle ou C_1-C_4 -dihydroxyalkyle; R_n est C_1-C_4 -alkyle ou C_1-C_4 -alcoyloxycarbonyl;

n est 2 à 5; et

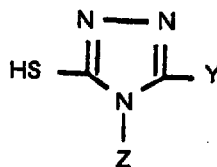
x est l'oxygène ou le soufre;

ou d'un sel d'addition d'acide ou d'ammonium quaternaire de ce composé,

qui comprend la réaction d'un composé de formule II,



dans laquelle

 R_1 est tel que défini ci-dessus, et R_5 est le chlore, le brome ou $-OSO_2R_7$, dans lequel R_7 est alkyle ou aryle, avec un composé de formule III,

dans laquelle

Y et Z sont tels que définis ci-dessus, et, si désire, la transformation d'un composé de formule I ainsi obtenu en un sel d'addition d'acide ou d'ammonium quaternaire de ce composé, ou vice versa.

2. Un procédé tel que revendiqué à la revendication 1, dans lequel le composé ainsi obtenu est la 19,20-dihydro-14-O-[3-amino-1,2,4-triazole-5-yl]-thioacétylemutiline ou un sel d'addition d'acide ou d'ammonium quaternaire de ce composé.

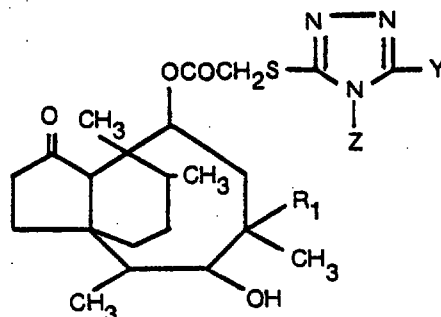
3. Un composé de formule I selon la revendication 1 ou un sel d'addition d'acide ou d'ammonium quaternaire de ce composé, préparé selon un procédé tel que revendiqué à la revendication 1.



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4. Une composition chimiothérapeutique comprenant un composé de formule I selon la revendication 3, sous forme de base libre ou sous la forme d'un sel d'addition d'acide ou d'ammonium quaternaire chimiothérapeutiquement acceptable, en association avec un diluant ou véhicule chimiothérapeutiquement acceptable.

5. Un procédé de préparation d'une composition chimiothérapeutique, qui comprend le mélange d'un composé de formule I



dans laquelle

R_1 est éthyle ou vinyle;

Y est hydrogène, amino, trifluorométhyle, C_1-C_4 -alkyle, pyridyle ou $-N(R_3)(R_4)$;

Z est hydrogène, C_1-C_4 -alkylsulfonyle, amino, formyle, $-N(R_3)(R_4)$, $-\dot{S}(CH_2)_nN(R_3)(R_4)$ ou $CX.NHR_6$;

R_3 et R_4 sont identiques ou différents et chacun est hydrogène, C_1-C_4 -hydroxyalkyle, C_1-C_4 -dihydroxyalkyle, C_1-C_4 -alcanoyle non substitué ou substitué, C_1-C_4 -alkylsulfonyle ou C_1-C_4 -alkyle ou ensemble avec l'atome d'azote représentent un radical pipérazinyle qui peut être substitué sur le second atome d'azote par C_1-C_4 -alkyle, C_1-C_4 -hydroxyalkyle ou C_1-C_4 -dihydroxyalkyle;

R_6 est C_1-C_4 -alkyle ou C_1-C_4 -alcoxy-carbonyle;

n est 2 à 5; et

x est l'oxygène ou le soufre;

sous forme de base libre ou sous la forme d'un sel d'addition d'acide ou d'ammonium quaternaire chimiothérapeutiquement acceptable, ensemble avec un diluant ou véhicule chimiothérapeutiquement acceptable.