(12) UK Patent Application (19) GB (11) 2 195 998 (13) A

(43) Application published 20 Apr 1988

(21) Application No 8713443

(22) Date of filing 9 Jun 1987

(30) Priority data
(31) 8614323 (32) 12 Jun 1986 (33) GB

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(51) INT CL[4]
C07H 15/252 A61K 31/65 31/70 C07D 491/052

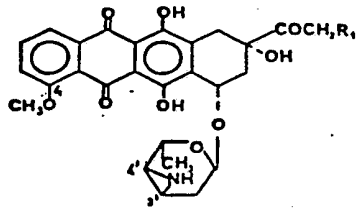
(52) Domestic classification (Edition J):
C2C 1253 1292 1672 214 215 22X 22Y 253 255 25Y 29X 29Y 305 30Y 321 32Y 351 353 355 35Y 360 361 362 363 364 365 36Y 388 620 634 643 645 652 662 665 670 672 801 80Y AA LM UA
U1S 1313 C2C

(56) Documents cited
Chemical Abstracts Vol 106 No 11 16th March, 1987 No 84994v

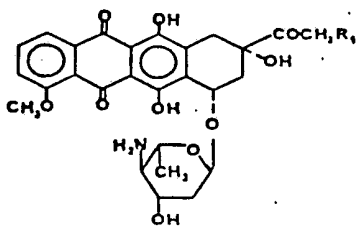
(58) Field of search
C2C

(54) New anthracyclines

(57) Anthracycline glycosides having the general formula I and II:



I



II

wherein R_1 represents a hydrogen atom or a hydroxyl group and their pharmaceutically acceptable acid addition salts are *antitumor agents*.

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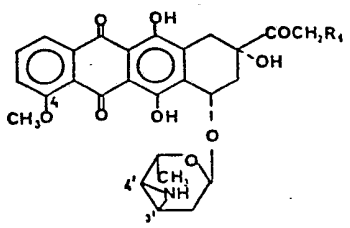
SPECIFICATION

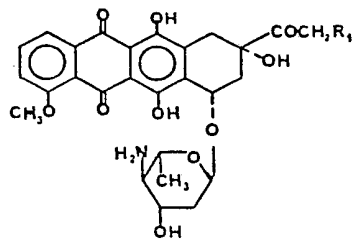
New anthracyclines

The invention relates to novel anthracycline glycoside derivatives, to their preparation and to pharmaceutical compositions containing them as well as to intermediates useful in the preparation of the glycosides.

The present invention provides anthracycline glycosides having the general formulae (I) and (II):



I a,b



II a,b

a: R_1 = H

b: R_1 = OH

wherein R_1 represents a hydrogen atom or hydroxyl group; and pharmaceutically acceptable acid addition salts thereof.

The invention further provides a process for the preparation of a glycoside of formula (I) wherein R_1 represents a hydrogen atom, i.e. compound (Ia), which process comprises reacting 3'-epi-daunorubicin with salicylaldehyde so as to obtain the corresponding 3'-epi-N-salicylidene derivative; converting the 4'-hydroxy group of the said 3'-epi-N-salicylidene derivative into a trifluoromethanesulfonate group; and removing from the 3' epi-N-salicylidene-4'-O-trifluoromethanesulfonate thus obtained the salicylidene group by acid hydrolysis so as to cause the desired glycoside of formula (I) to be obtained via displacement of the 4'-O-trifluoromethanesulfonate group.

The compound (Ia) may therefore be prepared by reaction of the 3'-amino group of 3'-epi-daunorubicin (III) [F. Arcamone, A. Bargiotti, G. Cassinellic: Ger.Patent 2752115 (June 1, 1978] with salicylaldehyde, in a mixture of water and acetone at room temperature, to obtain the corresponding 3'-epi-N-salicylidene derivative (IVc) which by treatment with trifluoromethanesulfonic anhydride in anhydrous methylene dichloride and in the presence of pyridine gives the corresponding 3'-epi-N-salicylidene-4'-O-trifluoromethansulfonate (IVd). This compoud, dissolved in methanol, can then be subjected to acidic hydrolysis of the salicylidene protecting group by means of p-toluensulfonic acid at room temperature to give, via the displacement of trifluoromethanesulfonate leaving group, the desired compound of formula (Ia).

The invention also provides a process for the preparation of a glycoside compound of formula (I) wherein R_1 represents a hydroxyl group, i.e. compound (Ib), which process comprises reacting 3'-epi-doxorubicin with salicylaldehyde so as to obtain the corresponding 3'-epi-N-salicylidene derivative; protecting the 14-hyroxy group of the said 3'-epi-N-salicylidene derivative with a tert.butyl-diphenyl-silyl group, converting the 4'-hydroxy group of the 3'-epi-N-salicylidene-14-O-[tert.butyl-dephenyl-silyl]-doxorubicin thus obtained into a trifluoromethanesulfonate group; and removing from the 14-O-[tert.butyl-diphenyl-silyl]-3'-epi-N-salicylidene-4'-O-trifluoromethanesulfonate thus obtained the salicylidene group by acid hydrolysis and the 14-O-[tert.butyl-diphenyl-silyl] group so as to cause the desired glycoside of formula (I) to be obtained via displacement of the 4'-O-trifluoromethanesulfonate group.

The compound (Ib) may therefore be prepared by the conversion of the 3'-amino group of 3'-epi-doxorubicin (V) [see F. Arcamone et al. Ger.Patent 2752155] into 3'-epi-N-salicylidene-doxorubicin (VIe) by reaction with salicylaldehyde, protection of the 14-hydroxy group with a tert-butyl-diphenyl-silyl group, obtaining 3'-epi-N-salicylidene-14-O-[tert-butyl-diphenyl-silyl]-doxorubicin (VIf); conversion of the 4'-hydroxy group into a trifluoromethanesulfonate (VIg), hydrolysis by means of p-toluensulfonic acid with formation of compound (Ih), and reaction with tetra-n-butyl-ammonium fluoride to remove the 14-O-[tert-butyl-diphenyl-silyl]-protecting group and obtain compound of formula (Ib).

Typically 3'-epi-doxorubicin, dissolved in a mixture of water and acetone, is reacted at room temperature with salicyaldehyde to obtain the corresponding 3'-epi-N-salicylidene derivative which is subsequently treated, in anhydrous dimethylformamide, at room temperature, with t-butyl-diphenylchlorosilane in the presence of imidazole to give its 3'-epi-N-salicylidene-14-O-[t-butyl-diphenyl-silyl]ether, which dissolved in anhydrous methylene dichloride is converted, by treatment

with trifluoromethanesulfonic anhydride, in the presence of dry pyridine, into its 3'-epi-N-salicylidene-4'-O-trifluoromethanesulfonate-14-O-[t-butyl-diphenyl-silyl] ether of which the salicylidene protecting group is subjected to acid hyrolysis at room temperature and in a methanolic solution by means of a catalytic amount of p-toluensulfonic acid and from which subsequently the 14-O-[t-butyl-diphenyl-silyl] protecting group is removed by treatment with tetra-n-butyl ammonium fluoride in tetrahydrofuran, at room temperature, to obtain the desired glycoside of formula (I).

The invention also provides a process for the preparation of a glycoside formula (II) wherein R_1 represents a hydrogen atom, i.e. compound (IIa), or a hydroxy group, i.e. compound (IIb), or a pharmaceutically acceptable acid addition salt thereof, which process comprises converting 3'-deamino-4'-deoxy-3'-epi-4'-epi-3',4'-epimino-daunorubicin into the corresponding N-trifluoroacetyl derivative; converting the said N-trifluoroacetyl derivative into 4'-deoxy-4'-epi-N-trifluoroacetyl-3'-deamino-3'-hydroxy daunorubicin; removing the N-trifluoroacetyl group from the 4'-deoxy-4'-epi-N-trifluoroacetyl-3'-deamino-3'-hydroxy daunorubicin so as to obtain the glycoside of formula (II) wherein R_1 is a hydrogen atom; if desired, converting the said glycoside of formula (II) into a pharmaceutically acceptable acid addition salt thereof; if desired, brominating the said glycoside of formula (II) or pharmaceutically acceptable salt thereof and hydrolysing the 14-bromo derivative thus obtained so as to form the glycoside of formula (II) wherein R_1 is a hydroxy group; and, if desired, converting the said glycoside of formula (II) wherein R_1 is a hydroxy group into a pharmaceutically acceptable acid addition salt thereof.

Treatment of the 3',4'-epimino daunorubicin derivative (Ia) with trifluoroacetic anhydride gives the corresponding N-trifluoroacetyl derivative (VIIi). Reaction of this compound with a catalytic amount of sulfuric acid in acetone gives 4'-deoxy-4'-epi-N-trifluoroacetyl-3'-deamino-3'-hydroxy-daunorubicin (VIII) which, by treatment with aqueous sodium hydroxide, gives the compound (IIa). Typically, the N-trifluoroacetyl group may be removed by mild alkaline hydrolysis, at a temperature of 0°C by means of 0.1N aqueous sodium hydroxide. Glycoside (IIa) can be isolated as its hydrochloride by treatment with hydrogen chloride in methanol.

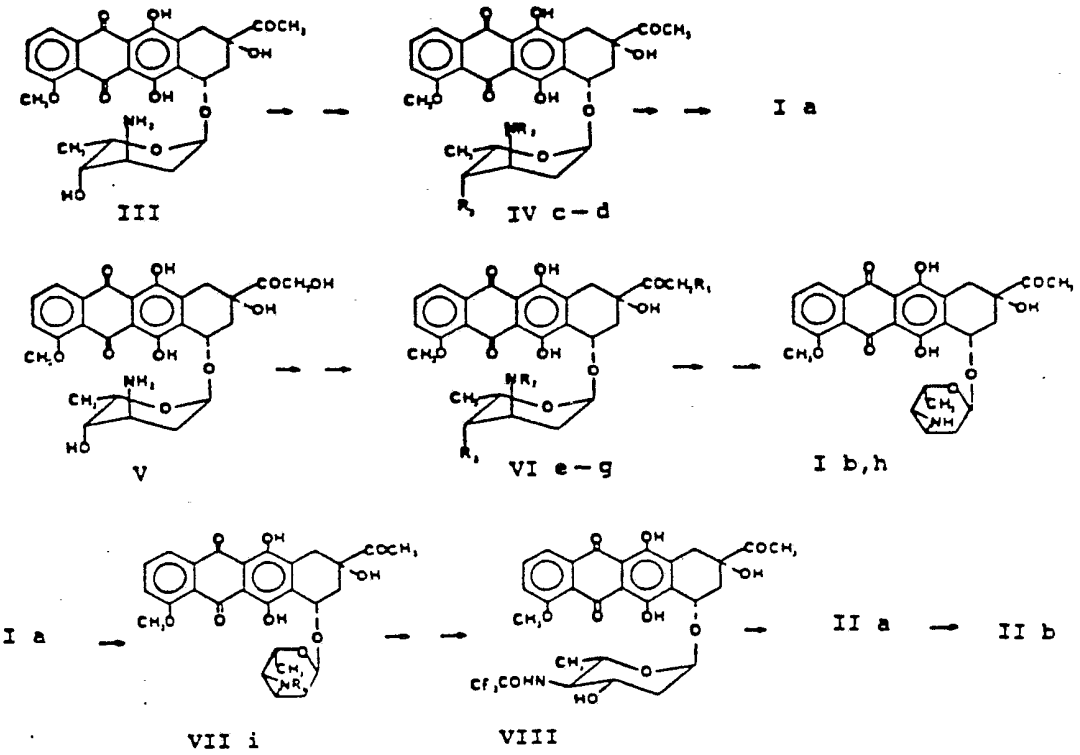
The compound (IIb) can be prepared by bromination of (IIa) followed by treatment of the resultant 14-bromo derivative with aqueous sodium formate at room temperature, according to the procedure described in United Patent Specification No. 3803124. It may be isolated as its hydrochloride in the same manner as glycoside (IIa).

The processes of the invention are summarized in the reaction scheme below.

The present invention also provides a pharmaceutical composition comprising as active ingredient an anthracycline glycoside of the invention or pharmaceutically acceptable acid addition salt thereof together with a pharmaceutically acceptable carrier or diluent. A therapeutically effective amount of a compound of formula (I) is combined with an inert carrier. Conventional carriers may be used and the composition may be formulated in conventional manner.

The compounds of the invention are useful in methods of treatment of the human or animal body by therapy. In particular, the compounds of the invention are useful as antitumor agents.

REACTION SCHEME



c R_2: $oOHC_6H_4CH=$ R_3: OH

d R_2: $oOHC_6H_4CH=$ R_3: OSO_2CF_3

e $R_1 = R_3 =$ OH R_2: $oOHC_6H_4CH=$

f R_1: $-O-Si(C_6H_5)_2-t-Bu$ R_2: $oOHC_6H_4CH=$ R_3: OH

g R_1: $-O-Si(C_6H_5)_2-t-Bu$ R_2: $oOHC_6H_4CH=$ R_3: OSO_2CF_3

h R_1: $-O-Si(C_6H_5)_2-t-Bu$

i R_4: $COCF_3$

The following Examples illustrate the invention.

EXAMPLE 1

3'-Epi-N-salicylidene-daunorubicin (IVc)

A solution of 2 g of 3'-epi-daunorubicin (III) in a mixture of 80 ml of water and 20 ml of acetone, was treated at room temperature with 0.5 ml of salicylaldehyde at pH 8. After 10 min. ethyl acetate was added and the organic phase separated off, washed with water twice, dried over anhydrous sodium sulphate, filtered and evaporated to dryness under vacuum.

The residue was first triturated with hexane to eliminate the traces of salicylaldehyde, then collected and dried under vacuum at 30°C to give (IVc) in almost quantitative yield.
Rf 0.21 on TLC Kieselgel F 254 (Merck) using as eluent the solvent mixture CH_2Cl_2-Acetone (8/2 v/v).

EXAMPLE 2

3'-deamino-4'deoxy-3'-epi-4'-epi-3',4'-epimino-daunorubicin (Ia)

To a solution of 2 g of 3'-epi-N-salicylidene daunorubicin (IVc) in 20 ml of anhydrous dichloromethane and 2 ml of dry pyridine kept at −10°C, was added a solution of 0.8 ml of trifluoromethane sulfonic anhydride in 10 ml of dichloromethane. After 1 hour at −10°C, the mixture was diluted with dichloromethane and washed with water, cold 0.1M hydrocloric acid, cold

aqueous 5% sodium hyrogen carbonate and water. The organic phase, dried over anhydrous sodium sulphate, was filtered off and the solvent removed in vacuo to give (IVd)
Rf 0.50 on TLC Kieselgel F 254 (Merck) using as eluent the solvent mixture CH_2Cl_2-Acetone (95/5 v/v).

The crude product was dissolved in 50 ml of methanol and added with 0.2 g of p-toluensulfonic acid monohydrate. The solution was kept at room temperature for 1 hr, then was added 100 ml of water and extracted with little dichloromethane. The aqueous phase was adjusted to pH 8 with 0.1M sodium hydroxyde and dichloromethane added. The organic phase was separated off, washed with water, dried over anhydrous sodium sulphate and the solvent evaporated to small volume.

The mixture was purified by chromatography on a column of silica gel buffered at pH 7 using dichloromethane-ethanol as eluent. The eluate containing the product (Ia) was washed with water, evaporated in vacuum, picked up with a little dichloromethane and crystallyzed FD MS 509 [M+] m.p. 135–137°C

Rf 0.38 on TLC Kieselgel F 254 (Merck) using as eluent the mixture CH_2Cl_2–CH_3OH–CH_3COOH–H_2O (30/4/1/0.5 v/v).

^{1}H–NMR (200 MHz, $CDCl_3$):
8.02 (dd, J=1.1, 7.7Hz, 1H, H-1)
7.76 (dd, J=7.7, 7.7Hz, 1H, H-2)
7.37 (dd. J=1.1, 7.7Hz, 1H, H-3)
5.31 (dd, J=3.0, 4.8Hz, 1H, H-1')
5.17 (dd, J=2.0, 3.6Hz, 1H, H-7)
4.32 (qd, J=<1, 6.7Hz, 1H, *H*-5')
4.07 (s, 3H, OCH_3-4)
3.17 (dd, J=19.2Hz, 1H, *H*-10e)
2.95 (d, J=19.2Hz, 1H, *H*-10ax)
2.46 (ddd, J=2.0, 2.0, 15.0Hz, 1H, *H*-8e)
2.43 (s, 3H, $COCH_3$)
2.30 (ddd, J=1.5, 4.3, 6.4Hz, 1H, *H*-3')
1.9–2.0 (m, 2H, H-8ax, *H*-2'ax)
1.87 (ddd, J=1.5, 3.0, 14.6Hz, 1H, *H*2'e)
1.44 (d, J=6.7Hz, 3H, CH_3-5')

EXAMPLE 3

3'-epi-N-salicilydene doxorubicin (VIe)

The title compound was prepared from the corresponding 3'-epi-doxorubicin (V) as described in Example 1.
Rf 0.15 on TLC, Kieselgel F 254 (Merck) using as eluent the solvent mixture CH_2Cl_2-Acetone (4/1 v/v).

EXAMPLE 4

3'-epi-N-salicylidene-14-O-[tert-butyl-diphenyl-silyl]-doxorubicin (Vf)

A solution of 1 g of 3'-epi-N-salicylidene doxorubicin (VIe) in 20 ml of anhydrous dimethylformamide was treated with 0.5 ml of tetr-butyl-diphenyl-chlorosilane and 0.3 g of imidazole. The reaction mixture was left standing overnight at room temperature, after which 200 ml of water was added and the solution was extracted with methylene dichloride.

The organic layer was separated off, dried over anhydrous sodium sulphate, filtered and evaporated to dryness under vacuum. The residue was triturated with hexane and collected on a sintered glass, washed with hexane-diethyl ether and dried in vacuum to give the compound (VIf).
Rf 0.25 on TLC, Kieselgel F 254 (Merck) using as eluent the solvent mixture CH_2Cl_2-acetone (4/1 v/v).

EXAMPLE 5

3'-epi-3'-deamino-4'-deoxy-4'-epi-3',4'-epimino doxorubicin (Ib)

The title compound was prepared starting from (VIf) "via" its 3'-epi-4'-O-trifluoromethanesulfonate (VIg) prepared as described in example 2.

Acidic hydrolysis of VIg in methanol with a catalytic amount of p-toluensulfonic acid monohydrate, gave, after work up Ih. The crude product was triturated with hexane and collected on a sintered glass, washed with hexane-diethyl ether and dissolved in 100 ml of tetrahydrofurane. The solution was treated with 0.5 g of tetra-n-butyl-ammonium fluoride. After 2 hours the hydrolysis of the tert-butyl-diphenyl-silyl group was complete. The residue obtained by evaporating off the solvent under vacuum was purified by chromatography on a column of silica gel buffered at pH 7 using dichloromethane-ethanol as eluting system to afford pure Ib. The precipitated was collected on a sintered glass, washed with hexane-diethyl ether and dried in vacuum.

Rf 0.20 on TLC Kieselgel F 254 (Merck) using as eluent the solvent mixture CH_2Cl_2–CH_3OH–CH_3COOH–H_2O (30/4/1/0.5 v/v)

EXAMPLE 6

3′-deamino-4′-deoxy-3′-hydroxy-4′-epi-4′-amino-daunorubicin (IIa)

The title compound was prepared starting from the aziridine Ia. 1 g of Ia was transformed into the N-trifluoroacetyl derivative VIIi by treatement with 1.2 ml of trifluoroacetic anhydride in anhydrous methylene dichloride. After work up the crude material [Rf 0.7 on TLC, Kieselgel F 254 (Merck) using as eluent the solvent mixture CH_2Cl_2-Acetone (4/1 v/v)] was dissolved in 20 ml of acetone and treated with a catalitic amount of sulforic acid at 10°C.

The mixture was diluted 200 ml of methylene dichloride, washed with water, aqueous 5% sodium hydrogen carbonate and water. The solvent was removed in vacuum and the residue purified on a column of silic gel using methylene dichloride as the eluting system to afford 0.7 g of pure IIa.

Rf 0.21 on TLC, Kieselgel F 254 (Merck) using as eluent the solvent mixture CH_2Cl_2-Acetone (4/1 v/v).

The product IIa was slowly dissolved in aqueous 0.1N sodium hydroxyde, at 0°C in order to perform the hydrolysis of the N-trifluoroacetyl protecting group.

After 1 hr at 0°C, the solution was adjusted to pH 8.6 with 0.1N hydrochloric acid and extracted with methylene dichloride. The solvent was evaporated off, affording 0.5g of a residue that was converted by treatment with methanolic hydrogen chloride into the hydrochloride of 4′-deoxy-4′-amino-4′-epi-3′-deamino-3′-hydroxy-daunorubicin.

MS FD 527 [M+], m.p.153°C (dec).

Rf 0.18 on TLC Kieselgel F 254 (Merck) using the solvent system CH_2Cl_2–CH_3OH–CH_3COOH–H_2O (30/4/1/0.5/v/v)

^{1}H–NMR (200 MHz, $CDCl_3$)

8.02 (dd, J=0.9, 8.5Hz, 1H, *H*-1)
7.77 (dd, J=8.5, 8.5Hz, 1H, *H*-2)
7.38 (dd, J=0.9, 8.5Hz, 1H, *H*-3)
5.52 (dd, J=<1, 4.0Hz, 1H, *H*-1′)
5.28 (dd, J=1.8, 4.0Hz, 1H, *H*-7)
4.07 (s, 3H, OCH_3-4)
3.69 (dq, J=6.3, 9.5Hz, 1H, *H*-5′)
3.22 (dd, J=1.9, 18.9Hz, 1H, *H*-10e)
2.94 (d, J=18.9Hz, 1H, *H*-10ax)
2.40 (s, 3H, $COCH_3$)
2.2–2.4 (m, 1H, *H*-8ax)
2.30 (dd, J=9.5, 9.5Hz, 1H, *H*-4′)
2.0–2.2 (m, 2H, H-8e, H-2′e)
1.70 (ddd, J=4.0, 4.6, 13.2Hz, 1H, *H*-2′ax)
1.31 (d, J=6.3Hz, 3H, CH_3-5′)

EXAMPLE 7

3′-deamino-3′-hydroxy-4′-deoxy-4′-epi-4′-amino-doxorubicin (IIb)

0.5g of IIa was dissolved in a mixture of methanol and dioxane. The solution was treated, as described in United Patent Specification No.3,803,124, first with bromine to give the 14-bromo-derivative and then with aqueous sodium formate to give the title compound.

This was converted into its hydrochloride by treatment with methanolic hydrogen chloride. FD-MS 543 [M+], TLC on Kieselgel F254 (Merck) using the solvent system CH_2Cl_2–CH_3OH–CH_3COOH–H_2O (30/4/1/0.5 v/v) Rf 0.10

BIOLOGICAL ACTIVITY

The cytotoxic activity of the new anthracycline glycoside of the invention (FCE 24782/X00–0333) was tested "in vitro" against HeLa cells, P388, P388/DX, LoVo and Lo-Vo/DX.

Time of exposure to the compound: 24 hours/in comparison with daunorubicin.

The results are shown in Table 1..

The compound, when tested "in vivo" against P-388 ascitic leukemia and Gross leukemia, exibited good antitumour activity, in comparison with daunorubicin, especially when orally administered.

The results are given in Tables 2 and 3.

Table 1

In vitro activity of 3'-deamino-4'-deoxy-3'-hydroxy-4'-epi-4'-amino-daunorubicin (FCE 24782/X00-0333) in comparison with DNR

Compound	ID_{50} (ng/ml) [a]				
	[b] HeLa	[c] P388	[d] P388/DX	[e] LoVo	[f] LoVo/Dx
DNR	19	10.5	730	43	820
FCE 24782/X00-0333	11	24.5	235	37	230

a) Dose giving 50% reduction of cell number in comparison with untreated controls.

b) Human cervix epithelioid carcinoma cells

c) P 388 leukemia cells sensitive to Doxorubicin

d) P 388 leukemia cells resistant to Doxorubicin

e) Human colon adenocarcinoma cells sensitive to Doxorubicin

f) Human colon adenocarcinoma cells resistant to Doxorubicin

Table 2 Effect against P 388 ascitic leukemia[a]

Compound	dose[b]	T/C%[c]	Toxic[d] deaths
DNR	2.9	155	0/10
	4.4	170	8/10
FCE 24782/ X00-0333	1.96	155	0/10
	2.9	150	0/10
	4.4	140	9/10
	6.6	100	10/10

[a]Experiments were performed in CDF_1 mice, inoculated with 10^6 leukemia cells i.p.
[b]Treatment i.p. on day 1 after tumor inoculum.
[c]Median survival time of treated mice/median survival timeof controls × 100.
[d]Evaluated on the basis of autoptic findings.

Table 3 Effect against Gross leukemia[a]

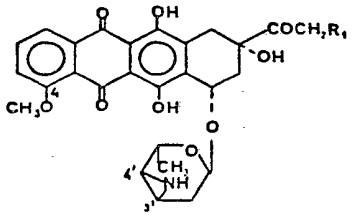
Compound	dose[b] mg/Kg	T/C%[c]	Toxic[d] deaths
DNR	10	165	0/20
	15	192	2/20
FCE 24782/ X00-0333	8.2	175	0/20
	11.5	230	0/10
	16.1	240	0/10
	22.5	130	0/10

[a]Experiments were performed in C3H mice, inoculated with 2×10^6 leukemia cells i.v.

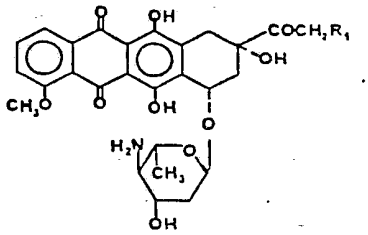
[b]Treatment i.v. on day 1 after tumor inoculum.
[c]Median survival time of treated mice/median survival time of controls × 100.
[d]Evaluated on the basis of autoptic findings.

CLAIMS

1. An anthracycline glycoside having the general formula (I) or (II):



I



II

wherein R_1 represents a hydrogen atom or a hydroxyl group, and pharmaceutically acceptable acid addition salts thereof.

2. A compound according to claim 1, which is 3'-deamino-4'-deoxy-3'-epi-4'-epi-3',4'-epimino-daunorubicin.

3. A compound according to claim 1, which is 3'-deamino-4'-deoxy-3'-epi-4'-epi-3',4'-epimino-doxorubicin.

4. A compound according to claim 1, which is 3'-deamino-4'-deoxy-3'-hydroxy-4'-epi-4'-amino-daunorubicin or its hydrochloride.

5. A compound according to claim 1, which is 3'-deamino-4'-deoxy-3'-hydroxy-4'-epi-4'-amino-doxorubicin or its hydrochloride.

6. A process for the preparation of a glycoside of formula (I) as defined in claim 1 wherein R_1 represents a hydrogen atom, which process comprises reacting 3'-epi-daunorubicin with salicylaldehyde so as to obtain the corresponding 3'-epi-N-salicylidene derivative; converting the 4'-hydroxy group of the said 3'-epi-N-salicylidene derivative into a trifluoromethanesulfonate group; and removing from the 3'epi-N-salicylidene-4'-O-trifluoromethanesulfonate thus obtained the salicylidene group by acid hydrolysis so as to cause the desired glycolside of formula (I) to be obtained via displacement of the 4'-O-trifluoromethanesulfonate group.

7. A process according to claim 6, wherein 3'-epi-daunorubicin dissolved in a mixture of water and acetone is reacted, at room temperature, with salicylaldehyde to obtain the corresponding 3'-epi-N-salicylidene derivative which is subsequently treated, in anhydrous methylene dichloride and in the presence of dry pyridine, with trfluoromethanesulfonic anhydride to give the corresponding N-salicylidene-3'-epi-4'-O-trifluoromethanesulfonate of which the salicylidene protecting group is subjected to acidic hydrolysis by means of p-toluensulfonic acid, at room temperature with the said trifluoromethanesulfonate being dissolved in methanol, to obtain, via the displacement of the trifluoromethanesulfonate leaving group, the desired glycoside of formula (I).

8. A process for the preparation of a glycoside of formula (I) as defined in claim 1 wherein R_1 represents a hydroxy group, which process comprises reacting 3'-epi-doxorubicin with salicylaldehyde so as to obtain the corresponding 3'-epi-N-salicylidene derivative; protecting the 14-hydroxy group of the said 3'-epi-N-salicylidene derivative with a tert.butyl-diphenyl-silyl group, converting the 4'-hydroxy group of the 3'-epi-N-salicylidene-14-O-[tert.butyl-diphenyl-silyl]-doxorubicin thus obtained into a trifluoromethanesulfonate group; and removing from the 14-O-[tert.butyl-diphenyl-silyl]-3'-epi-N-salicylidene-4'-O-trifluoromethanesulfonate thus obtained the salicylidene group by acid hydrolysis and the 14-O-[tert.butyl-diphenyl-silyl] group so as to cause the desired glycoside of formula (I) to be obtained via displacement of the 4'-O-trifluoromethanesulfonate group.

9. A process according to claim 8, wherein 3'-epi-doxorubicin, dissolved in a mixture of water and acetone, is reacted at room temperature with salicylaldehyde to obtain the corresponding 3'-epi-N-salicyldene derivative which is subsequently treated, in anhydrous dimethylformamide, at room temperature, with t-butyl-diphenylchlorosilane in the presence of imidazole to give its 3'-epi-N-salicylidene-14-O-[t-butyl-diphenyl-silyl]ether, which dissolved in anhydrous methylene dichloride is converted, by treatment with trifluoromerthanesulfonic anhydride, in the presence of dry pyridine, into its 3'-epi-N-salicylidene-4'-O-trifluoromethanesulfonate-14-O-[t-butyl-diphenyl-silyl] ether of which the salicylidene protecting group is subjected to acidic hyrolysis at room temperature and in a methanolic solution by means of a catalytic amount of p-toluensulfonic acid and from which subsequently the 14-O-[t-butyl-diphenyl-silyl] protecting group is removed by treatment with tetra-n-butyl ammonium fluoride in tetrahydrofuran, at room tempera-

ture, to obtain the desired glycoside of formula (I).

10. A process for the preparation of a glycoside of formula (II) as defined in claim 1 or a pharmaceutically acceptable salt thereof, which process comprises converting 3'-deamino-4'-deoxy-3'-epi-3,4'-epimino-daunorubicin into the corresponding N-trifluoroacetyl derivative; converting the said N-trifluoroacetyl derivative into 4'-deoxy-4'-epi-N-trifluoroacetyl-3'-deamino-3'-hydroxy daunorubicin; removing the N-trifluoroacetyl group from the 4'-deoxy-4'-epi-N-trifluoroacetyl-3'-deamino-3'-hydroxy daunorubicin so as to obtain the glycoside of formula (II) wherein R_1 is a hydrogen atom; if desired, converting the said glycoside of formula (II) into a pharmaceutically acceptable acid addition salt thereof; if desired, brominating the said glycoside of formula (II) or pharmaceutically acceptable salt thereof and hyrolysing the 14-bromo derivative thus obtained so as to form the glycoside of formula (II) wherein R_1 is a hydroxy group; and, if desired, converting the said glycoside of formula (II) wherein R_1 is a hydroxy group into a pharmaceutically acceptable acid addition salt thereof.

11. A process according to claim 10, wherein the 3'-deamino-4'-deoxy-3'-epi-4'-epi-3',4'-epimino-daunorubicin is reached with trifluoroacetic anhydride to obtain the corresponding N-trifluoroacetyl derivative which, by treatment with a catalytic amount of sulfuric acid in acetone gives 4'-deoxy-4'-epi-N-trifluoroacetyl-3'-deamino-3'-hydroxy-daunorubicin; removing the N-trifluoroacetyl protecting group therefrom by mild alkaline hyrolysis, at a temperature of 0°C, by means of 0.1N aqueous sodium hydroxide; optionally, isolation the glycoside of formula (II) wherein R_1 is a hydrogen atom as its hydrochloide by treatment with hydrogen chloride in methanol; optionally, converting the said glycoside of formula (II) or hydrochloride thereof to the glycoside of formula (II) wherein R_1 is a hydroxy group by bromination followed by treatment of the resultant 14-bromo derivative with aqueous sodium formate at room temperature; and, optionally, isolating the said glycoside of formula (II) wherein R_1 is a hydroxy group as its hydrochloride by treatment with a methanolic solution of hydrogen chloride.

12. A pharmaceutical composition comprising an anthracycline glycoside of formula (I) or (II) as defined in claim 1 or a pharmaceutically acceptable acid addition salt thereof, together with a pharmaceutically acceptable carrier or diluent.

13. An anthracycline glycoside of formula (I) or (II) as defined in claim 1, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of the human or animal body by therapy.

14. An anthracycline glycoside or salt thereof according to claim 13 for use an an antitumor agent.

15. A process for the preparation of an anthracycline glycoside of formula (I) as defined in claim 1, said process being substantially as hereinbefore described in Examples 1 and 2 together or Examples 3 to 5 together.

16. A process for the preparation of an anthracycline glycoside of formula (II) as defined in claim 1 or a pharmaceutically acceptable salt thereof, said process being substantially as hereinbefore described in Example 6 or Example 6 and 7 together.

Published 1988 at The Patent Office, State House, 66/71 High Holborn, London WC1R 4TP. Further copies may be obtained from The Patent Office, Sales Branch, St Mary Cray, Orpington, Kent BR5 3RD. Printed by Burgess & Son (Abingdon) Ltd. Con. 1/87.