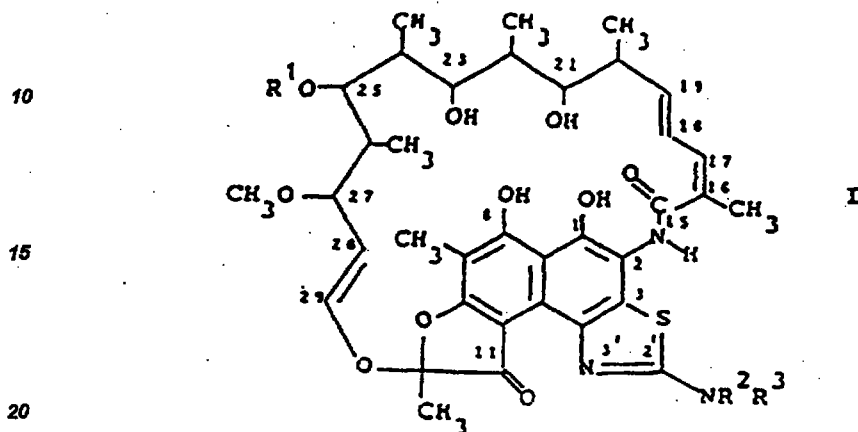


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4-deoxy-thiazolo[5,4-c]rifamycin SV (also called "rifamycin P") has been obtained both by fermentation
35 of *Nocardia* strains and by chemical processes.

2'-Alkyl-4-deoxy-thiazolo[5,4-c]rifamycin SV derivatives are described in US 4169834 :

40 2-deoxythiazolo[5,4-c]rifamycin SV having a mono-amino substituent or a hydrazino substituent in position 2' are disclosed in DE-A-2741066 and are prepared by reacting 3-bromo rifamycin S with the proper thiourea derivative.

"(C₁-C₄) alkoxy" either alone or in combination with other groups represents alkoxy groups of 1 to 4 carbon atoms such as methoxy, ethoxy, propoxy, 1-methylethoxy, 2-methylpropoxy, 2-methyl-2-propoxy and butoxy.

The further ring nitrogen, when present, may bear a substituent R⁴ which is defined as reported above.

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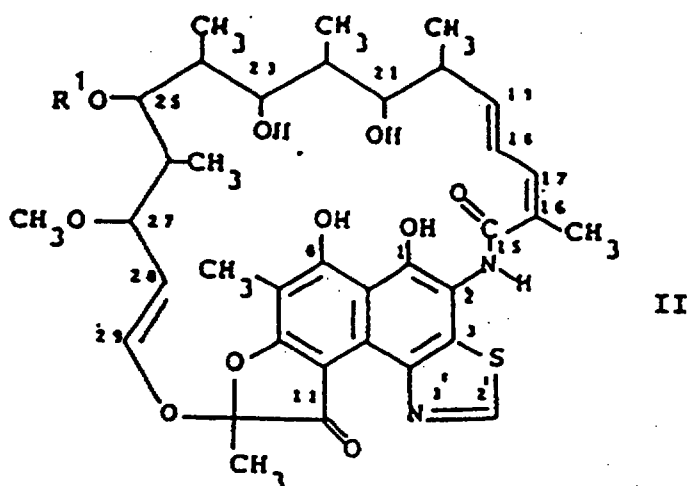
piperazinyl, oxazolidinyl, pyrazolidinyl, thiazolidinyl, morpholinyl, imidazolidinyl groups and the further ring nitrogen atom when present bears a substituent R^4 which is as defined above.

A further preferred group of compounds of the invention includes those compounds of formula I wherein R^1 represents acetyl and R^2 and R^3 independently represent methyl or ethyl, or R^2 and R^3 taken together with the adjacent nitrogen atom represents a pyrrolidinyl, morpholinyl, piperidinyl or piperazinyl group optionally substituted as defined above with reference to the meanings of R^4 .

Specific preferred embodiments of the invention are represented by the following compounds of formula I:

- 2'-(4"-morpholinyl) rifamycin P
- 2'-(1"-piperidinyl) rifamycin P
- 2'-(4"-methyl-1"-piperazinyl) rifamycin P
- 2'-(N,N-diethylamino) rifamycin P

The compounds of the invention are prepared by reacting 4-deoxy-thiazolo[5,4-c]rifamycin SV (i.e. rifamycin P) or 25-desacetyl-4-deoxy-thiazolo[5,4-c]rifamycin SV, i.e. a compound of the following formula II



wherein R^1 represents hydrogen or acetyl, with an amine of formula HNR^2R^3 in the presence of an inert organic solvent, with the proviso that when the HNR^2R^3 amine is piperazine R^4 is different from hydrogen.

To obtain the piperazine derivative wherein R^4 is hydrogen, the corresponding phenyl (C_1 - C_4) alkoxy-carbonyl derivative is submitted to hydrogenolysis under conditions that prevent the hydrogenation of the ansa double bonds.

The reaction temperature is generally between 5°C and 40°C and preferably between 15°C and 30°C , the preferred reaction temperature is room temperature.

The inert organic solvent may be one of the organic solvents which do not unfavourably interfere with the reaction course which are capable of at least partially dissolve the starting material of formula II and the amine HNR^2R^3 while it is not necessary that either the starting materials or the final products be completely dissolved into the reaction so as to form a homogeneous phase.

Representative examples of inert organic solvents are saturated "cyclic" ethers like tetrahydrofuran or dioxane, glycol ethers like dimethoxyethanol and (C_1 - C_4) alkyl alkanoates such as ethyl acetate, propyl acetate or ethylpropionate, and mixtures thereof.

The hydrogenolytic step which is required to obtain the piperazine derivative wherein R^4 is hydrogen starting from the corresponding compound wherein R^4 is as defined above but different from hydrogen must be carried out under conditions that do not lead to a substantial hydrogenation of the ansa double bonds.

This hydrogenolysis is preferably conducted in a polar organic solvent such as a lower alkanol in the presence of a hydrogenation catalyst like palladium on carbon.

Most preferred conditions are the presence of absolute ethanol as the solvent and 10% palladium on carbon as the catalyst.

The reaction course is monitored as known in the art by HPLC or TLC techniques so that the skilled man is capable of adjusting the specific reaction conditions and deciding when the reaction is to be considered completed.

Usual purification procedures such as extraction with solvents, precipitation by addition of non-solvents, or by changing the pH of the medium, and chromatographic procedures are suitable for the purification of the compounds of the invention.

Chromatographic procedures includes preparative TLC, column chromatography and HPLC.

5 The physico-chemical data, and purification methods, of some representative compounds of the invention are reported in the following Tables I and II.

More particularly, the compounds listed below are compounds of formula I wherein R¹ represents acetyl, with the exception of compound 3b wherein R¹ represents hydrogen.

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TABLE I

Compound of Example	R ² R ³	Reaction Conditions			Purification	yield
		Rifamycin P	HNR ² R ³	Time (h)		
		(g)/solvent (ml)	(ml)	1)	2)	
1a	-(CH ₂) ₄ -	1/150 THF	10	5	a, c, f	18.3
1b	-(CH ₂) ₂ O(CH ₂) ₂ -	1/100 THF	5	5	a, c, e	20.7
1c	-(CH ₂) ₂ N(CH ₂) ₂ - C ₆ H ₅	1/50 EtOAc	5+5	2; 18	a, h, g	30.5
1d	-(CH ₂) ₂ N(CH ₂) ₂ - CH ₂ C ₆ H ₅	1/50 EtOAc	5	15	a, c, f	20.0
1e	-(CH ₂) ₂ N(CH ₂) ₂ - COOC ₂ H ₅	0.6/40 EtOAc	4	15	a, c, f	34.5

TABLE I

Compound of Example	R ²	R ³	Reaction Conditions			Time (h) ¹⁾	Purification 2)	Yield
			Rifamycin P (g)/solvent (ml)	HNR ² R ³ (ml) ¹⁾				
1f		$-(CH_2)_2N(CH_2)_2-$ $COOCH_2-C_6H_5$	1.5/100 EtOAc	2		18	a, c, f	17.6
2		$-(CH_2)_5-$	1/-	15		30	a, c, f	13.6
3a		$-(CH_2)_2N(CH_2)_2-$ CH_3	2/300 EtOAc	10+10		1.5; 3.5	b, c	57.6
3b		$-(CH_2)_2N(CH_2)_2-$ CH_3 25-desacetyl	0.8/100 EtOAc	4+4		1.5; 3.5	b, d, e	32.8
3c		$-(CH_2)_2N(CH_2)_2-$ $(CH_2)_2OH$	1/50 EtOAc	5+4		4; 24	b, h, f	17.1

TABLE I

Continued.....

Compound of Example	R ²	R ³	Reaction Conditions			Time (h) ¹⁾	Purification 2)	Yield
			Rifamycin P (g)/solvent (ml)	HNR ² R ³ (ml) ¹⁾				
3d	$-(CH_2)_2N(CH_2)_2-$ C_6H_4Cl		1/200 EtOAc	2g		12	b, d, f	30.2
3e	$-(CH_2)_2N(CH_2)_2-$ $C_6H_4OCH_3P.$		2/400 EtOAc	4		12	b, d, f	9.6
4	$-(CH_2)_2N(CH_2)_2-$ H		-	-		-	-	17.9
5	C_2H_5	C_2H_5	0.5/25 EtOAc	5		120	-	6.0

Notes to Table I

- 1) When two quantities are reported the reagent was added in two portions at the times indicated.
- 2) a) Acid treatment as described for compound 1a ; b) acid/base treatment as described for compound 3a ; c) preparative TLC eluent mixture $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 95 : 5, the compound is collected dissolved with a mixture of EtOAc and acid water, the organic layer is separated, and concentrated to a small volume ; the product is precipitated with petroleum ether ;
- d) preparative TLC, eluent mixture $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 95 : 5, then worked up as described for compound 4 ;
- e) crystallized from EtOAc ; f) precipitated from EtOAc with petroleum ether ;
- g) precipitated from CH_2Cl_2 with petroleum ether ; h) column chromatography, on Silica Gel 60 (0.06-0.2 mm ; Merck Co.) eluent mixture $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 95 : 5.

TABLE II

Compound of Example	Formula 1)	TLC, R _f ²⁾	mp, °C (dec) 3)	MW (LC/MS)	UV 4) (MeOH) lambda max, (nm) log epsilon
1a	C ₄₂ H ₅₃ N ₃ O ₁₁ S	0.36	180-184	807.8 (M+H) ⁺ m/z 808)	228 4.62 308 4.46 432 4.11
1b	C ₄₂ H ₅₃ N ₃ O ₁₂ S	0.41	198-200	823.9	228 4.62 308 4.47 432 4.08
1c	C ₄₈ H ₅₈ N ₄ O ₁₁ S	0.38	179-180	899.1	230 sh 242 4.68 308 4.51 430 4.08
1d	C ₄₉ H ₆₀ N ₄ O ₁₁ S	0.46	171-174	913.1	n.d.

TABLE II

Continued....

Compound of Example	Formula ¹⁾	TLC, R _f ²⁾	mp, °C (dec) ³⁾	MW (LC/MS)	UV ⁴⁾ (MeOH) lambda max, (nm) log epsilon
1e	C ₄₅ H ₅₈ N ₄ O ₁₃ S	0.38	165-167	895.0 (M-H) ⁺ m/z 894)	n.d.
1f	C ₅₀ H ₆₀ N ₄ O ₁₁ S	0.75	163-166	925.1	229 4.59 310 4.44 432 3.99
2	C ₄₃ H ₅₅ N ₃ O ₁₁ S	0.40	172-175	821.9 (M) ⁻ m/z 821) (M+H) ⁺ m/z 822)	228 4.76 308 4.61 430 4.25
3a	C ₄₃ H ₅₆ N ₄ O ₁₁ S	0.57	183-185	837.0 (M) ⁻ m/z 837)	227 4.62 308 4.47 430 4.08
3b	C ₄₁ H ₅₄ N ₄ O ₁₀ S	0.51	190-192	794.9	228 4.64 308 4.50 432 4.12

Continued.....

TABLE II

Compound of Example	Formula ¹⁾	TLC, R _F ²⁾	mp, °C (dec) ³⁾	MW (LC/MS)	UV ⁴⁾ (MeOH) lambda max, (nm) log epsilon
3c	C ₄₄ H ₅₈ N ₄ O ₁₂ S	0.53	183-185	867.0	227 4.61 308 4.46 430 4.07
3d	C ₄₈ H ₅₇ ClN ₄ O ₁₁ S	0.39	182-183	933.5	228 4.67 252 4.72 307 4.54 431 4.11
3e	C ₄₉ H ₆₀ N ₄ O ₁₂ S	0.41	176-179	929.1	237 sh 242 4.69 309 4.51 432 4.08

TABLE II

Continued.....

Compound of Example	Formula 1)	TLC, R _f ²⁾	mp, °C (dec) 3)	MW (LC/MS)	UV 4) (MeOH) lambda max, (nm) log epsilon
4	C ₄₂ H ₅₄ N ₄ O ₁₁ S	0.30	200-201	822.9	230 4.55 312 4.41 436 3.97
5	C ₄₂ H ₅₅ N ₃ O ₁₁ S	0.39	180-183	809.9	228 4.61 307 4.46 429 4.12

Notes to Table II

On Silica Gel 60 F₂₅₄ plates (Merck) ; solvent-run 10.0 cm

1) The analytical results for C, H, N, S (and Cl) were within $\pm 0.4\%$ of the theoretical values.

2) Eluent mixture CHCl₃/MeOH 9/1. Under these conditions the R_f of rifamycin P is 0.42.

3) Determined in glass capillary tubes

4) Rifamycin P shows the following values of $\lambda_{\max}$ in methanol nm : 225, 260, 305, 352, 412.
n.d. = not determined

The compounds of the invention possess antimicrobial activity against gram positive and some gram negative bacteria and are also active against Mycobacteria strains, in particular against Mycobacterium tuberculosis.

The minimum inhibitory concentration (MIC) of representative compounds of the invention was determined using two-fold dilution method in microtiter system.

The media used were : Todd-Hewitt broth (Difco) for streptococci ; Iso-Sensitest broth (Oxoid) for staphylococci and gram-negative bacteria.

The final inoculum was about 10⁴ cfMy/ml. MIC was read as the lowest concentration which showed no visible growth after 18-24 hours incubation at 37°C.

For M. tuberculosis H₃₇R_v the inoculum consisted of 0.5-1% of a 7-9 day culture in Dubos medium.

The tests were carried out in Kirschner medium supplemented with 10% horse serum.

Observations were made after 7-days incubation at 37°C.

The results obtained are summarized in the following Table III :

TABLE III

In vitro antibacterial activity (MIC, mg/l)

Organism	1a	2	1b	1c	1d	1e	1f
<u>Staphylococcus aureus</u> ATCC 6538	0.016	0.003	0.001	0.004	0.004	0.032	0.064
<u>S. aureus</u> TOUR L 165	0.004	0.006	0.002	0.008	0.008	0.064	0.064
<u>S. aureus</u> TOUR ^{a)} L 165	0.016	0.2	0.008	0.016	0.016	0.064	0.064
<u>S. aureus</u> TOUR ^{b)} L 1282	>128	>100	64	>128	>128	128	>128
<u>Streptococcus pyogenes</u> C203	0.008	0.05	0.032	0.032	0.064	0.064	0.125
<u>S. faecalis</u> ATCC 7080	2	1.6	1	1	1	4	2
<u>S. faecalis</u> ATCC 10541	n.t.	n.t.	n.t.	n.t.	n.t.	n.t.	n.t.
<u>S. pneumoniae</u> UC 41	0.032	0.05	0.016	0.004	0.064	0.064	0.064
<u>Proteus vulgaris</u> XI9H ATCC 881	16	6.25	8	16	32	16	64
<u>Escherichia coli</u> SKF 12140	16	12.5	16	4	32	16	>128
<u>Klebsiella pneumoniae</u> ISM	32	25	32	>128	64	32	>128
<u>Pseudomonas aeruginosa</u> ATCC 10145	8	6.25	16	8	16	32	32
<u>Mycobacterium tuberculosis</u> H37RV							
ATCC 9360	2	0.2	2	1	0.125	2	0.5

a) Supplemented with 30% bovine serum; b) Rifampicin resistant strain; n.t. means not tested

Continued.....

TABLE III

In vitro antibacterial activity (MIC, mg/l)

Organism	3a	3b	3c	3d	3e	4	5
<u>Staphylococcus aureus</u> ATCC 6538	0.001	0.008	0.008	0.064	0.064	0.125	0.032
<u>S. aureus</u> TOUR L 165	0.004	0.008	0.016	0.064	0.064	0.125	0.064
<u>S. aureus</u> TOUR ^{a)} L 165	0.004	0.016	0.032	0.25	0.5	0.125	0.5
<u>S. aureus</u> TOUR ^{b)} L 1282	32	>128	64	>128	>128	>128	>128
<u>Streptococcus pyogenes</u> C203	0.032	0.063	0.016	0.064	0.125	0.125	0.064
<u>S. faecalis</u> ATCC 7080	2	1	4	2	4	2	1
<u>S. faecalis</u> ATCC 10541	n.t.	n.t.	n.t.	n.t.	n.t.	n.t.	n.t.
<u>S. pneumoniae</u> UC 41	0.032 [*]	0.063	0.008	0.125	0.064	0.064	0.032
<u>Proteus vulgaris</u> XI9H ATCC 881	8	8	16	>128	64	8	32
<u>Escherichia coli</u> SKF 12140	16	8	8	1	8	8	32
<u>Klebsiella pneumoniae</u> ISM	32	16	32	>128	>128	16	64
<u>Pseudomonas aeruginosa</u> ATCC 10145	16	8	16	128	128	8	16
<u>Mycobacterium tuberculosis</u> H37RV							
ATCC 9360	1	1	4	1	0.25	n.t.	0.5

a) Supplemented with 30% bovine serum; b) Rifampicin resistant strain; n.t. means not tested

The antimicrobial activity of the compounds of the invention is also confirmed in "in vivo" tests.

The results of experimental septicemia in mice are reported in the following Table IV.

The animals (groups of five mice) were infected by intraperitoneal injection of 16-hour broth culture of *S. aureus* tour L 165.

Inocula were adjusted so that untreated animals died of septicemia within 48 hours.

Animals were treated once daily for three days starting immediately after infection. On the 10th day the value for the ED₅₀ in mg/kg/day was calculated by the method of SPEARMAN-KÄRBER (Finney, D.J., Statistical method in biological assay, page 524. C. Griffin Ltd., London, 1952), on the basis of the percentage of surviving animals at each dose.

TABLE IV

Compound of Example	ED ₅₀ (mg/Kg/day)	
	os	sc
1b	0.21	0.21
1c	2.5	0.63
3a	0.36	0.16
3b	13	10
3c	>20	3.3
3d	3.3	3.3
3e	1.9	0.63
5	0.82	0.21
2	0.63	0.16

The following examples further illustrate the invention.

Example 1:

a) 2'-(1"-Pyrrolidinyl) rifamycin P

Pyrrolidine (10 ml) is added to a solution of 1.0 g (1.35 mmole) of rifamycin P in 150 ml of THF at room temperature. The reaction mixture is stirred for 5 hours then it is poured into ice-water, acidified with diluted hydrochloric acid and extracted with ethyl acetate (EtOAc) (2x100 ml). The combined extracts are washed with water to neutrality, dried on anhydrous sodium sulphate and concentrated to a small volume at 45°C under vacuum. The addition of petroleum ether gives a precipitate that was collected and purified by preparative TLC as follows: the solid is dissolved in few milliliter of MeOH and the solution is applied to Silica Gel plates 60 PF₂₅₄ (Merck) that are developed with a mixture of CH₂Cl₂/MeOH 95:5. The zone corresponding to the title product is scraped off and eluted with methanol (MeOH). The extract is evaporated to dryness, the residue is dissolved in ethyl acetate and washed with diluted hydrochloric acid, dried on sodium sulphate and concentrated to a small volume. By adding petroleum ether a precipitate forms which is filtered off and dried under vacuum.

The yield and the physico-chemical data are reported in Tables I and II.

By following the procedure of the above Example (1a) and using the appropriate amine reactant the

following compounds are obtained whose reaction conditions, purification details, yields and physicochemical data are reported in Tables I and II :

- b) 2'-(4"-morpholinyl) rifamycin P HNR^2R^3 = morpholine
- c) 2'-(4"-phenyl-1"-piperazinyl) rifamycin P HNR^2R^3 = 1-phenylpiperazine
- d) 2'-(4"-phenylmethyl-1"-piperazinyl) rifamycin P HNR^2R^3 = 1-benzylpiperazine
- e) 2'-(4"-ethoxycarbonyl-1"-piperazinyl) rifamycin P HNR^2R^3 = 1-ethoxycarbonylpiperazine
- f) 2'-(4"-phenylmethoxycarbonyl-1"-piperazinyl) rifamycin P HNR^2R^3 = 1-phenylmethoxycarbonylpiperazine

Example 2 : 2'-(1"-Piperidinyl) rifamycin P

Rifamycin P (1.0 g, 1.35 mmole) is dissolved in 15 ml of piperidine and the resulting solution is stirred for 30 hours at room temperature.

The reaction mixture is poured in ice-water and worked up as described in the foregoing Example (1a).

Purification details, yield and physico-chemical data are reported in Tables I and II.

Example 3 :

a) 2'-(4"-Methyl-1"-piperazinyl) rifamycin P

1-Methylpiperazine (10 ml) is added to a solution of rifamycin P (2.0 g, 2.7 mmole) in 300 ml of EtOAc and the reaction mixture is stirred for 90 min at room temperature, then an additional 10 ml of 1-methylpiperazine is added. Stirring is continued for 3.5 hours, then the reaction mixture is poured into ice-water and made acidic with diluted hydrochloric acid, maintaining the pH between 4 and 5.

The organic layer is discarded and the aqueous phase is brought to about pH 7 with NaHCO_3 and extracted with EtOAc. The organic extract is dried over sodium sulfate and concentrated to a small volume. By cooling the compound of the title is obtained as crystalline powder which precipitates. Purification details, yield and physico-chemical data are reported in Tables I and II.

By following the procedure of the above Example (3a) and using the appropriate amine reactant the following compounds are obtained whose purification details, yield and physico-chemical data are reported in Tables I and II.

b) 25-Desacetyl-2'-(4"-methyl-1-piperazinyl) rifamycin P (starting from 25-desacetyl rifamycin P) HNR^2R^3 = 1-methylpiperazine

c) 2'-[4"(2"-hydroxyethyl)-1"-piperazinyl]-rifamycin P HNR^2R^3 = 1-(2-hydroxyethyl) piperazine

d) 2'-[4"(4"-chlorophenyl)-1-piperazinyl]rifamycin P HNR^2R^3 = 1-(4-chlorophenyl) piperazine

e) 2'-[4"(4"-methoxyphenyl)-1-piperazinyl] rifamycin P, HNR^2R^3 = 1-(4-methoxyphenyl)-piperazine.

Example 4 : 2'-(1"-Piperazinyl) rifamycin P

A solution of 0.22 g (0.23 mmole) of 2'-[4"-phenylmethoxycarbonyl-1"-piperazinyl] rifamycin P in 40 ml of absolute ethanol is left under hydrogen stream with stirring at room temperature and atmospheric pressure in the presence of 50 mg of 10% palladium on carbon for 1 hour.

The reaction is monitored by TLC (R_f 0.4, relative to the starting compound). Once the reaction is complete the reaction mixture is filtered and the solvent evaporated.

The residue is dissolved with MeOH and purified by preparative TLC on Silica Gel 60 PF₂₅₄ plates (eluent mixture $\text{CHCl}_3/\text{MeOH}$ 9 : 1).

The zones which contain the product of the title are eluted with MeOH.

The methanolic extracts are evaporated to dryness, the residue is dissolved with ethyl acetate and the solution is washed with an aqueous NaHCO_3 solution at pH 8.5, dried over sodium sulfate and concentrated to a small volume.

Upon adding petroleum ether the compound of the title precipitates which is filtered off and dried under vacuum.

Example 5 : 2'-(N,N-diethylamino) rifamycin P

N,N-Diethylamine (5 ml) is added to a solution of rifamycin P (0.5 g, 0.67 mmole) in 25 ml of EtOAc and the reaction mixture is allowed to stand at room temperature for five days, then it is poured into ice-water and made acid with diluted hydrochloric acid.

The organic layer is separated, washed with water to neutrality, dried on sodium sulphate and evapo-

rated to dryness.

The residue is dissolved with 2 ml of CH_2Cl_2 and subjected to flash chromatography by applying it to a column of 35 g of Silica Gel 60 (0.04-0.06 mm) Merck which is developed with :

- a) CH_2Cl_2 (250 ml),
- b) CH_2Cl_2 containing 0.5% (v/v) of methanol (500 ml),
- c) CH_2Cl_2 containing 1% (v/v) of methanol (500 ml),
- d) CH_2Cl_2 containing 1.8% (v/v) of methanol (1 liter).

This last mixture elutes the product of the title and is collected in fractions of 100 ml each (12 fractions).

Those fractions which contain the product of the title are combined and evaporated to dryness obtaining 33 mg of pure compound.

Preparation of the starting materials :

rifamycin P : (4-deoxy-thiazolo[5,4-c]rifamycin) SV

rifamycin P is prepared as described in GB patent 1470426, US patent 4144234 or US patent 4129562.

2'-Methoxycarbonyl rifamycin P :

2'-Methoxycarbonyl rifamycin P is prepared as described by Cricchio et al., in Tetrahedron, 36, 1415-1421 (1981) and US patent 4129562.

25-Desacetyl rifamycin P :

A solution of 4.5 g (5.5 mmole) of 2'-methoxycarbonyl rifamycin P in 200 ml of acetone and 100 ml of 50% aqueous NaOH is allowed to stand at room temperature with stirring.

The reaction is monitored by TLC ($\text{CHCl}_3/\text{MeOH}$, 95 : 5) until the starting compound disappears (about 30 min).

The reaction mixture is poured into ice-water and extracted with EtOAc. The extracts are dried on sodium sulfate and then evaporated to dryness under vacuum during 30 min.

The residue is dissolved into 300 ml of the same acetone/aqueous NaOH mixture and the solution is evaporated again.

The residue is dissolved with CHCl_3 and purified by silica gel (220 g) column chromatography eluting with CHCl_3 containing increasing amounts of MeOH (from 1.5 to 2% in volume).

Fractions containing the desired product are pooled, and the solvents are evaporated to dryness.

By crystallization from EtOAc, 3.5 g (90%) of the desired compound is obtained ; mp 172-174°C ; UV (MeOH) λ_{max} nm (log epsilon) 224 (4.26), 260 (4.21) 298 (4.17), 405 (4.14).

Anal. Calcd for $\text{C}_{36}\text{H}_{44}\text{N}_2\text{O}_{10}\text{S}$: C 62.05. H 6.36 ; N 4.02 ; S 4.60.

Found : C 61.76 ; H 6.30 ; N 3.95 ; S 4.47.

Claims

Claims for the contracting states : BE DE CH GB FR IT NL LU SE

1. 2'-substituted-4-deoxy-thiazolo[5,4-c] rifamycin SV derivatives of formula I



rated to dryness.

The residue is dissolved with 2 ml of CH_2Cl_2 and subjected to flash chromatography by applying it to a column of 35 g of Silica Gel 60 (0.04-0.06 mm) Merck which is developed with :

- a) CH_2Cl_2 (250 ml),
- b) CH_2Cl_2 containing 0.5% (v/v) of methanol (500 ml),
- c) CH_2Cl_2 containing 1% (v/v) of methanol (500 ml),
- d) CH_2Cl_2 containing 1.8% (v/v) of methanol (1 liter).

This last mixture elutes the product of the title and is collected in fractions of 100 ml each (12 fractions).

Those fractions which contain the product of the title are combined and evaporated to dryness obtaining 33 mg of pure compound.

Preparation of the starting materials :

rifamycin P : (4-deoxy-thiazolo[5,4-c]rifamycin) SV

rifamycin P is prepared as described in GB patent 1470426, US patent 4144234 or US patent 4129562.

2'-Methoxycarbonyl rifamycin P :

2'-Methoxycarbonyl rifamycin P is prepared as described by Cricchio et al., in Tetrahedron, 36, 1415-1421 (1981) and US patent 4129562.

25-Desacetyl rifamycin P :

A solution of 4.5 g (5.5 mmole) of 2'-methoxycarbonyl rifamycin P in 200 ml of acetone and 100 ml of 50% aqueous NaOH is allowed to stand at room temperature with stirring.

The reaction is monitored by TLC ($\text{CHCl}_3/\text{MeOH}$, 95 : 5) until the starting compound disappears (about 30 min).

The reaction mixture is poured into ice-water and extracted with EtOAc. The extracts are dried on sodium sulfate and then evaporated to dryness under vacuum during 30 min.

The residue is dissolved into 300 ml of the same acetone/aqueous NaOH mixture and the solution is evaporated again.

The residue is dissolved with CHCl_3 and purified by silica gel (220 g) column chromatography eluting with CHCl_3 containing increasing amounts of MeOH (from 1.5 to 2% in volume).

Fractions containing the desired product are pooled, and the solvents are evaporated to dryness.

By crystallization from EtOAc, 3.5 g (90%) of the desired compound is obtained ; mp 172-174°C ; UV (MeOH) λ_{max} nm (log epsilon) 224 (4.26), 260 (4.21) 298 (4.17), 405 (4.14).

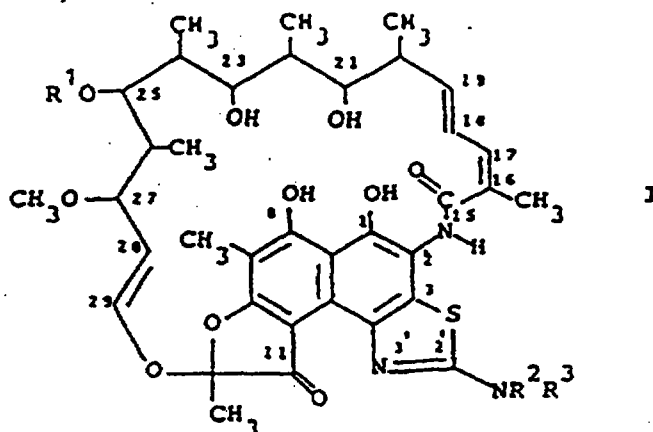
Anal. Calcd for $\text{C}_{38}\text{H}_{44}\text{N}_2\text{O}_{10}\text{S}$: C 62.05, H 6.36 ; N 4.02 ; S 4.60.

Found : C 61.76 ; H 6.30 ; N 3.95 ; S 4.47.

Claims

Claims for the contracting states : BE DE CH GB FR IT NL LU SE

1. 2'-substituted-4-deoxy-thiazolo[5,4-c] rifamycin SV derivatives of formula I



wherein R¹ represents hydrogen or acetyl,

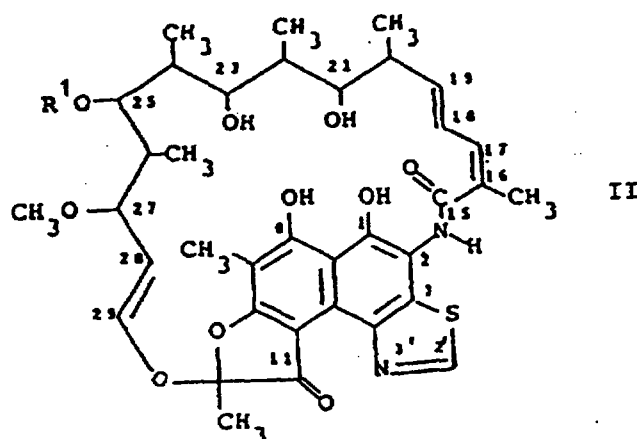
R² and R³ each independently represent (C₁-C₄) alkyl or R² and R³ taken together with the adjacent nitrogen atom represent a 4-7 membered saturated heterocyclic ring selected from azetidiny, pyrrolidiny, piperidiny, piperaziny, oxazolidiny, pyrazolidiny, thiazolidiny, morpholiny, imidazolidiny, wherein a ring nitrogen atom may be substituted with a substituent R⁴ which is selected from (C₁-C₄) alkyl, hydroxy (C₂-C₄) alkyl, (C₂-C₄) alkanoyl, (C₁-C₄) alkoxy carbonyl, phenyl optionally substituted with 1 to 3 substituents selected from halogeno, hydroxy, (C₁-C₄) alkyl and (C₁-C₄) alkoxy ; phenyl (C₁-C₄) alkyl wherein the phenyl ring may be optionally substituted with 1 to 3 substituents selected from halogeno, hydroxy, (C₁-C₄) alkyl, and (C₁-C₄) alkoxy ; and phenyl-(C₁-C₄) alkoxy carbonyl wherein the phenyl ring may be substituted with from 1 to 3 substituents selected from halogeno, hydroxy, (C₁-C₄) alkyl and (C₁-C₄) alkoxy, and the pharmaceutically acceptable acid addition salts thereof.

2. A compound of claim 1 wherein R¹ represents acetyl.

3. A compound of claim 1 wherein R¹ represents acetyl, R² and R³ independently represent methyl or ethyl, or R² and R³ taken together with the adjacent nitrogen atom represent a pyrrolidinyl, morpholinyl, piperidinyl or piperazinyl group optionally substituted as defined in claim 1 with reference to the meanings of R⁴.

4. A compound according to claim 1 wherein R¹ represents acetyl and NR²R³ represents 4-morpholinyl, 1-piperidinyl, 4-methyl-1-piperazinyl, or diethylamino.

5. A process for preparing a compound of claim 1 which comprises reacting a compound of formula II



wherein R¹ represents hydrogen or acetyl,

a) with an amine of formula HNR^2R^3 in the presence of an inert organic solvent, to obtain a compound of formula I wherein the NR^2R^3 group is as defined in claim 1 with the exclusion of the compound wherein NR^2R^3 represents an unsubstituted piperazine ;





b) when a compound of formula I is desired wherein the NR^2R^3 group is an unsubstituted piperazine, subjecting to controlled hydrogenolysis the corresponding compound of formula I wherein R^4 represent phenyl-(C_1 - C_4)alkoxycarbonyl.

6. A process as claimed in claim 5 wherein the reaction temperature of step a) is between 5 and 40°C.

7. A process as claimed in claim 5 wherein the reaction temperature of step a) is room temperature.

8. A process as claimed in claim 5 wherein the hydrogenolysis of step b) is carried out in a polar organic solvent in the presence of a hydrogenation catalyst.

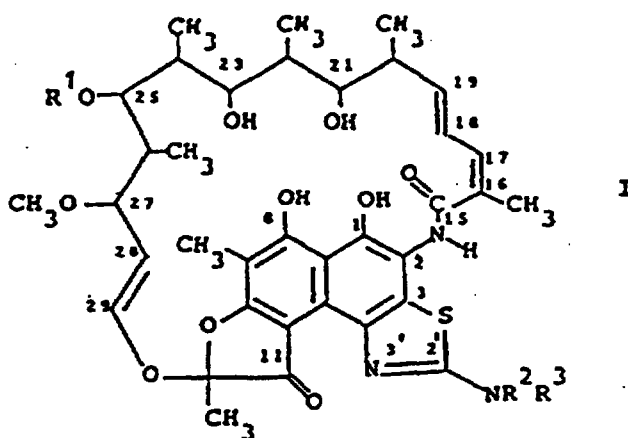
9. A compound of claim 1 for use as a medicine.

10. Use of a compound of claim 1 for preparing a medicament for antibacterial use.

11. A pharmaceutical composition which comprises a compound of claim 1 in admixture with a pharmaceutically acceptable carrier.

Claims for the following Contracting States : AT, ES, GR.

1. A process for preparing a 2'-substituted-4-deoxy-thiazolo[5,4-c]rifamycin SV derivatives of formula I

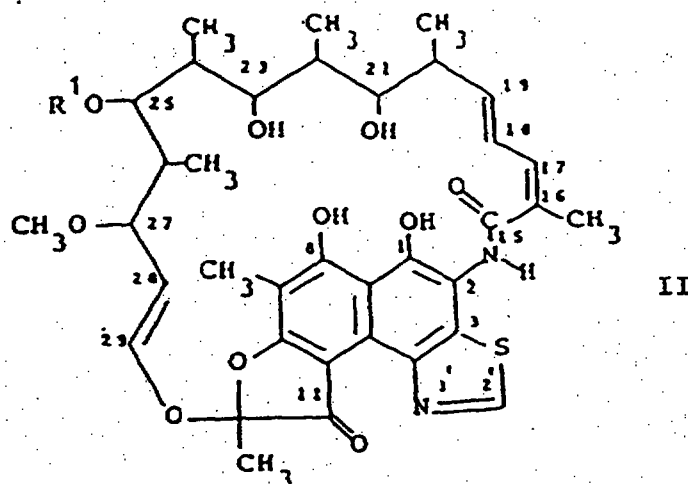


wherein R^1 represents hydrogen or acetyl,

R^2 and R^3 each independently represent (C_1 - C_4) alkyl or R^2 and R^3 taken together with the adjacent nitrogen atom represent a 4-7 membered saturated heterocyclic ring selected from azetidiny, pyrrolidinyl, piperidinyl, piperazinyl, oxazolidinyl, pyrazolidinyl, thiazolidinyl, morpholinyl, imidazolidinyl, wherein a ring nitrogen atom may be substituted with a substituent R^4 which is selected from (C_1 - C_4) alkyl, hydroxy (C_2 - C_4) alkyl, (C_2 - C_4) alkanoyl, (C_1 - C_4) alkoxycarbonyl, phenyl optionally substituted with 1 to 3 substituents selected from halogeno, hydroxy, (C_1 - C_4) alkyl and (C_1 - C_4) alkoxy; phenyl-(C_1 - C_4) alkyl wherein the phenyl ring may be optionally substituted with 1 to 3 substituents selected from halogeno, hydroxy, (C_1 - C_4) alkyl, and (C_1 - C_4) alkoxy; and phenyl (C_1 - C_4) alkoxycarbonyl wherein the phenyl ring may be substituted with from 1 to 3 substituents selected from halogeno, hydroxy, (C_1 - C_4) alkyl and (C_1 - C_4) alkoxy, and the pharmaceutically acceptable acid addition salts thereof.

Which comprises reacting a compound of formula II





wherein R^1 represents hydrogen or acetyl,

a) with an amine of formula HNR^2R^3 in the presence of an inert organic solvent, to obtain a compound of formula I wherein the NR^2R^3 group is as defined in claim 1 with the exclusion of the compound wherein NR^2R^3 represents an unsubstituted piperazine; and

b) when a compound of formula I is desired wherein the NR^2R^3 group is an unsubstituted piperazine, subjecting to controlled hydrogenolysis the corresponding compound of formula I wherein R^4 represent phenyl-(C_1 - C_4) alkoxycarbonyl.

2. A process as in claim 1 for preparing a compound of formula I wherein R^1 represents acetyl.

3. A process as in claim 1 for preparing a compound of formula I wherein R^1 represents acetyl, R^2 and R^3 independently represent methyl or ethyl, or R^2 and R^3 taken together with the adjacent nitrogen atom represent a pyrrolidinyl, morpholinyl, piperidinyl or piperazinyl group optionally substituted as defined in claim 1 with reference to the meanings of R^4 .

4. A process for preparing a compound according to claim 1 wherein R^1 represents acetyl and NR^2R^3 represents 4-morpholinyl, 1-piperidinyl, 4-methyl-1-piperazinyl, or diethylamino.

5. A process as claimed in claim 1 wherein the reaction temperature of step a) is between 5 and 40°C.

6. A process as claimed in claim 1 wherein the reaction temperature of step a) is room temperature.

7. A process as claimed in claim 1 wherein the hydrogenolysis of step b) is carried out in a polar organic solvent in the presence of a hydrogenation catalyst.

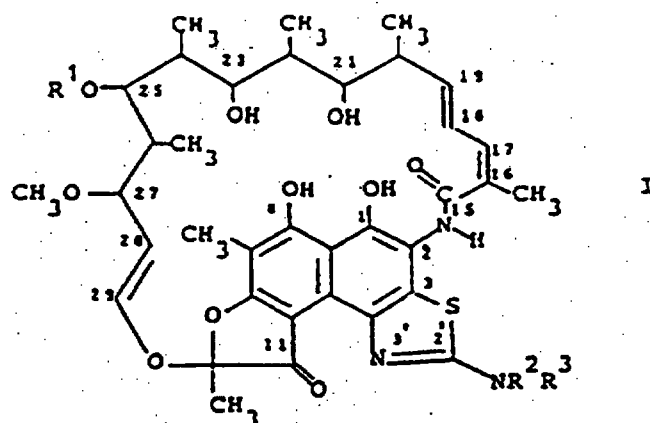
8. Use of a compound of claim 1 for preparing a medicament for antibacterial use.

Ansprüche

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

1. 2'-substituierte 4-Deoxy-thiazolo[5,4-c]-rifamycin SV-Derivate der Formel I





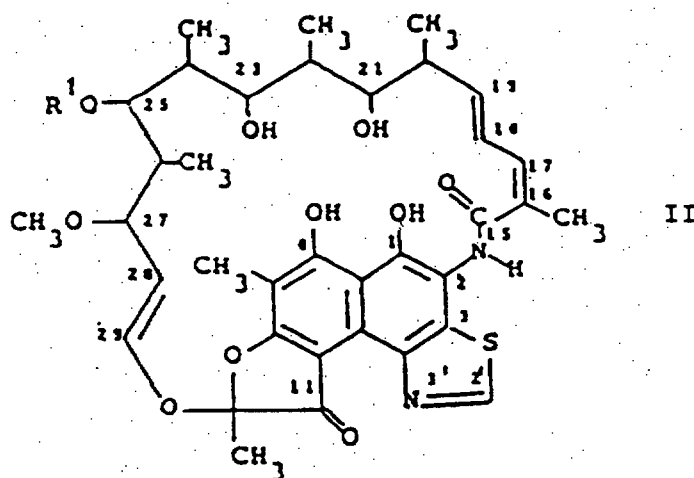
in der R¹ ein Wasserstoffatom oder eine Acetylgruppe bedeutet, R² und R³ jeweils unabhängig einen (C₁-C₄)-Alkylrest darstellen oder R² und R³ zusammen mit dem anliegenden Stickstoffatom einen 4-7-gliedrigen gesättigten heterocyclischen Ring, nämlich eine Azetidiny-, Pyrrolidiny-, Piperidiny-, Piperaziny-, Oxazolidiny-, Pyrazolidiny-, Thiazolidiny-, Morpholiny- oder Imidazolidinygruppe darstellen, wobei ein Ring-Stickstoffatom mit einem Substituenten R⁴ substituiert sein kann, der ausgewählt ist aus (C₁-C₄)-Alkyl-, Hydroxy-(C₂-C₄)-alkyl-, (C₂-C₄)-Alkanoyl-, (C₁-C₄)-Alkoxy-carbonyl-, Phenyl-, gegebenenfalls substituiert mit 1 bis 3 Substituenten, nämlich Halogenatomen, Hydroxyl-, (C₁-C₄)-Alkyl- und (C₁-C₄)-Alkoxyresten, Phenyl-(C₁-C₄)-alkyl-, wobei der Phenylring gegebenenfalls mit 1 bis 3 Substituenten substituiert sein kann, nämlich Halogenatomen, Hydroxyl-, (C₁-C₄)-Alkyl- und (C₁-C₄)-Alkoxyresten, und Phenyl-(C₁-C₄)-alkoxy-carbonylresten, wobei der Phenylring substituiert sein kann mit 1 bis 3 Substituenten, ausgewählt aus Halogenatomen, Hydroxyl-, (C₁-C₄)-Alkyl- und (C₁-C₄)-Alkoxyresten, und die pharmazeutisch verträglichen Säureadditionssalze davon.

2. Verbindung nach Anspruch 1, wobei R¹ eine Acetylgruppe bedeutet.

3. Verbindung nach Anspruch 1, wobei R¹ eine Acetylgruppe bedeutet, R² und R³ unabhängig Methyl- oder Ethylgruppen darstellen, oder R² und R³ zusammen mit dem anliegenden Stickstoffatom eine Pyrrolidiny-, Morpholiny-, Piperidiny- oder Piperazinygruppe, gegebenenfalls substituiert wie in Anspruch 1 mit Bezug auf die Bedeutungen von R⁴ definiert, bedeuten.

4. Verbindung nach Anspruch 1, wobei R¹ eine Acetylgruppe bedeutet und NR²R³ eine 4-Morpholiny-, 1-Piperidiny-, 4-Methyl-1-piperaziny- oder Diethylaminogruppe bedeutet.

5. Verfahren zur Herstellung einer Verbindung nach Anspruch 1, welches Umsetzung einer Verbindung der Formel II



in der R¹ ein Wasserstoffatom oder eine Acetylgruppe bedeutet,

a) mit einem Amin der Formel HNR²R³ in Gegenwart eines inerten organischen Lösungsmittels, um eine

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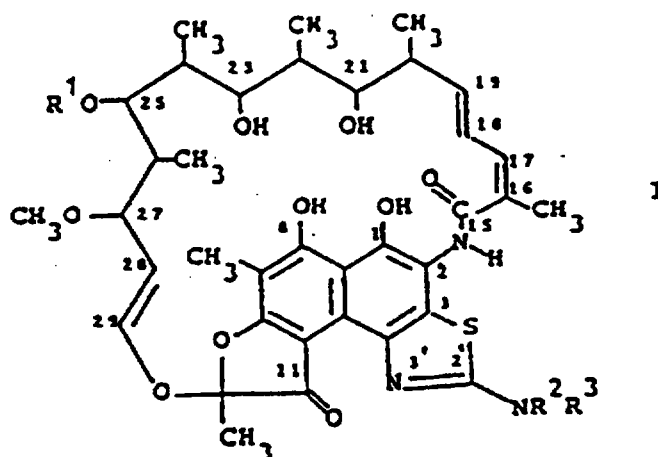
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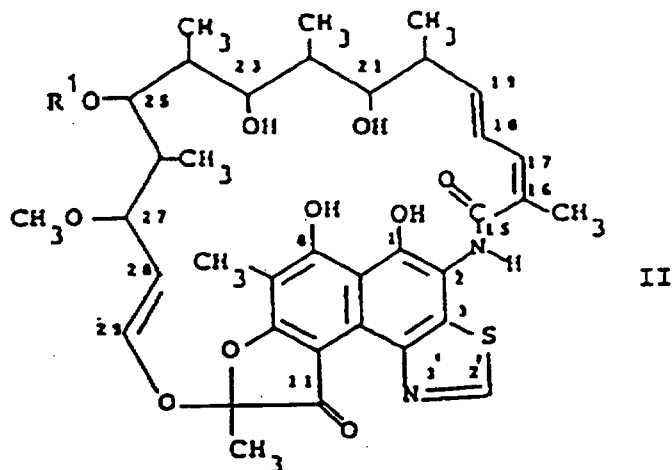
1. Verfahren zur Herstellung von 2'substituierten 4-Deoxythiazolo[5,4-c]-rifamycin SV-Derivate der Formel I

1. Verfahren zur Herstellung von 2'substituierten 4-Deoxythiazolo[5,4-c]-rifamycin SV-Derivate der For-

mel 1



in der R¹ ein Wasserstoffatom oder eine Acetylgruppe bedeutet, R² und R³ jeweils unabhängig einen (C₁-C₄)-Alkylrest darstellen oder R² und R³ zusammen mit dem anliegenden Stickstoffatom einen 4-7-gliedrigen gesättigten heterocyclischen Ring, nämlich eine Azetidiny-, Pyrrolidiny-, Piperidiny-, Piperaziny-, Oxazolidiny-, Pyrazolidiny-, Thiazolidiny-, Morpholin- oder Imidazolidinygruppe darstellen, wobei ein Ring-Stickstoffatom mit einem Substituenten R⁴ substituiert sein kann, der ausgewählt ist aus (C₁-C₄)-Alkyl-, Hydroxy-(C₂-C₄)-alkyl-, (C₂-C₄)-Alkanoyl-, (C₁-C₄)-Alkoxy-carbonyl-, Phenyl-, gegebenenfalls substituiert mit 1 bis 3 Substituenten, nämlich Halogenatomen, Hydroxyl-, (C₁-C₄)-Alkyl- und (C₁-C₄)-Alkoxyresten, Phenyl-(C₁-C₄)-alkyl-, wobei der Phenylring gegebenenfalls mit 1 bis 3 Substituenten substituiert sein kann, nämlich Halogenatomen, Hydroxyl-, (C₁-C₄)-Alkyl- und (C₁-C₄)-Alkoxyresten, und Phenyl-(C₁-C₄)-alkoxy-carbonylresten, wobei der Phenylring substituiert sein kann mit 1 bis 3 Substituenten, ausgewählt aus Halogenatomen, Hydroxyl-, (C₁-C₄) Alkyl- und (C₁-C₄)-Alkoxyresten, und der pharmazeutisch verträglichen Säureadditionssalze davon, welches die Umsetzung einer Verbindung der Formel II



in der R¹ ein Wasserstoffatom oder eine Acetylgruppe bedeutet,

a) mit einem Amin der Formel HNR^2R^3 in Gegenwart eines inerten organischen Lösungsmittels, um eine Verbindung der Formel I, in der der Rest NR^2R^3 wie vorstehend definiert ist, zu erhalten, jedoch unter Ausschuß der Verbindung, in der NR^2R^3 eine unsubstituierte Piperazingruppe bedeutet, umfaßt, und, b) wenn eine Verbindung der Formel I gewünscht wird, in der der Rest NR^2R^3 eine unsubstituierte Piperazingruppe bedeutet, Durchführung einer kontrollierten Hydrogenolyse der entsprechenden Verbindung der Formel I, in der R^4 einen Phenyl-(C_1 - C_4)-alkoxycarbonylrest bedeutet.

2. Verfahren nach Anspruch 1 zur Herstellung einer Verbindung der Formel I, in der R¹ eine Acetylgruppe bedeutet.

3. Verfahren nach Anspruch 1 zur Herstellung einer Verbindung der Formel I, in der R¹ eine Acetylgruppe bedeutet, R² und R³ unabhängig eine Methyl- oder Ethylgruppe bedeuten, oder R² und R³ zusammen mit dem anliegenden Stickstoffatom eine Pyrrolidinyl-, Morpholinyl-, Piperidinyl- oder Piperazinylgruppe, die gegebenenfalls gemäß der Definition in Anspruch 1 mit Bezug auf die Bedeutungen von R⁴ substituiert sind, bedeuten.

4. Verfahren zur Herstellung einer Verbindung nach Anspruch 1, in der R¹ eine Acetylgruppe bedeutet und NR²R³ eine 4-Morpholinyl-, 1-Piperidinyl-, 4-Methyl-1-piperazinyl- oder Diethylaminogruppe bedeutet.

5. Verfahren nach Anspruch 1, wobei die Reaktionstemperatur in Stufe a) zwischen 5 und 40°C liegt.

6. Verfahren nach Anspruch 1, wobei die Reaktionstemperatur in Stufe a) Raumtemperatur ist.

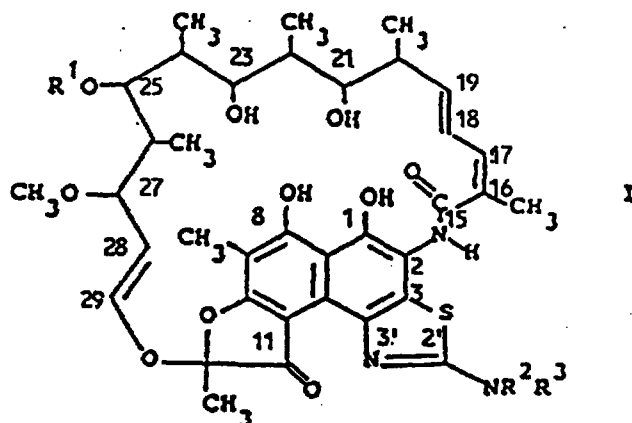
7. Verfahren nach Anspruch 1, wobei die Hydrogenolyse von Stufe b) in einem polaren organischen Lösungsmittel in Gegenwart eines Hydrierungskatalysators durchgeführt wird.

8. Verwendung einer Verbindung nach Anspruch 1 zur Herstellung eines Arzneimittels zur antibakteriellen Verwendung.

Revendications

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

1. Dérivés 2'-substitués de la 4-désoxythiazolo[5,4-c]-rifamycine SV de formule I



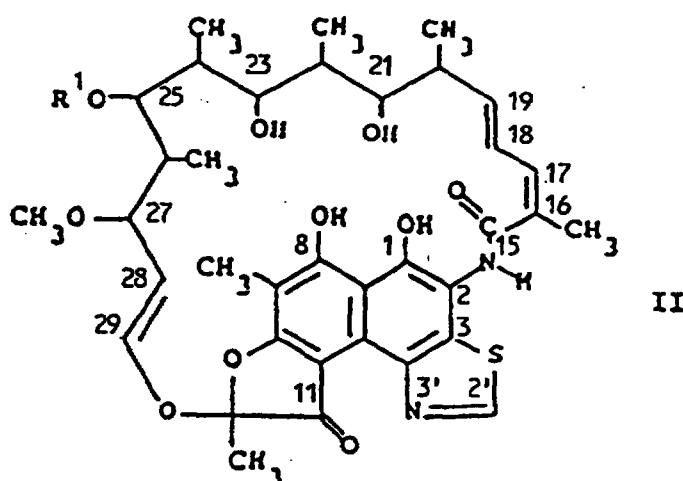
dans laquelle R^1 représente l'hydrogène ou un groupe acétyle, R^2 et R^3 représentent chacun indépendamment un groupe alkyle en C_1-C_4 ou bien R^2 et R^3 pris ensemble avec l'atome d'azote voisin représentent un noyau hétérocyclique saturé à 4-7 chaînons choisi parmi azétidinyne, pyrrolidinyne, pipéridinyne, pipérazinyne, oxazolidinyne, pyrazolidinyne, thiazolidinyne, morpholinyne, imidazolidinyne, dans lequel un atome d'azote cyclique peut être substitué par un substituant R^4 choisi parmi alkyle en C_1-C_4 , hydroxy-alkyle en C_2-C_4 , alcanoyne en C_2-C_4 , (alcoxy en C_1-C_4) carbonyle, phényle facultativement substitué par 1 à 3 substituants choisis parmi halogéno, hydroxy, alkyle en C_1-C_4 et alcoxy en C_1-C_4 ; phényl-alkyle en C_1-C_4 dans lequel le noyau phényle peut être facultativement substitué par 1 à 3 substituants choisis parmi halogéno, hydroxy, alkyle en C_1-C_4 et alcoxy en C_1-C_4 ; et phényl-(alcoxy en C_1-C_4) carbonyle dans lequel le noyau phényle peut être substitué par 1 à 3 substituants choisis parmi halogéno, hydroxy, alkyle en C_1-C_4 et alcoxy en C_1-C_4 et leurs sels d'addition d'acides pharmaceutiquement acceptables.

2. Un composé selon la revendication 1 dans lequel R^1 représente le groupe acétyle.

3. Un composé selon la revendication 1 dans lequel R^1 représente un groupe acétyle, R^2 et R^3 représentent indépendamment méthyle ou éthyle, ou bien R^2 et R^3 pris ensemble avec l'atome d'azote voisin représentent un groupe pyrrolidinyne, morpholinyne, pipéridinyne ou pipérazinyne facultativement substitué comme décrit à la revendication 1 en référence aux significations de R^4 .

4. Un composé selon la revendication 1 dans lequel R^1 représente un groupe acétyle et NR^2R^3 représente un groupe 4-morpholinyne, 1-pipéridinyne, 4-méthyl-1-pipérazinyne ou diéthylamino.

5. Un procédé pour fabriquer un composé selon la revendication 1 qui consiste à faire réagir un composé de formule II



dans laquelle R^1 représente un atome d'hydrogène ou un groupe acétyle,

a) avec une amine de formule HNR^2R^3 en présence d'un solvant organique inerte pour obtenir un composé de formule I dans laquelle le groupe NR^2R^3 est défini comme à la revendication 1, à l'exclusion



du composé dans lequel NR^2R^3 représente une pipérazine non substituée ;

b) lorsque l'on désire un composé de formule I dans laquelle le groupe NR^2R^3 est une pipérazine non substituée, à soumettre le composé correspondant de formule I dans laquelle R^4 représente le groupe phényl-(alcoxy en C_1-C_4) carbonyle à une hydrogénolyse contrôlée.

6. Un procédé selon la revendication 5 dans lequel la température de réaction de l'étape a) est comprise entre 5 et 40°C.

7. Un procédé selon la revendication 5 dans lequel la température de réaction dans l'étape a) est la température ambiante.

8. Un procédé selon la revendication 5 dans lequel l'hydrogénolyse de l'étape b) est effectuée dans un solvant organique en présence d'un catalyseur d'hydrogénation.

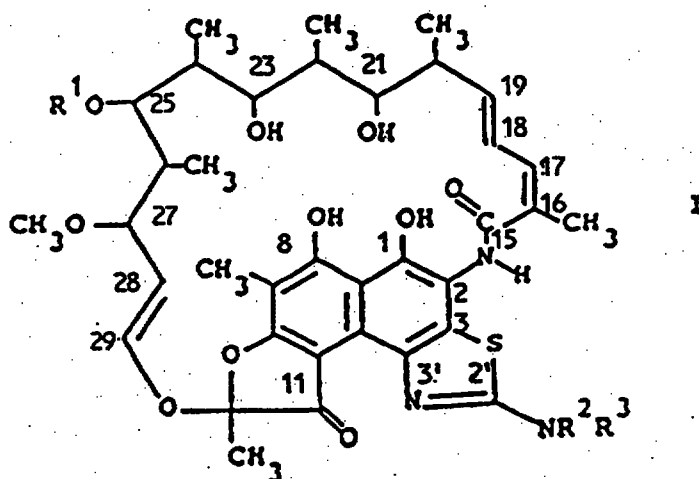
9. Un composé selon la revendication 1 pour l'utilisation comme médicament.

10. Utilisation d'un composé selon la revendication 1 pour la préparation d'un médicament pour l'utilisation comme antibactérien.

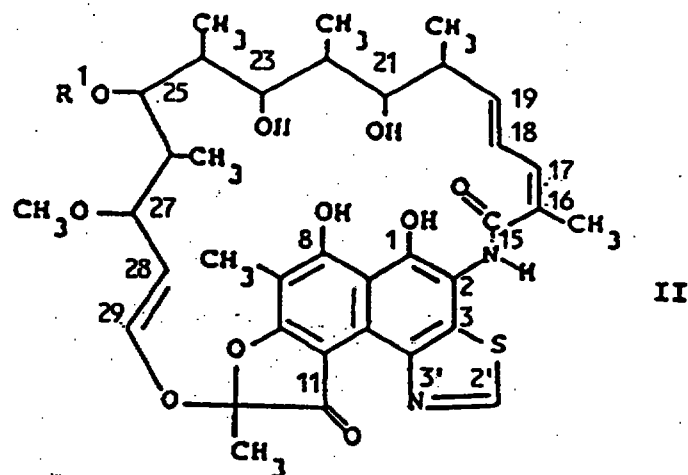
11. Une composition pharmaceutique qui comprend un composé selon la revendication 1 en mélange avec un support pharmaceutiquement acceptable.

Revendications pour les Etats Contractants : AT, ES, GR.

1. Un procédé pour fabriquer des dérivés 2'-substitués de la 4-désoxythiazolo[5,4-c]rifamycine SV de formule I



dans laquelle R^1 représente l'hydrogène ou un groupe acétyle, R^2 et R^3 représentent chacun indépendamment un groupe alkyle en C_1-C_4 ou bien R^2 et R^3 pris ensemble avec l'atome d'azote voisin représentent un noyau hétérocyclique saturé à 4-7 chaînons choisi parmi azétidinyle, pyrrolidinyle, pipéridinyle, pipérazinyle, oxazolidinyle, pyrazolidinyle, thiazolidinyle, morpholinyle, imidazolidinyle, dans lequel un atome d'azote cyclique peut être substitué par un substituant R^4 choisi parmi alkyle en C_1-C_4 , hydroxy-alkyle en C_2-C_4 , alcanoylé en C_2-C_4 , (alcoxy en C_1-C_4) carbonyle, phényle facultativement substitué par 1 à 3 substituants choisis parmi halogéno, hydroxy, alkyle en C_1-C_4 et alcoxy en C_1-C_4 ; phénylalkyle en C_1-C_4 dans lequel le noyau phényle peut être facultativement substitué par 1 à 3 substituants choisis parmi halogéno, hydroxy, alkyle en C_1-C_4 et alcoxy en C_1-C_4 ; et phényl (alcoxy en C_1-C_4) carbonyle dans lequel le noyau phényle peut être substitué par 1 à 3 substituants choisis parmi halogéno, hydroxy, alkyle en C_1-C_4 et alcoxy en C_1-C_4 et leurs sels d'addition d'acides pharmaceutiquement acceptables, qui consiste à faire réagir un composé de formule II



- 20 dans laquelle R^1 représente l'hydrogène ou un groupe acétyle,
- a) avec une amine de formule HNR^2R^3 en présence d'un solvant organique inerte, pour obtenir un composé de formule I dans laquelle le groupe NR^2R^3 est défini comme à la revendication 1, à l'exclusion du composé dans lequel NR^2R^3 représente une pipérazine non substituée ; et
- 25 b) lorsque l'on désire un composé de formule I dans laquelle le groupe NR^2R^3 est une pipérazine non substituée, à soumettre le composé correspondant de formule I dans laquelle R^4 représente un groupe phényl-(alcoxy en C_1-C_4) carbonyl à une hydrogénolyse contrôlée.
2. Un procédé selon la revendication 1 pour fabriquer un composé de formule I dans laquelle R^1 représente le groupe acétyle.
3. Un procédé selon la revendication 1 pour fabriquer un composé de formule I dans lequel R^1 représente un groupe acétyle, R^2 et R^3 représentent chacun indépendamment méthyle ou éthyle, ou bien R^2 et R^3 pris ensemble avec l'atome d'azote voisin représentent un groupe pyrrolidinyle, morpholinyle, pipéridinyle ou pipérazinyle facultativement substitué par un substituant comme défini à la revendication 1 en référence aux significations de R^4 .
- 35 4. Un procédé pour fabriquer un composé selon la revendication 1 dans lequel R^1 représente un groupe acétyle et NR^2R^3 représente un groupe 4-morpholinyle, 1-pipéridinyle, 4-méthyl-1-pipérazinyle ou diéthylamino.
5. Un procédé selon la revendication 1 dans lequel la température de réaction de l'étape a) est comprise entre 5 et 40°C.
- 40 6. Un procédé selon la revendication 1 dans lequel la température de réaction de l'étape a) est la température ambiante.
7. Un procédé selon la revendication 1 dans lequel l'hydrogénolyse de l'étape b) est effectuée dans un solvant organique polaire en présence d'un catalyseur d'hydrogénation.
8. Utilisation d'un composé selon la revendication 1 pour fabriquer un médicament pour l'utilisation comme antibactérien.