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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
E S D

Re Expediente No 000085 195
Solicitud de patente a nombre de NOVARTIS AG

Yo, JIMENA ESCOBAR URIBE, identificada como aparece al pie de mi firma, domiciliada en la carrera 11 A No 94-76, Of 305, obrando como apoderada de la sociedad NOVARTIS AG domiciliada en Basilea, Suiza, solicitante de la patente de la referencia, en ampliacion a los argumentos presentados el día 8 de mayo de 2006, me permito manifestar que en cuanto a la referencia del Committee for veterinary Medical Products Tiamulin Summary Report (1) The European Agency for the Evaluation of Medicinal Products, *veterinary Medicines & Information Technology Unit*, dirijo la atencion de ese despacho al primer parrafo en la pagina 1 de esta referencia, donde se establece que la tiamulina es un diterpeno antimicrobial con una estructura quimica de pleuromutilina similar a la de la valnemulina. La actividad de la tiamulina es dirigida en gran manera a los microorganismos Gram -positivo y al micoplasma. De hecho, la tiamulina actua mediante la inhibicion de síntesis proteínica a nivel ribosomal.

Dicha referencia tambien establece que en la medicina veterinaria, la tiamulina se emplea para el tratamiento y prevención de la disenteria, neumonia e infecciones micoplasmiales en cerdos y aves de corral. La tiamulina se encuentra disponible como una pre-mezcla de 2, 10 o 20 % para cerdos y aves de corral, y en solución al 12.5% o 45% en polvos solubles en agua para la adicion al agua de bebida para los cerdos y para las aves de corral, o al 10% en formulaciones inyectables para cerdos. Las dosis reveladas son de 100 a 200 mg/kg de alimento por 5 a 10 días y hasta 6 semanas a dosis de 50 mg/kg de alimento para cerdos y de 160 a 320 mg/kg de alimento para aves de corral.

Adicionalmente, revela que en el agua de beber, se emplean las dosis de 4 a 25 mg/kg de peso corporal hasta para una semana para cerdos y dosis de 30 a 60 mg/kg de peso corporal por 3 a 5 días en aves de corral, tambien revela dosis

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intramusculares de 10 a 20 mg por peso corporal que se pueden proporcionar de manera diaria hasta por 5 días

Espero que estas aclaraciones y ampliaciones sean tenidas en cuenta junto con mi memorial de 8 de mayo de 2006

Señor Superintendente,


JIMENA ESCOBAR URIBE
C.C. 39.779.452 de Usaquen
T.P. 68.228

United States Patent [19]
Knauseder et al.

[11] **3,716,579**
[45] **Feb. 13, 1973**

[54] **ESTER DERIVATIVES OF
PLEUROMUTILIN**

[75] **Inventors.** Franz Knauseder, Ernst Brandl, both
of Tirol, Austria

[73] **Assignee** Biochemie Gesellschaft m.b.H.,
Vienna, Austria

[22] **Filed** July 20, 1970

[21] **Appl. No** 56,752

[30] **Foreign Application Priority Data**

July 21 1969 Austria A 7004/69

[52] **U.S. CL** .260/488 B, 99/2 G 99/2 AB
99/4 195/49, 260/410, 260/484 R, 260/586
A, 424/299

[51] **Int. CL** .C07c 69/16, C12d 9/22

[58] **Field of Search** 260/488 B, 410

[56] **References Cited**

OTHER PUBLICATIONS

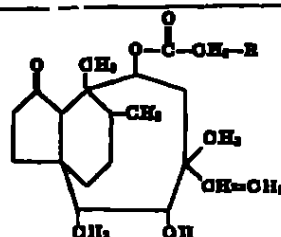
Chem Abstracts, 58 7981d-7982h

Primary Examiner—Vivian Garner

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Frederick H. Weinfeldt, Richard E. Vila, Walter F.
Jewell, Alvin Browdy and Browdy and Neimark

[57] **ABSTRACT**

The invention concerns new pleuromutilin derivatives
of the formula.



wherein R is CH₃-(CH₂)₇-CH=CH-(CH₂)₇-CO
O-, CH₃-(CH₂)₆-CH=CH-CH₂-CH=CH
-(CH₂)₇-COO-, CH₃-(CH₂)₆-CH=CH-(CH₂)₇-
COO-, or hydrogen

The derivatives are useful animal feed additives, and
also find application in veterinary medicine

2 Claims, No Drawings

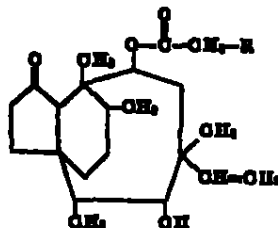
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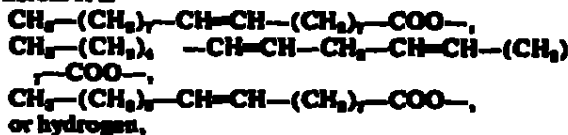
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ESTER DERIVATIVES OF PLEUROMUTILIN

The invention relates to new pleuromutilin derivatives of formula I,



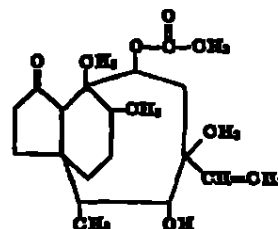
wherein R is



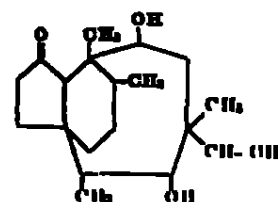
as well as processes for the production thereof

a. In accordance with the invention, there is provided a process for the production of pleuromutilin derivatives of formula I, which comprises cultivating the strain NRRL 3100 of the species *Clitopilus passeckerianus* (Pil) Sing., the variant NRRL 3279 of said strain NRRL 3100, the strain NRRL 3473 of the species *Clitopilus prunulus* (Scop. ex Fr) Kummer, the strain NRRL 3474 of the species *Clitopilus pinis* (Fr) as Romagn. Jom., or a mutant or variant of any one of said strains or variants, in an aqueous nutrient medium containing assimilable sources of nitrogen and carbon, and isolating the resulting compounds of formula I.

b. Further, in accordance with the invention, there is provided a process for the production of 14-deoxy-14-acetoxymutilin of formula Ia,



which comprises enzymatically acetylating mutilin of formula II



with the strain NRRL 3100 of the species *Clitopilus passeckerianus* (Pil) Sing., the variant NRRL 3279 of said strain NRRL 3100, the strain NRRL 3473 of the species *Clitopilus prunulus* (Scop. ex Fr) Kummer, the strain NRRL 3474 of the species *Clitopilus pinis* (Fr) as Romagn. Jom. or a mutant or variant of any one of said strains or variants, or with an enzyme ex-

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tract or dry mycelia containing said strains or mutants or variants thereof, in an aqueous medium containing assimilable sources of nitrogen and carbon, and isolating the resulting compound of formula Ia

5 The microorganisms used in accordance with the invention belong to the family of *Tricholomataceae*, order of *Agaricales*, and class of *Basidiomycetes*. Cultures of these organisms have been deposited with the Fermentation Division of the Northern Regional Research Laboratories (NRRL), Peoria, Illinois, and were allocated the NRRL numbers indicated above

The fermentation described in embodiment (a) of the process is conveniently effected in accordance with the submerged culture technique, although it is also possible to use the surface culture technique. Sugars, especially glucose, lactose or starch, may be used as carbon sources, and inorganic or organic nitrogen compounds such as sodium nitrate, ammonium sulphate, autolyzed yeast or cornsteep liquor may be used as nitrogen sources. In their impure forms they simultaneously cover the usual mineral substance requirement. The fermentation process is comparable with a penicillin fermentation in regard to change of pH, oxygen absorption, metabolism of nutritive material and formation of the desired products. Fermentation temperatures between 25° and 28°C lead to good growth and high yields. The formation of the pleuromutilin derivatives of the invention is stimulated by the addition of maize oil, sun flower oil, olive oil, sperm oil and other oils of animal and vegetable origin, using amounts between 0.05 and 5 percent. The duration of fermentation is explicitly dependent on the conditions used. Normally it lasts 3 to 5 days, but this period may also be shorter or longer. The desired products are partially deposited in the surrounding medium and are partially accumulated in the cells. Their isolation may therefore be effected from both the culture filtrate and the mycelium

One preferred method of effecting the fermentation described in embodiment (a) of the process consists in that the microorganism of the species *Clitopilus passeckerianus* (Pil) Sing. (NRRL 3100) is first cultivated in a preculture medium containing malt extract, bean flour, yeast extract, agar and peptone as carbon and nitrogen sources, as well as mineral salts, and the resulting fermentation mash is subsequently added to a fermentation solution containing glucose as carbohydrate source and autolyzed beer yeast as nitrogen source, as well as mineral salts, for further cultivation. The resulting fermentation mash is optionally again added to a fermentation solution of the last-named type for further cultivation. After cultivation is completed the resulting pleuromutilin derivatives are isolated in known manner. A separation of the substance mixture into a pleuromutilin fatty acid ester mixture and 14-deoxy 14-acetoxymutilin may optionally be effected

A further method of effecting the above embodiment (a) of the process consists in that a preculture cultivated as indicated above is added to a fermentation solution containing glucose as carbon source, and autolyzed compressed yeast as nitrogen source, as well as mineral salts. The resulting mycelium mash is again transferred to a fermentation solution of the type indicated above. After this cultivation is completed the

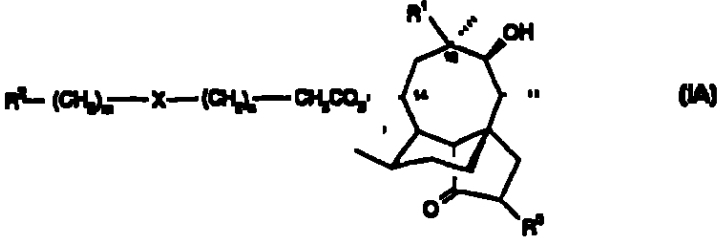
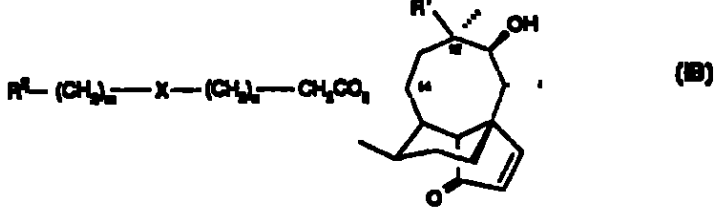
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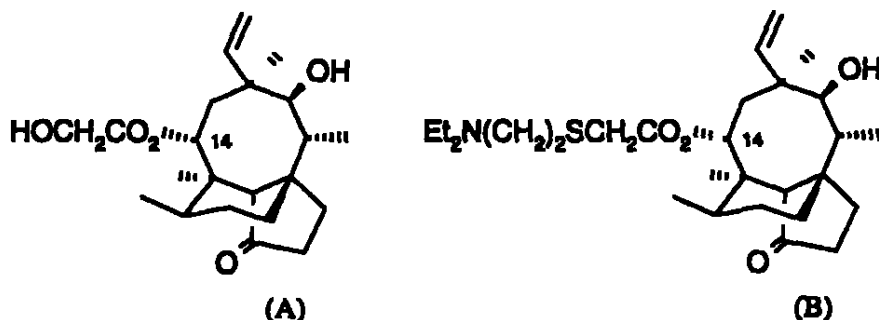
(51) International Patent Classification⁶ C07D 453/02, A61K 31/435, C07D 451/02, 471/08, 487/08, 211/62, A61K 31/445	A1	(11) International Publication Number- WO 99/21855 (43) International Publication Date- 6 May 1999 (06.05.99)						
(21) International Application Number PCT/GB98/03211 (22) International Filing Date: 27 October 1998 (27.10.98) (30) Priority Data <table border="0"> <tr> <td>9722817.5</td> <td>29 October 1997 (29.10.97)</td> <td>GB</td> </tr> <tr> <td>9813689.8</td> <td>25 June 1998 (25.06.98)</td> <td>GB</td> </tr> </table> (71) Applicants (for all designated States except US): SMITHKLINE BEECHAM P.L.C. [GB/GB] New Horizons Court, Brentford, Middlesex TW8 9EP (GB) SMITHKLINE BEECHAM CORPORATION [US/US], One Franklin Plaza, P.O. Box 7929, Philadelphia, PA 19103 (US). (72) Inventors; and (73) Inventors/Applicants (for US only): BERRY Valerie [GB/US] SmithKline Beecham Pharmaceuticals 1250 South Collegeville Road, P.O. Box 5089 Collegeville, PA 19426-0989 (US). DABBS, Stephen [GB/GB]; SmithKline Beecham Pharmaceuticals, New Frontiers Science Park South, Third Avenue, Harlow Essex CM19 5AW (GB). FRYDRYCH, Colin, Henry [GB/GB] SmithKline Beecham Pharmaceuticals, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB). HUNT Eric [GB/GB], SmithKline Beecham Pharmaceuticals, New		9722817.5	29 October 1997 (29.10.97)	GB	9813689.8	25 June 1998 (25.06.98)	GB	Frontiers Science Park South Third Avenue, Harlow, Essex CM19 5AW (GB). WOODNUTT Gary [GB/US]; SmithKline Beecham Pharmaceuticals, 1250 South Collegeville Road P.O. Box 5089 Collegeville, PA 19426-0989 (US). SANDERSON Francis, Dominic [GB/GB]; SmithKline Beecham Pharmaceuticals, New Frontiers Science Park South, Third Avenue, Harlow Essex CM19 5AW (GB). (74) Agent: CONNELL, Anthony, Christopher SmithKline Beecham, Corporate Intellectual Property Two New Horizons Court, Brentford, Middlesex TW8 9EP (GB). (81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published With international search report.
9722817.5	29 October 1997 (29.10.97)	GB						
9813689.8	25 June 1998 (25.06.98)	GB						
(54) Title: PLEUROMUTILIN DERIVATIVES AS ANTIMICROBIALS  (IA)  (IB) (57) Abstract Derivatives of pleuromutilin of formula (IA) or (IB) in which the glycolic ester moiety at position (14) is replaced by R²(CH₂)_nX(CH₂)_mCH₂COO are of use in antimicrobial therapy. In which, each of n and m is independently 0, 1 or 2; X is selected from -O-, -S-, S(O)-, -SO₂-, -CO-O-, -NH-, -CONH-, NHCONH- and a bond, R¹ is vinyl or ethyl, R² is a non-aromatic monocyclic or bicyclic group containing one or two basic nitrogen atoms and attached through a ring carbon atom. R³ is H or OH, or the moiety R²(CH₂)_nX(CH₂)_mCH₂COO at position 14 of (IA) or (IB) is replaced by R^aR^bC-CHCOO in which one of R^a and R^b is hydrogen and the other is R² or R^a and R^b together form R² or a pharmaceutically acceptable salt thereof.								

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PLEUROMUTILIN DERIVATIVES AS ANTIMICROBIALS

The present invention relates to novel compounds, to processes for their preparation, to pharmaceutical compositions containing them and to their use in medical therapy, particularly antibacterial therapy

Pleuromutulin, the compound of formula (A), is a naturally occurring antibiotic which has antimycoplasmal activity and modest antibacterial activity. It has been shown that the antimicrobial activity can be improved by replacing the glycolic ester moiety at position 14 by an R-X-CH₂CO₂- group, where R is an aliphatic or aromatic moiety and X is O, S, or NR' (H Egger and H Reinshagen, J Antibiotics, 1976, 29, 923). Tiamulin, the compound of formula (B), which is used as a veterinary antibiotic, is a derivative of this type (G Hogenauer in Antibiotics, Vol V, part 1, ed F E Hahn, Springer-Verlag, 1979, p 344)



In this application, the non-conventional numbering system which is generally used in the literature (G Hogenauer loc cit) is used

WO 97/25309 (SmithKline Beecham) describes further modification of the acyloxy group, disclosing 14-O-carbamoyl derivatives of mutulin or 19, 20-dihydromutulin, in which the N-atom of the carbamoyl group is unsubstituted, mono- or di-substituted.

WO 98/05659 (SmithKline Beecham) discloses 14-O-carbamoyl derivatives of mutulin or 19, 20-dihydromutulin in which the N-atom of the carbamoyl group is acylated by a group which includes an azabicyclic moiety

WO 98/14189 (SmithKline Beecham International Publication Date 9 April 1998) discloses the use of the topical antibacterial agent mupirocin for treating bacterial infections associated with the colonisation of the nasopharynx by pathogenic organisms, in particular, the prophylactic treatment of recurrent sinusitis and recurrent otitis media, especially with novel spray or cream formulations adapted for administration to the

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Where intermediates disclosed for the above processes are novel compounds, they also form part of this invention

5 The compounds of the present invention may contain a chiral centre, and therefore the products of the above processes may comprise a mixture of diastereoisomers or a single diastereoisomer. A single diastereoisomer may be prepared by separating such a mixture of diastereoisomers which has been synthesised using a racemic starting material, or by synthesis using an optically pure starting material

10 The products of the processes of this invention may be in crystalline or non-crystalline form, and, if crystalline, may optionally be hydrated or solvated. When some of the compounds of this invention are allowed to crystallise or are recrystallised from organic solvents, solvent of crystallisation may be present in the crystalline product. This invention includes within its scope such solvates. Similarly, some of the compounds of this
15 invention may be crystallised or recrystallised from solvents containing water. In such cases water of hydration may be present in the crystalline product. This invention includes within its scope stoichiometric hydrates as well as compounds containing variable amounts of water that may be produced by processes such as lyophilisation

20 The compounds obtained according to the processes of the invention are suitably worked up to a substantially pure form, for example at least 50% pure, suitable at least 60% pure, advantageously at least 75% pure, preferably at least 85% pure, more preferably at least 95% pure, especially at least 98% pure, all percentages being calculated as weight/weight. An impure or less pure form of a compound according to the invention may, for example,
25 be used in the preparation of a more pure form of the same compound or of a related compound (for example a corresponding derivative) suitable for pharmaceutical use

The present invention also includes pharmaceutically acceptable salts and derivatives of the compounds of the invention. Salt formation may be possible when one of the substituents carries an acidic or basic group. Salts may be prepared by salt exchange in conventional manner.
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35 Acid-addition salts may be pharmaceutically acceptable or non-pharmaceutically acceptable. In the latter case, such salts may be useful for isolation and purification of the compound of the invention, or intermediates thereto, and will subsequently be converted into a pharmaceutically acceptable salt or the free base. Pharmaceutically acceptable acid-addition salts include those described by Berge, Bighley, and Monkhouse, *J Pharm Sci* 1977, 66 1-19. Suitable salts include the hydrochloride, maleate and methanesulphonate, particularly the hydrochloride

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It will also be understood that where the compound of the invention contains a free carboxy moiety, it can form a zwitterion

5 The compounds of the present invention and their pharmaceutically acceptable salts or derivatives have antimicrobial properties and are therefore of use in therapy, in particular for treating microbial infections in animals, especially mammals, including humans, in particular humans and domesticated animals (including farm animals) The compounds may be used for the treatment of infections caused by, for example, Gram-positive and
10 Gram-negative bacteria and mycoplasmas, including, for example, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Enterococcus faecalis*, *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus pneumoniae*, *Haemophilus sp*, *Neisseria sp*, *Legionella sp*, *Chlamydia sp*, *Moraxella catarrhalis*, *Mycoplasma pneumoniae* and *Mycoplasma gallisepticum*

15 The present invention also provides a method of treating microbial infections in animals, especially in humans and in domesticated mammals, which comprises administering a compound of the invention or a pharmaceutically acceptable salt or derivative or solvate thereof, or a composition according to the invention, to a patient in need thereof

20 The invention further provides the use of a compound of the invention or a pharmaceutically acceptable salt or derivative or solvate thereof in the preparation of a medicament for use in the treatment of microbial infections

25 Compounds of the present invention may be used to treat skin and soft tissue infections and acne, by topical application. Accordingly, in a further aspect the present invention provides the use of a compound of the invention or a pharmaceutically acceptable salt or derivative or solvate thereof in the preparation of a medicament adapted for topical administration for use in the treatment of skin and soft tissue infections and also in the
30 treatment of acne in humans

Compounds of the present invention may also be used for the elimination or reduction of nasal carriage of pathogenic bacteria such as *S aureus*, *H influenzae*, *S pneumoniae* and *M catarrhalis*, in particular colonisation of the nasopharynx by such organisms, by the
35 administration of a compound of the present invention thereto. Accordingly, in a further aspect, the present invention provides for the use of a compound of the invention or a pharmaceutically acceptable salt or derivative or solvate thereof in the manufacture of a medicament adapted for administration to the nasal cavity for reducing or eliminating the

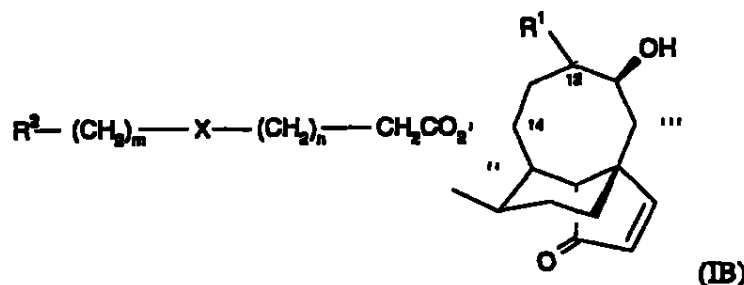
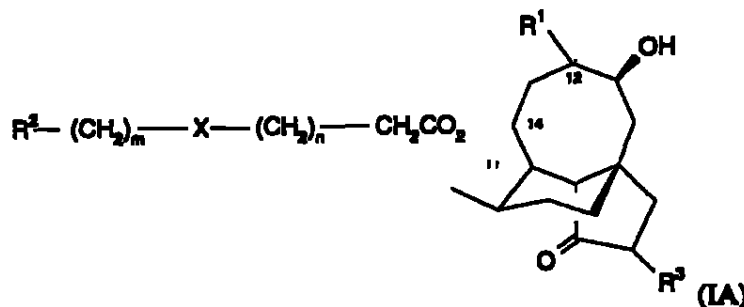
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WO 99/21855

PCT/GB98/03211

Claims

1 A compound of general formula (IA) or (IB)



in which

- 10 each of n and m is independently 0, 1 or 2,
X is selected from -O-, -S-, -S(O)-, -SO₂-, -CO O-, -NH-, -CONH-, -NHCONH- and a
bond
R¹ is vinyl or ethyl,
R² is a non-aromatic monocyclic or bicyclic group containing one or two basic nitrogen
15 atoms and attached through a ring carbon atom,
R³ is H or OH, or
the moiety R²(CH₂)_mX(CH₂)_nCH₂COO at position 14 of (IA) or (IB) is replaced by
R^aR^bC=CHCOO in which one of R^a and R^b is hydrogen and the other is R² or R^a and R^b
together form R² or
20 a pharmaceutically acceptable salt thereof

- 2 A compound according to claim 1 in which R² is selected from optionally
substituted piperidinyl, pyrrolidyl, quinclidinyl, azabicyclo[2.2.1]heptyl,
azabicyclo[4.3.0]nonyl, azabicyclo[3.2.1]octyl, azabicyclo[3.3.0]octyl,
25 azabicyclo[2.2.2]octyl, azabicyclo[3.2.1]octenyl, azabicyclo[3.3.1]nonyl and
azabicyclo[4.4.0]decyl

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- 3 A compound according to claim 1 or 2 in which R² is substituted by alkyl, alkyloxy, alkenyl or alkenyloxy, which are optionally further substituted by one or more groups selected from aryl, heterocyclyl, (C₁₋₆)alkoxy, (C₁₋₆)alkylthio, aryl(C₁₋₆)alkoxy, aryl(C₁₋₆)alkylthio, amino, mono- or di-(C₁₋₆)alkylamino, cycloalkyl, cycloalkenyl, carboxy and esters thereof, amides of carboxy, ureido, carbamimidoyl (amidino), guanidino, alkyl-sulfonyl, amino-sulfonyl (C₁₋₆)acyloxy, (C₁₋₆)acylamino, azido, hydroxy, and halogen
- 5
- 10 4 A compound according to claim 1 selected from
mutilin 14-(quinuclidin-4-yl-sulfanyl)-acetate
mutilin 14-(quinuclidin-4-yl-sulfanyl)-acetate
19,20-dihydromutilin 14-(quinuclidin-4-yl-sulfanyl)-acetate
mutilin 14-(quinuclidin-3-yloxy)-acetate
- 15 mutilin 14-(quinuclidin-3-ylsulfanyl)-acetate
mutilin 14-(quinuclidin-4-yl-sulfanyl)-acetate
mutilin 14-[N-(2,2-dimethylazabicyclo[4.3.0]non-4-ylmethyl)]-aminoacetate
mutilin 14-(quinuclidin-4-ylcarbonylamino)-acetate
mutilin 14-[(3R,4R)-azabicyclo[2.2.1]hept-3-ylcarbonylamino]-acetate
- 20 mutilin 14-(1-methylpiperid-4-ylcarbonylamino)-acetate
mutilin 14-[3-(1-methylpiperid-4-yl)]-propionate
mutilin 14-(quinuclid-4-ylmethylsulfanyl)-acetate
19,20-dihydromutilin 14-(quinuclidin-4-ylsulfonyl)acetate
19,20-dihydromutilin 14-(quinuclidin-4-ylsulfoxy)-acetate
- 25 mutilin-14-(1-methylpiperid-4-ylsulfanyl)-acetate
mutilin 14-[(3RS,4SR)-1-aza-bicyclo[2.2.1]hept-3-yl-sulfanyl]-acetate
mutilin 14-[(3RS,4SR)-1-aza-bicyclo[2.2.1]hept-3-yl-sulfanyl]-acetate
mutilin 14-(quinuclidin-3-ylidene)-acetate
mutilin 14-[quinuclidin-3-yl]-acetate
- 30 mutilin 14-[quinuclidin-3-ylacetoxyl]-acetate
mutilin 14-(quinuclidin-3-ylmethylsulfanyl)-acetate
1,2-didehydromutilin 14-(quinuclidin-4-ylsulfanyl)-acetate
2 α -hydroxymutilin 14-(quinuclidin-4-ylsulfanyl)-acetate
mutilin 14-(quinuclidin-4-yl)-acetate
- 35 mutilin 14-(quinuclidin-4-ylmethyl)-aminoacetate
mutilin 14-[3-(quinuclidin-4-yl)-acrylate]
mutilin 14-[3-(quinuclidin-4-yl)]-propionate
mutilin 14-(quinuclidin-4-ylmethyloxy)-acetate

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- mutulin 14-[(3R)-quinuclidin-3-ylamino]-acetate
mutulin 14-(quinuclidin-4-yl-amino)-acetate
mutulin 14-[4-(quinuclidin-4-yl)]-butyrate
mutulin 14-(1-azabicyclo[3,3,0]oct-4-ylmethylsulfanyl)-acetate
5 mutulin 14-(1-azabicyclo[3,3,0]oct-3-ylsulfanyl)-acetate
mutulin 14-(*endo* 8-methyl-8-azabicyclo[3,2,1]oct-3-ylsulfanyl)-acetate
mutulin 14-(1-azabicyclo[4,3,0]non-4-ylsulfanyl)-acetate
19,20-dihydromutulin 14-(1-azabicyclo[4,3,0]non-4-ylsulfanyl)-acetate
mutulin 14-(1-carboxymethylpiperidin-4-ylsulfanyl)-acetate
10 mutulin 14-(piperidin-4-ylsulfanyl)-acetate
mutulin 14-(1-methylpiperidin-4-ylmethylsulfanyl)-acetate
mutulin 14-[(3S,4R)-1-azabicyclo[2,2,1]hept-3-ylmethylsulfanyl]-acetate
mutulin 14-(quinuclidin-2-ylmethylsulfanyl)-acetate
mutulin 14-(1-azabicyclo[2,2,1]hept-4-ylmethylsulfanyl)-acetate
15 mutulin 14-[(3R,4S)-1-azabicyclo[2,2,1]hept-3-ylmethylsulfanyl]-acetate
mutulin 14-(1-azabicyclo[3,2,1]oct-5-ylmethylsulfanyl)-acetate
mutulin 14-[(R)-1-methylpiperid-2-ylmethylsulfanyl]-acetate
mutulin 14-[(S)-1-methylpyrrolid-2-ylmethylsulfanyl]-acetate
mutulin 14-[(R)-1-methylpiperid-3-ylmethylsulfanyl]-acetate
20 mutulin 14-(quinuclidin-4-ylmethylsulfanyl)-acetate
mutulin 14-(8-methyl-8-azabicyclo[3,2,1]oct-3-ylmethylsulfanyl)-acetate
mutulin 14-(*exo*-8-methyl-8-azabicyclo[3,2,1]oct-3-ylsulfanyl)-acetate
mutulin 14-[(3-(quinuclidin-4-ylsulfanyl)]-propionate
mutulin 14-[3-(quinuclidin-4-ylmethylsulfanyl)]-propionate
25 mutulin 14-[3-(1-methylpiperid-4-ylsulfanyl)]-propionate
19,20-dihydromutulin 14-(1-methylpiperid-4-ylsulfanyl)-acetate
19,20-dihydromutulin 14-(8-methyl-8-azabicyclo[3,2,1]oct-3-ylmethylsulfanyl)-acetate
mutulin 14-[4-(quinuclidin-4-ylsulfanyl)]-butyrate
1,2-didehydromutulin 14-(1-methylpiperidin-4-ylmethylsulfanyl)-acetate
30 mutulin 14-(*exo*-8-methyl-8-azabicyclo[3,2,1]oct-3-ylsulfanyl)-acetate, or
mutulin 14-(1-carboxamidomethylpiperidin-4-ylsulfanyl)-acetate
- 5 A process for preparing a compound according to any one of claims 1 to 4 which comprises
- 35 (a) coupling mutulin or epi-mutulin having a protected hydroxy group at position 11, with an active derivative, such as an acid chloride of a carboxylic acid
 $R^{2A}-(CH_2)_m-X-(CH_2)_n-CH_2CO_2H$, where R^{2A} is R^2 as defined in claim 1 or a group convertible thereto and n , m and X are as defined in claim 1 and if necessary converting

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the epi-mutulin to mutulin, and where necessary or desired, before or after the coupling, modifying the mutulin nucleus to introduce 2-OH 19,20-dihydro, or 1,2-dehydro substituents, or

- 5 (b) providing a mutulin or epi-mutulin derivative having $(CH_2)_nCH_2CO$ as an *O*-acyl group at position 14, where the acyl group is substituted with R^L , which is a leaving group, OH or NH, coupling the 14-*O*-acyl-(epi)mutulin derivative with a compound $R^2A(CH_2)_mXH$ or an active derivative thereof, and if necessary converting the epi-mutulin configuration to mutulin, and where necessary or desired, before or after the coupling, modifying the mutulin
10 nucleus to introduce 2-OH, 19,20-dihydro, or 1,2-dehydro substituents

- 6 A process for preparing a compound according to claim 5(b) in which
(a) when X is O, S or NH, R^L is a leaving group and is reacted with
15 (i) the alcohol $R^2-(CH_2)_m-OH$,
(ii) the thiol $R^2-(CH_2)_m-SH$,
(iii) the amine $R^2-(CH_2)_m-NH_2$,
(b) when X is CONH, R^L is amino and is reacted with the acid $R^2A-(CH_2)_m-CO_2H$,
or an acylating agent derived therefrom,
20 (c) when X is CO O, R^L is hydroxy and is reacted with an acylating agent derived from the acid $R^2A-(CH_2)_m-CO_2H$

- 7 A pharmaceutical composition comprising a compound according to claim 1 and a
25 pharmaceutically acceptable carrier

8 A pharmaceutical composition according to claim 7 in the form of a spray adapted for administration to the nasal cavity

- 30 9 A pharmaceutical composition according to claim 8 in which the spray is an aqueous spray

- 10 A compound of formula (IA) or (IB) according to claim 1 for use in therapy

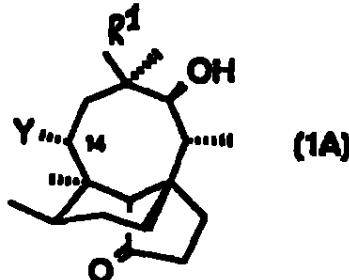
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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(30) Priority Data. 9600048.4 3 January 1996 (03.01.96) GB 9616305.0 2 August 1996 (02.08.96) GB		
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(54) Title: CARBAMOYLOXY DERIVATIVES OF MUTILINE AND THEIR USE AS ANTIBACTERIALS		
(57) Abstract		
Derivatives of mutiline of formula (1A) and pharmaceutically acceptable salts and derivatives thereof, in which R ¹ is ethyl or vinyl, Y is a carbamoyloxy group, in which the N-atom is unsubstituted, or mono- or di-substituted, are useful in the treatment of bacterial infections		
		

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same compound or of a related compound (for example a corresponding derivative) suitable for pharmaceutical use

5 The present invention also includes pharmaceutically acceptable salts and derivatives of the compounds of the invention. Salt formation may be possible when one of the substituents carries an acidic or basic group. Salts may be prepared by salt exchange in conventional manner.

10 The compounds of the present invention and their pharmaceutically acceptable salts or derivatives have antimicrobial properties and are useful for the treatment of microbial infections in animals, especially mammals, including humans, in particular humans and domesticated animals (including farm animals). The compounds may be used for the treatment of infections caused by, for example, Gram-positive and Gram-negative bacteria and mycoplasmas, including, for
15 example, *Staphylococcus aureus*, *Enterococcus faecalis*, *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus pneumoniae*, *Haemophilus* sp., *Neisseria* sp., *Legionella* sp., *Mycoplasma pneumoniae*, and *Mycoplasma gallisepticum*.

20 The present invention provides a pharmaceutical composition comprising a compound of formula (3) or a pharmaceutically acceptable salt or derivative thereof together with a pharmaceutically acceptable carrier or excipient.

25 The present invention also provides a method of treating microbial infections in animals, especially in humans and in domesticated mammals, which comprises administering a compound of formula (3) or a pharmaceutically acceptable salt or derivative thereof, or a composition according to the invention, to a patient in need thereof.

30 The invention further provides the use of a compound of the invention or a pharmaceutically acceptable salt or derivative thereof in the preparation of a medicament composition for use in the treatment of microbial infections.

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The compounds and compositions according to the invention may be formulated for administration in any convenient way for use in human or veterinary medicine, by analogy with other antibiotics.

- 5 The compounds and compositions according to the invention may be formulated for administration by any route, for example oral, topical or parenteral. The compositions may, for example, be made up in the form of tablets, capsules, powders, granules, lozenges, creams, syrups, or liquid preparations, for example solutions or suspensions, which may be formulated for oral use or in sterile form
10 for parenteral administration by injection or infusion.

Tablets and capsules for oral administration may be in unit dosage form, and may contain conventional excipients including, for example, binding agents, for example, syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrrolidone;
15 fillers, for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tableting lubricants, for example magnesium stearate, talc, polyethylene glycol or silica, disintegrants, for example potato starch, and pharmaceutically acceptable wetting agents, for example sodium lauryl sulphate. The tablets may be coated according to methods well known in normal pharmaceutical practice.

20 Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for reconstitution with water or another suitable vehicle before use. Such liquid preparations may contain conventional additives, including, for example,
25 suspending agents, for example sorbitol, methyl cellulose, glucose syrup, gelatin, hydroxyethyl cellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate or acacia non-aqueous vehicles (which may include edible oils), for example almond oil, oily esters (for example glycerine), propylene glycol, or
30 ethyl alcohol, preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and, if desired, conventional flavouring and colour agents.

Compositions according to the invention intended for topical administration may, for example, be in the form of ointments, creams, lotions, eye ointments, eye
35 drops, ear drops, nose drops, nasal sprays, impregnated dressings, and aerosols,

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and may contain appropriate conventional additives, including, for example, preservatives, solvents to assist drug penetration, and emollients in ointments and creams. Such topical formulations may also contain compatible conventional carriers, for example cream or ointment bases, and ethanol or oleyl alcohol for
5 lotions. Such carriers may constitute from about 1% to about 98% by weight of the formulation, more usually they will constitute up to about 80% by weight of the formulation.

10 Compositions according to the invention may be formulated as suppositories, which may contain conventional suppository bases, for example cocoa-butter or other glycerides.

Compositions according to the invention intended for parenteral administration may conveniently be in fluid unit dosage forms, which may be prepared utilizing
15 the compound and a sterile vehicle, water being preferred. The compound, depending on the vehicle and concentration used, may be either suspended or dissolved in the vehicle. In preparing solutions, the compound may be dissolved in water for injection and filter-sterilised before being filled into a suitable vial or ampoule, which is then sealed. Advantageously, conventional additives
20 including, for example, local anaesthetics, preservatives, and buffering agents can be dissolved in the vehicle. In order to enhance the stability of the solution, the composition may be frozen after being filled into the vial, and the water removed under vacuum, the resulting dry lyophilized powder may then be sealed in the vial and a accompanying vial of water for injection may be supplied to
25 reconstitute the liquid prior to use. Parenteral suspensions may be prepared in substantially the same manner except that the compound is suspended in the vehicle instead of being dissolved and sterilisation cannot be accomplished by filtration. The compound may instead be sterilised by exposure to ethylene oxide before being suspended in the sterile vehicle. Advantageously, a surfactant or
30 wetting agent is included in such suspensions in order to facilitate uniform distribution of the compound.

A compound or composition according to the invention may suitably be
35 administered to the patient in an antimicrobially effective amount.

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United States Patent [19]
Berner et al.

[11] **Patent Number:** **4,675,330**
[45] **Date of Patent:** **Jun. 23, 1987**

[54] PLEUROMUTILIN DERIVATIVES PROCESS FOR THEIR PREPARATION AND THEIR USE

- [75] **Inventors:** Helmut Berner; Hermann Vypiel, both of Vienna, Austria
[73] **Assignee:** Sandoz Ltd., Basel, Switzerland
[21] **Appl. No.** 869,266
[22] **Filed:** May 6, 1986

Related U.S. Application Data

- [63] **Continuation of Ser. No. 700,611, Feb. 11, 1983, abandoned.**

[30] Foreign Application Priority Data

Feb. 17, 1984 [DE] Fed. Rep. of Germany 3405632
Apr. 12, 1984 [DE] Fed. Rep. of Germany 3413708

- [51] **Int. Cl.⁴** A61N 31/06; C07D 277/06; C07D 207/09; C07D 149/23
[52] **U.S. Cl.** 514/368; 514/423, 514/350; 548/200; 548/537; 560/153
[58] **Field of Search** 548/200, 537; 560/153, 514/365, 423, 550

[56] References Cited

U.S. PATENT DOCUMENTS

3,919,290 11/1975 Egger et al. 560/153
4,060,542 11/1977 Riedl 560/190 X
4,086,339 4/1978 Darach 560/153 X
4,107,434 8/1978 Waldvogel 560/153 X
4,390,558 6/1983 Ridgway et al. 514/350 X

FOREIGN PATENT DOCUMENTS

2121035A 12/1983 United Kingdom 560/153

OTHER PUBLICATIONS

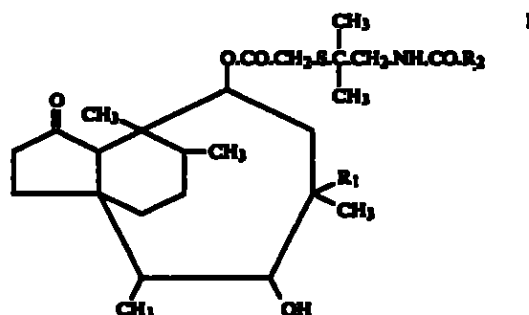
Egger, et al., *The Journal of Antibiotics*, vol. 29, pp. 923-927 (1976).

Schuster, et al., *Cytochrome P-450*, Biochem., Biophys., Implic., (1982), pp. 555-558.

Primary Examiner—Joseph Paul Brust
Attorney, Agent, or Firm—Gerald D. Sharkin, Richard E. Vila, Frederick H. Weinfeldt

[57] ABSTRACT

A compound of formula I



wherein

R₁ represents ethyl or vinyl and

R₂ represents a five membered saturated heterocycle or aminoalkyl unsubstituted or substituted in its alkyl moiety by hydroxy,

in free or in the form of an acid addition or quaternary salt, which compounds are indicated for use as chemotherapeutic agents e.g. as anti-bacterially active antibiotics and as veterinary agents e.g. in combatting micro-organism infections and promoting growth in domestic animals.

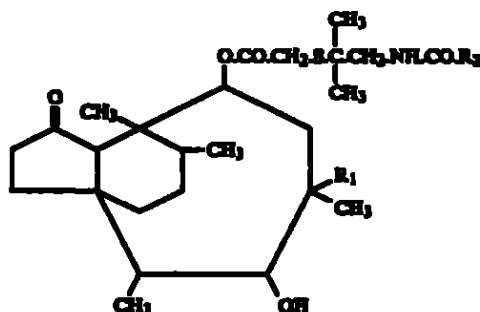
20 Claims, No Drawings

PLEUROMUTILIN DERIVATIVES PROCESS FOR THEIR PREPARATION AND THEIR USE

This is a continuation of application Ser. No. 700,611, filed Feb. 11, 1985, now abandoned.

The present invention concerns derivatives of 14-O-[(1-Amino-2-methylpropan-2-yl)thioacetyl]-mutilin and -19,20-dihydro-mutilin. In particular it concerns an N-Acyl-14-O-[(1-amino-2-methylpropan-2-yl)thioacetyl]-mutilin or -19,20-dihydro-mutilin.

More particularly the invention concerns compounds of formula I

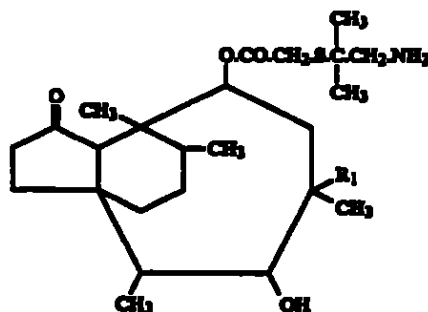


wherein

R₁ represents ethyl or vinyl and

R₂ represents a five membered saturated heterocycle or aminocyclyl unsubstituted or substituted in its alkyl moiety by hydroxy, in free form or in the form of an acid addition or quaternary salt.

The compounds of the invention may be obtained by acylating 14-O-[(1-Amino-2-methylpropan-2-yl)thioacetyl]mutilin or -19,20-dihydro-mutilin and more particularly by reacting a compound of formula II



with a reactive ester of a compound of formula III



whereby R₂' has the same meaning as R₂ above except that any amino groups present therein are protected, deprotecting any protected amino groups and recovering the compound thus obtained in free form or in the form of an acid addition salt or a quaternary salt.

This process according to the invention can be carried out by dissolving or suspending a compound of formula II and a compound of formula III in a solvent inert under the reaction conditions e.g. in a di(lower)alkylcarboxylic acid amide such as dimethylformamide, and allowing the reaction to proceed at room temperature or at a raised temperature preferably at room tem-

perature. The subsequent splitting-off of protecting groups can be carried out according to conventional methods for example by reductive deprotection with Pd/active charcoal and hydrogen or by treatment with trifluoroacetic acid. The final products can be isolated from the reaction mixture and if necessary purified according to conventional methods.

The compounds of formula I can be converted into their acid addition salts and vice versa in conventional manner. Corresponding quaternary salts can be obtained from the compounds of formula I in conventional manner.

The compounds of formula I may contain at least one asymmetric carbon atom and may thus exist in the form of diastereomeric isomers and mixtures thereof which may be separated in conventional manner. Use of optically active starting materials will lead to the corresponding enantiomers and mixtures thereof and reference is made to the latter unless otherwise stated.

The compounds of formula I exhibit interesting biological in particular chemotherapeutic activity and are therefore useful as medicaments. They display an inhibitory activity against bacteria as determined in tests in vitro with the series dilution test using various bacterial strains e.g. *Staph. aureus*, *Staph. epidermidis*, *Strept. pyogenes*, *Strept. pneumoniae*, *E. coli*, *Klebsiella pneumoniae*, *Haemophilus* spp., *Leptospira* spp., *Erysipelothrix rhusiopathiae* and obligatory anaerobes, e.g. *Bacteroides fragilis* from a concentration of ca. 0.008 to 25 µg/ml. In particular an inhibitory activity was also found against *Mycoplasma* and *Chlamydia* which exhibits itself from a concentration of ca. 0.008 to 0.5 µg/ml.

The chemotherapeutic activity of the compounds was established through tests on mice, using various bacterial strains, and on hens, using mycoplasma strains. This inhibitory activity was observed from a concentration of ca. 12 to 50 mg/kg of body weight. The compounds according to the invention can therefore be used as anti-bacterially active antibiotics.

In addition the above mentioned compounds display an anti-parasitic activity, in particular against coccidia as well as a growth promoting activity. To establish the activity against coccidia testing took place in vivo on the hen. The activities can be confirmed in these animal tests at dosages of 20-150 mg/kg of feed depending upon the period of application. The growth promoting properties were established in hen and pig in a dosage range of 10-50 mg/kg feed. The compounds of formula I are therefore suitable as veterinary agents in particular for the chemotherapeutic treatment of coccidiosis in fowl as well as growth promoters in the animal species mentioned.

In use, the effective dosage will, of course, vary depending on the particular compound employed, the mode of administration and the treatment desired. However, in general, satisfactory results as anti-bacterials and anti-anaerobics can be obtained when the compounds are administered at a daily dosage of from about 10 to 300 mg/kg of animal body weight, suitably given in divided doses two to four times daily. For most large mammals, the total daily dosage is from about 1 g to 3 g, and dosage forms suitable for internal administration comprise about 250 to 1500 mg of the compound in admixture with a solid or liquid pharmaceutical carrier or diluent.

For the prophylaxis or therapy of microorganism infections and for growth promotion in domestic animals, the dosage will of course vary depending upon the size and age of the animal and the effect desired, for example for prophylactic treatment relatively low doses would be administered over a long time. Preferred doses in drinking water are from 0.0125 to 0.05 weight by volume, particularly 0.0125 to 0.025, and in foodstuffs from 20 to 400 g/metric ton, particularly 20 to 200 g/metric ton. It is preferred to administer the active compound to hens in drinking water, and to pigs in the feedstuff.

The compounds may be used in free base form or in the form of chemotherapeutically/physiologically acceptable acid addition and quaternary salts. Such salt forms exhibit the same order of activity as the free base forms.

Examples of suitable acid addition salts are the hydrogen fumarate, fumarate, naphthalin-1,5-sulphonate and especially the hydrochloride.

The compounds may be administered orally, locally or parenterally and admixed with conventional chemotherapeutically acceptable diluents and carriers, and, optionally, other excipients and administered in such forms as tablets, capsules or injectable preparations.

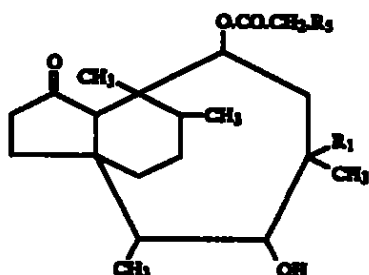
The compounds also form excellent additives for feed mixes (as premix) or for drink water as well as for diluting fluids for artificial insemination and for egg-dipping techniques.

Such compositions also form part of the invention.

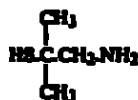
The invention therefore also concern a method of combatting bacteria and obligatory anaerobes comprising administering to a subject in need of such treatment an effective amount of a compound of formula I or a chemotherapeutically acceptable acid addition or quaternary salt thereof and such compounds for use as chemotherapeutic agents, in particular anti-bacterially active antibiotics and agents against infections caused by obligatory anaerobes.

The invention further provides a method of combatting microorganism infections and promoting growth in domestic animals which comprises administering to a subject in need of such treatment an effective amount of a compound of formula I or a physiologically acceptable acid addition or quaternary salt thereof and such compounds for use in combatting coccidia and promoting growth in domestic animals.

The starting materials of formula II are new and may be obtained by reacting a compound of formula IV



wherein R_1 is as defined above and R_2 stands for chlorine, bromine or a $O.SO_2.R_4$ group, wherein R_4 represents alkyl or aryl, with the compound of formula V



This reaction can be carried out for example by dissolving the compound of formula V in a solution of sodium in an anhydrous lower alcohol e.g. in ethanol or methanol. To this solution is then added a solution of a compound of formula IV in a solvent inert under the reaction conditions e.g. in an aliphatic ketone such as ethylmethylketone or acetone. The reaction proceeds preferably at room temperature up to boiling temperature of the reaction mixture, especially 25° to 55° C.

The starting materials of formula III, IV and V are either known or are preparable analogously to known methods e.g. for compounds V as described in F. J. Carroll, J. D. White and M. E. Wall, J. Org. Chem. 28/1240 (1963).

Alkyl groups appearing as substituents preferably represent lower alkyl groups, especially with 1 to 4 carbon atoms. When R_2 stands for a heterocycle then this may contain one or two heteroatoms, whereby one heteroatom is nitrogen and the optionally present second heteroatom is sulphur.

Protecting groups for the amino function in the starting materials of formula III include those commonly used as amino-protecting groups, for example $-CO.O.CH_2.C_6H_5(Z)$, $-CO.O.C(CH_3)_3$ (BOC) or $-CO.O.CH_2.CCl_3$.

Preferred substituent meanings are

$R_1 =$

(a) ethyl

(b) vinyl whereby vinyl is especially preferred

$R_2 =$

(a) aminoalkyl

(b) aminohydroxyalkyl

(c) as (a) or (b) with alkyl having C_{1-4} especially C_{1-4}

(d) 5-membered saturated heterocycle

(e) 5-membered saturated heterocycle containing one N atom and optionally one S atom.

Combinations of these groups are especially preferred.

A particularly preferred individual compound is 14-O-[1(2-Amino-3-methylbutyrylamino)-2-methylpropen-2-yl-thioacetyl]-mutilin as free base or hydrochloride, preferably in (D)-Form.

In the following examples which illustrate the invention but in no way limit its scope, references to temperature are in degrees Celsius.

EXAMPLE 1

14-O-[1-(D)-2-Amino-3-methylbutyrylamino)-2-methylpropen-2-yl-thioacetyl]-19,20-dihydromutilin-Hydrochloride

A solution of 1.85 g of 2-Valin-4-nitrophenylester and 2.35 g of 14-O-[1(2-Amino-3-methylpropen-2-yl)-thioacetyl]-19,20-dihydromutilin in 30 ml of dimethyl formamide is maintained for 7 hours at 25°. The reaction mixture is then poured onto water and repeated shaken with ethylacetate. After washing back the organic phase with 0.1N hydrochloric acid and then with NaCl-saturated water the protected final compound is obtained which can be employed for deprotection without further purification.

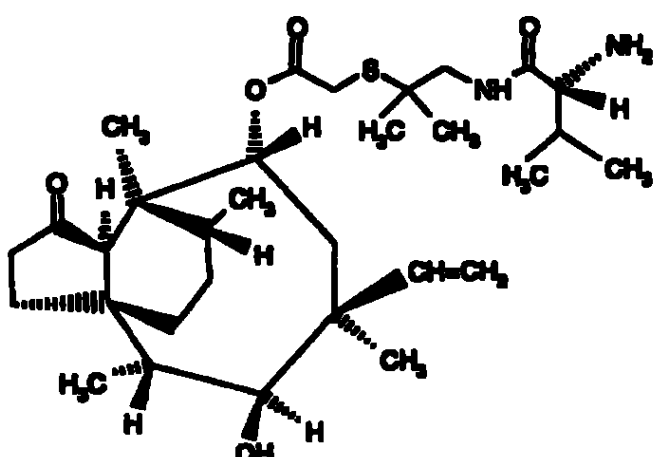
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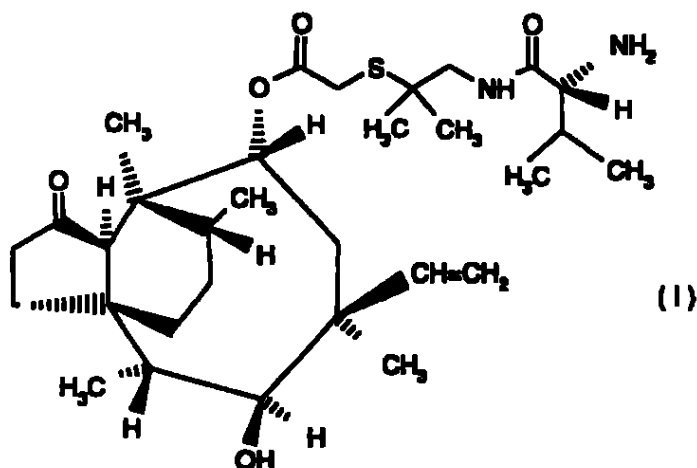
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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(21) International Application Number PCT/EP97/03518		(74) Agent: ROTH, Bernhard, M., Novartis AG, Patent- und Markenabteilung, Lichtstrasse 35, CH-4002 Basel (CH).
(22) International Filing Date 3 July 1997 (03.07.97)		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GR, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).
(30) Priority Data:		Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.
9614017.3 4 July 1996 (04.07.96) GB 9614016.5 4 July 1996 (04.07.96) GB 9614015.7 4 July 1996 (04.07.96) GB 9614014.0 4 July 1996 (04.07.96) GB 9614013.2 4 July 1996 (04.07.96) GB 9614012.4 4 July 1996 (04.07.96) GB 9614019.9 4 July 1996 (04.07.96) GB 9614018.1 4 July 1996 (04.07.96) GB		
(71) Applicant (for all designated States except US): BIOCHEMIE GESELLSCHAFT MBH [AT/AT], A-6250 Kundl (AT)		
(72) Inventors, and (73) Inventors/Applicants (for US only): BURCH, David George, Sidney [GB/GB]: The Round House, The Priory Old Windor, Berkshire SL4 2NR (GB). RIPLEY Paul, Howard [GB/GB]: North Lodge, Dene Park Gardens, Shipbourne Road, Tonbridge, Kent TN11 9NS (GB). ZHESL, Erich [AT/AT], Wiesing 74 B, A-6200 Jenbach (AT).		
(34) Title: VETERINARY USE OF A FLEUROMUTILIN DERIVATIVE		
(37) Abstract		
Use of the compound of formula (I) in the therapy of veterinary diseases, the ex- pression of which is enhanced by increasing stocking density		
 (I)		

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156**VETERINARY USE OF A PLEUROMUTILIN DERIVATIVE**

The invention relates to pleuromutillin derivatives. It concerns the veterinary use of the compound of formula I



ie 14-O-[1-[(R)-2-amino-3-methylbutyrylamino]-2-methylpropan-2-ylthioacetyl]mutillin in free base or in veterinarily acceptable salt form, in the therapy of veterinary diseases the expression of which is enhanced by increasing stocking density, hereinafter briefly named "the use of the invention"

The compound of formula I in free base or in veterinarily acceptable salt form (Econor[®]) is hereinafter briefly named "the agent of the invention". It preferably is in salt, especially in hydrochloride salt form. In that form it is known under the generic name valnemulin hydrochloride.

The term "therapy" is to be understood as applying for prophylactic as well as curative treatment.

The compound of formula I in free base form or in chemotherapeutically or veterinarily acceptable salt form is known from e.g. EP 153 277 and its equivalents, e.g. USP 4 675 330, specifically as Example 12 therein.

Known therefrom is, further,

- an inhibitory activity against various bacteria in vitro, at concentrations of ca. 0.008 to 25 µg/ml,
 - an inhibitory activity in vitro against mycoplasmas and chlamydia generally, at concentrations of ca. 0.008 to 0.5 µg/ml,
 - an inhibitory activity in vivo in mice, using various bacterial strains, and on hens, using mycoplasma strains, at a dosage of ca. 12 to 50 mg/kg body weight;
 - an anti-parasitic activity, in particular in vivo against coccidia in fowl, at dosages of 20-150 mg/kg of feed, and
 - growth-promoting activity in hen and pig in vivo, at a dosage of 10-50 mg/kg of feed,
- thus making the compound useful as an antibacterially active antibiotic generally and, as a veterinary agent, in particular for the chemotherapeutic treatment of coccidiosis in fowl as well as a growth promoter in hen and pig

It has now been found that, surprisingly, the agent of the invention is particularly effective in the therapy of veterinary diseases the expression of which is enhanced by increased stocking density, such as enzootic pneumonia in swine caused by *Mycoplasma hyopneumoniae* infection, swine dysentery caused by *Serpulina* (formerly *Treponema*) *hyodysenteriae* infection, swine colitis (inflammation of the colon) associated with *Serpulina pilosicoli* infection, ileitis in swine (porcine proliferative enteropathy, porcine intestinal adenomatosis) associated with *Lawsonia intracellularis* infection, chronic respiratory disease and arthritis in poultry associated with *Mycoplasma gallisepticum* infection, secondary pneumonia in swine associated with *Pasteurella multocida*, *Actinobacillus* (*Haemophilus*) *pleuropneumoniae* and/or *Haemophilus parasuis* infection, pneumonia in lambs, sheep and cattle (Shipping Fever, Transit Fever, Calf Respiratory Complex, Bovine Pneumonic Pasteurellosis) associated with *Pasteurella haemolytica* infection and polyarthritis in swine associated with *Mycoplasma hyosynoviae* infection

Further, even more surprisingly, it has been found that induction of resistance to the drug is extremely low

The invention thus concerns the veterinary use as defined above

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It also concerns the use of the agent of the invention for the manufacture of a medicament for use in the therapy of veterinary diseases the expression of which is enhanced by increasing stocking density

It further concerns a method of treatment of veterinary diseases the expression of which is enhanced by increasing stocking density, comprising administration of a therapeutically effective amount of the agent of the invention to an animal in need of such treatment.

It further concerns a veterinary agent for use in the therapy of veterinary diseases the expression of which is enhanced by increasing stocking density, comprising the compound of formula I in free base or in veterinarily acceptable salt form, together with at least one veterinarily acceptable carrier or diluent

It further concerns a process for the preparation of a medicament for use as defined above which comprises mixing the agent of the invention together with at least one veterinarily acceptable carrier or diluent.

The animal suffering from veterinary diseases the expression of which is enhanced by increasing stocking density may e.g. not already be treated antibacterially with the agent of the invention or not already be receiving the agent of the invention for growth promotion

A) Mycoplasma hyopneumoniae infection.

Mycoplasma hyopneumoniae infection may be diagnosed in conventional manner, e.g. as described in veterinary manuals such as Taylor, D.J., in Pig Diseases, 6th Ed (1995), Publ. D.J. Taylor, Glasgow, U.K. on page 164-165. The beneficial activity of the agent of the invention in this use is determined e.g. as follows

1 Activity in vitro

Ten field isolates from outbreaks of enzootic pneumonia in different herds and the type strain "J" are included in the test. The isolates are filter-cloned, identified by the disc growth inhibition test and used in 7th to 10th passage. The test for minimal inhibitory concentration (MIC) is performed in liquid medium (Frile, N.F. et al., Acta Vet. Scand. 32 [1991] 425-429) in tubes of 1.8 ml containing 2-fold concentration of valnemulin and tiamulin hydrogen fumarate. The mycoplasmas are inoculated in 10 fold dilutions, and the cultures read

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United States Patent [19]

Egger et al.

[11] 4,032,530

[45] June 28, 1977

[54] CERTAIN PLEUROMUTILINS

[75] Inventors: Helmut Egger, Hellmuth
Reischbagen, both of Vienna, Austria

[73] Assignee: Sandoz Ltd., Basel, Switzerland

[22] Filed: Aug. 21, 1975

[21] Appl. No. 606,430

Related U.S. Application Data

[60] Division of Ser. No. 427,514, Dec. 26, 1973, Pat. No. 3,919,290, which is a continuation-in-part of Ser. No. 294,642, Oct. 9, 1972, abandoned.

[30] Foreign Application Priority Data

Oct. 5, 1971	Switzerland	14450/71
Oct. 5, 1971	Switzerland	14451/71
May 25, 1972	Switzerland	7740/72
May 25, 1974	Switzerland	7738/72
May 25, 1972	Switzerland	7739/72

[52] U.S. Cl. 260/293.56

[51] Int. Cl.⁸ C07D 298/14

[50] Field of Search 260/481 R, 293.56

[56] References Cited

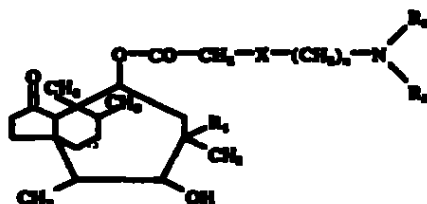
UNITED STATES PATENTS

3,919,290 11/1975 Egger et al. 260/481 R

Primary Examiner—R. Gallagher
Attorney, Agent, or Firm—Gerald D. Sharkin, Robert S. Honor, Thomas O. McGovern

[57] ABSTRACT

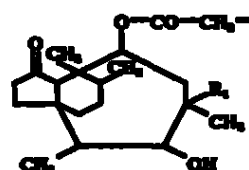
This invention relates to new pleuromutlins of the formula.



wherein
either R₁ is ethyl or vinyl,
n is an integer from 2 to 5,
X is sulphur,
a group



or a group $=N-R_4'$,
wherein
either Y and Z are both sulphur, or
one of Y and Z is oxygen and the other is sulphur,
and
R₄' is hydrogen or a group of the formula.



wherein R₁ is as defined above,
each of
R₂ and R₃ is alkyl of 1 to 10 carbon atoms, or
R₂ and R₃ together with the nitrogen atom form a
heterocycle of 5 to 7 ring members containing one
nitrogen atom or one nitrogen atom and a further
hetero member selected from sulphur, oxygen and
a group $=N-R_4''$,
wherein R₄' is alkyl of 1 to 5 carbon atoms or hydroxyl-
alkyl of 1 to 4 carbon atoms, or
R₂ and R₃ together with the nitrogen atom form a
piperazinyl radical, the second nitrogen atom of
which is substituted by a radical R₄'',
whereby R₄' is (acyloxy of 2 to 5 carbon atoms)alkyl
of 1 to 4 carbon atoms or (benzoyloxy)alkyl of 1 to
4 carbon atoms, or
wherein R₁ is as defined above,
n is the number 2,
R₂ is alkyl of 1 to 10 carbon atoms, hydroxyalkyl of
1 to 4 carbon atoms, (acyloxy of 2 to 5 carbon
atoms)alkyl of 1 to 4 carbon atoms or (benzoyloxy)
alkyl of 1 to 4 carbon atoms,
X is the group $=N-R_4''$, and
R₂ together with R₄' forms an ethylene bridge between
both nitrogen atoms,

and pharmaceutically acceptable acid addition salts
and quaternary salts thereof.

Processes for the preparation of such compounds are
described

The compounds are antibiotics with an antibacterial
effect.

9 Claims, No Drawings

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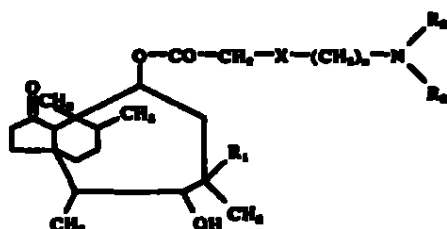
4,032,530

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CERTAIN PLEUROMUTILINS

This is a division of application Ser No 427,514, filed on Dec. 26, 1973, now U.S. Pat. No. 3,919,290, which is in turn a continuation-in-part of application Ser No 294,642, filed on Oct. 3, 1972, now abandoned

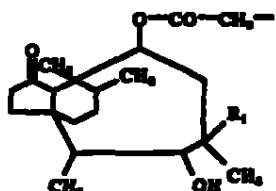
This invention relates to new pleuromutitins. In accordance with the invention there are provided new pleuromutitins of formula I,



wherein
either R₁ is ethyl or vinyl,
n is an integer from 2 to 5, x is sulphur,
a group



or a group =N-R₄',
wherein
either Y and Z are both sulphur, or
one of Y and Z is oxygen and the other is sulphur,
and
R₄' is hydrogen or a group of formula II,



wherein R₁ is as defined above,
each of
R₂ and R₃ is alkyl of 1 to 10 carbon atoms, or
R₂ and R₃ together with the nitrogen atom form a heterocycle of 5 to 7 ring members containing one nitrogen atom or one nitrogen atom and a further hetero member selected from sulphur, oxygen and a group =N-R₄',

wherein R₄' is alkyl of 1 to 5 carbon atoms or hydroxyalkyl of 1 to 4 carbon atoms, or
R₄ and R₅ together with the nitrogen atom form a piperaziny radical, the second nitrogen atom of which is substituted by a radical R₄'',

whereby R₄' is (acyloxy of 2 to 5 carbon atoms) alkyl of 1 to 4 carbon atoms or (benzoyloxy)alkyl of 1 to 4 carbon atoms, or

wherein
R₁ is as defined above,
n is the number 2
R₂ is alkyl of 1 to 10 carbon atoms, hydroxyalkyl of 1 to 4 carbon atoms, (acyloxy of 2 to 5 carbon atoms)al-

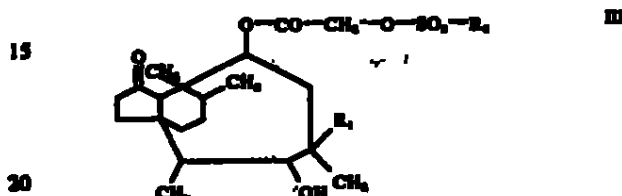
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ky of 1 to 4 carbon atoms or (benzoyloxy) alkyl of 1 to 4 carbon atoms,

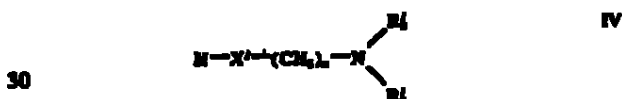
X is the group =N₄'', and
R₂ together with R₄' forms an ethylene bridge between both nitrogen atoms,
and acid addition salts and quaternary salts thereof.

Further, in accordance with the invention a compound of formula I and acid addition salts and quaternary salts thereof may be obtained by processes comprising

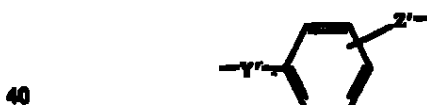
a. reacting a compound of formula III,



wherein
R₁ is as defined above, and
R₂ is alkyl or aryl,
with a compound of formula IV,



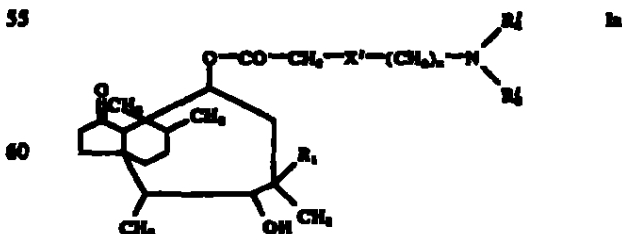
wherein
n is as defined above,
X' is sulphur or a group



wherein Y' and Z' have the same significance as Y and Z, defined above, provided Z is sulphur, and each of

R₂' and R₃' is alkyl of 1 to 10 carbon atoms, or
R₂' and R₃' together with the nitrogen atom form a heterocycle of 5 to 7 ring members containing one nitrogen atom or one nitrogen atom and a further hetero member selected from sulphur, oxygen and a group =N-R₄',

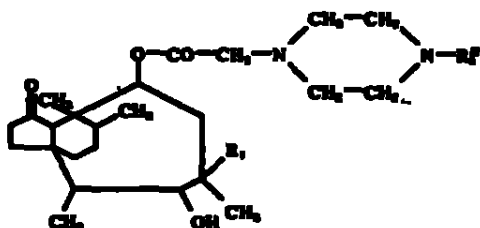
wherein R₄' is as defined above,
to produce a pleuromutitin of formula Ia,



wherein
R₁, n, X', R₂' and R₃' are as defined above, or
b. reacting a compound of formula III, indicated above, either with a compound of formula V,

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R_3^{III} and R_4^{III} together with the nitrogen atom form a piperaziny radical, the second nitrogen atom of which is substituted by a radical R_5^{II} , as defined above, or 2. to produce a pleuromutillin of formula I' ,



wherein R_1 and R_4^{II} are as defined above, and, if desired, converting the resulting compounds of formula I into an acid addition salt or quaternary salt.

Process (a) may, for example, be effected by dissolving an acid addition salt of a compound of formula IV, e.g. a hydrohalide, or the free base in a solution of sodium in an anhydrous lower alcohol, e.g. ethanol. A solution of a compound of formula III in an inert solvent, e.g. an aliphatic ketone such as ethylmethyl ketone or acetone, is then added to this solution. The reaction is preferably effected at a temperature between room temperature and the boiling temperature of the reaction mixture, especially at 25° to 55° C. The reaction time under preferred conditions is from 2 to 12 hours. The process may suitably be carried out under an inert atmosphere, eg. nitrogen R_1 in the compound of formula III may be, for example, alkyl of 1 to 6 carbon atoms or benzyl, although a wide variety of radicals may be used.

Process b) may, for example, be effected by adding a solution of a compound of formula III in an inert solvent, e.g. a lower aliphatic ketone such as ethylmethyl ketone or acetone, to a compound of formula V or Va. An acid-binding agent, e.g. a tertiary base such as triethylamine or pyridine, is conveniently added to the reaction mixture, and the reaction is conveniently carried out at an elevated temperature, preferably at the boiling temperature of the reaction mixture. The reaction usually has a duration of several hours and is generally concluded after 6 to 12 hours. When the reaction is effected with a primary amine, i.e. with a compound of formula V, then condensation products from one mol of a compound of formula V with one or two mol of a compound of formula III are preponderantly formed, depending on the reaction conditions (mol ratio of the reactants, reaction temperature and duration, addition and kind of reactant used, etc.), i.e. compounds of formula Ib wherein R_1 is hydrogen in the case of a mol ratio of 1:1, and R_1 is the radical of formula II in the case of a mol ratio of 1:2, result. Any mixtures of the two condensation products which may be obtained may be separated in known manner.

Process c) may, for example, be effected by dissolving a compound of formula IIIa in an inert solvent, e.g. an aliphatic ketone such as ethylmethyl ketone, or in a lower alcohol such as methanol or ethanol, subsequently adding a compound of formula VI, and allowing the reaction mixture to react, optionally in the presence of a base, e.g. an alkali metal carbonate such as potassium carbonate. The reaction is preferably effected at a temperature between room temperature

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and the boiling temperature of the reaction mixture and has a duration, e.g., of 2 to 20 hours.

Process d) may, for example, be effected by allowing a compound of formula Ia or Ia' to react in a solvent with an acid derivative of formula VII for some time. Preferably the acid derivative is used as solvent alone or in admixture with an inert solvent, e.g. a chlorinated hydrocarbon such as dichloromethane. The reaction product may be isolated from the reaction mixture in known manner and optionally purified.

The compounds of formula I may be converted into their acid addition salts and vice versa.

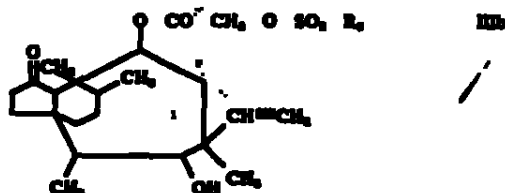
The corresponding quaternary salts may be obtained from the compounds of formula I in accordance with known methods.

The alkyl groups represented by the symbols R_2 and R_3 or R_3' and R_4' preferably contain 1 to 8 carbon atoms; the lower alkyl groups represented by R_3' preferably contain 1 to 3 carbon atoms.

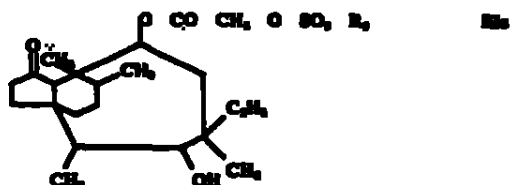
The lower hydroxyalkyl groups represented by R_5 , R_5' and R_5^{II} preferably contain two carbon atoms.

The lower acyloxy group contained in R_6 or R_6^{II} preferably signifies the acetyl group. The lower alkyl groups contained in the acyloxyalkyl or benzyloxyalkyl radicals of R_2 or R_4^{II} preferably contain 2 carbon atoms. The number n preferably denotes 2 or 3.

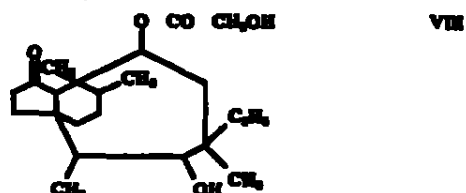
The starting materials of formula IIIb,



wherein R_5 is as defined above, are known. The starting materials of formula IIIc,



wherein R_5 is as defined above, may be obtained by a. reacting the compound of formula V/III



with a compound of formula IX,



wherein A and R_5 are as defined above, or b. reducing a compound of formula IIIb.

The reaction in accordance with process (a) can be effected in an inert solvent, e.g. an aromatic hydrocarbon such as toluene or benzene, preferably, however, in a solvent simultaneously acting as acid-binding

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**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES**

2020

Radicación No 99-70989

Clasificación Internacional de Patentes A61K9/32

Concepto Técnico No

Como resultado del examen definitivo, realizado con fundamento en el artículo 48 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica

Documentos estudiados

- ◆Capítulo descriptivo folios 3 a 31,
- ◆Capítulo reivindicatorio modificado, folios 133 a 137,
- ◆1° examen de forma, folio 41,
- ◆Solicitud de la cual se reivindica prioridad, folios 45 a 94, ✓
- ◆2° examen de forma folio 103,
- ◆Solicitud del examen de patentabilidad, folios 105 y 106
- ◆Examen de patentabilidad, folios 107 a 119,
- ◆Respuesta técnica al examen de patentabilidad, folios 138

Objeto de la invención

La presente solicitud cuyo título es "DERIVADOS DE PLEUROMUTILINA Y VALMUTILINA USADOS PARA LA FABRICACIÓN DE UN MEDICAMENTO PARA EL TRATAMIENTO TRANSDÉRMICO DE INFECCIONES BACTERIANAS EN HUMANOS Y ANIMALES Y COMPOSICIONES QUE LOS CONTIENEN" El objeto de la solicitud es un nuevo uso de valdemulina para la terapia en infecciones bacterianas en humanos y animales

El objeto de la invención se puede clasificar según la clasificación internacional como A61K 31/22

Determinación del estado de la técnica

El artículo 16 de la Decisión 486 de la Comisión establece "El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en

su caso, de la prioridad reconocida

Sólo para el efecto de la determinación de la novedad, también se considerará dentro del estado de la técnica, el contenido de una solicitud de patente en trámite ante la oficina nacional competente, cuya fecha de presentación o de prioridad fuese anterior a la fecha de presentación o de prioridad de la solicitud de patente que se estuviese examinando, siempre que dicho contenido esté incluido en la solicitud de fecha anterior cuando ella se publique o hubiese transcurrido el plazo previsto en el artículo 40 "

Se realizó la búsqueda del estado de la técnica con fecha anterior a la fecha de presentación de la presente solicitud, de la cual se reivindica prioridad, 22 de noviembre de 1999 Consultada la fuente de información con que cuenta este despacho se encontró los siguientes documentos

No	Documento No	Título	Fecha de Publicación
D1	US3716579	Esters derivaives of pleuromutilin	13-feb-1973
D2	WO9921855	Pleuro mutilinderivatives as antimicrobials	06-may-1999
D3	WO9725309	Carbamoyloxy derivatives of mutiline and their use as aantbacterial	17-jul-1997
D4	US4675330	Pleuromutilin derivatives process for their preparation and their use	23-jun-1978
D5	WO9801127	Vetennary use of a pleuromutilin dervatives	15-ene-1998
D6	US4032530	Certain pleuromutilin	28- jun-1997

Evaluación de los requisitos de patentabilidad

El artículo 14 de la Decisión 486 de la Comisión de la Comunidad Andina establece *"Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial "*

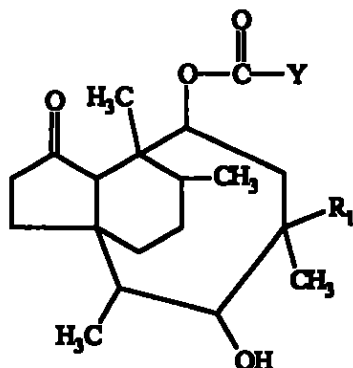
En cumplimiento con este artículo, se procedió a evaluar los requisitos de novedad, nivel inventivo y aplicación Industrial con el fin de establecer la patentabilidad de la invención reivindicada en la solicitud en estudio

Evaluación de la Novedad

El art 16 de la Decisión 486 de la Comisión de la Comunidad Andina establece **"Una invención se considerará nueva cuando no está comprendida en el estado de la técnica "** **"El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida**

Sólo para el efecto de la determinación de la novedad, también se considerará dentro del estado de la técnica, el contenido de una solicitud de patente en trámite ante la oficina nacional competente, cuya fecha de presentación o de prioridad fuese anterior a la fecha de presentación o de prioridad de la solicitud de patente que se estuviese examinando, siempre que dicho contenido esté incluido en la solicitud de fecha anterior cuando ella se publique o hubiese transcurrido el plazo previsto en el artículo 40 "

La solicitud en estudio reclama una composición farmacéutica de un compuesto de la fórmula I



-La anterioridad D1 enseña compuestos esteres de pleuromutilinas composiciones de alimentos que los comprenden y medicamentos La anterioridad en primer lugar comprende los compuestos que se usan en las composiciones de la solicitud en estudio, ya que su objeto es el uso de pleuromutilinas en medicamentos no es nuevos, tampoco es nuevo el que se haya descubierto su efecto antimicrobiano, tampoco es nuevo los medicamentos que se obtienen con dichos compuestos, tal y como son reivindicados Además las reivindicaciones se refieren a una composición definida como unica característica que comprenda una pleuromutilina, entonces su novedad esta ligada unidamente a la novedad del compuesto Entonces la "invención de la presente solicitud" ya era del estado de la técnica al momento de su radicación y se observa que la solución al problema técnico plantado no es nueva, no se observa ningún aporte nuevo al estado de la técnica

-D2 y D3 describen compuestos derivados de pleuromutilinas, métodos de síntesis, composiciones farmacéuticas que los comprenden. Estas anterioridades en primer lugar enseñan los compuestos que se usan en las composiciones de la solicitud en estudio, ya que su objeto es el uso tácito de las pleuromutilinas en medicamentos, tampoco es nuevo el que se haya descubierto su efecto antimicrobiano, tampoco es nuevo los medicamentos que se obtienen con dichos compuestos, tal y como son reivindicados. Además las reivindicaciones se refieren a una composición definida como única característica que comprenda una pleuromutilina, entonces su novedad está ligada únicamente a la novedad del compuesto.

-Por su parte D4 describe compuestos específicos de pleuromutilinas, composiciones que los comprenden, además de describir su efecto terapéutico. La anterioridad en primer lugar comprende los compuestos que se usan en las composiciones de la solicitud en estudio, ya que su objeto es el uso de pleuromutilinas en medicamentos no es nuevo, tampoco es nuevo el que se haya descubierto su efecto antimicrobiano, tampoco es nuevo los medicamentos que se obtienen con dichos compuestos, tal y como son reivindicados. Además las reivindicaciones se refieren a una composición definida como única característica que comprenda una pleuromutilina, entonces su novedad está ligada únicamente a la novedad del compuesto. Así las cosas, entonces la "invención de la presente solicitud" ya era del estado de la técnica y se observa que la solución al problema técnico planteado no es nueva, no se observa ningún aporte nuevo al estado de la técnica.

-D5 describe formulaciones y el uso de un derivado específico de pleuromutilina en composiciones para enfermedades veterinarias los comprenden, además de describir su efecto terapéutico. Los compuestos no son nuevos, porque es el uso en las composiciones de la solicitud en estudio, ya que su objeto es el uso de pleuromutilinas en medicamentos, no es nuevo, tampoco es nuevo el que se haya descubierto su efecto antimicrobiano, tampoco es nuevo los medicamentos que se obtienen con dichos compuestos, tal y como son reivindicados. Además las reivindicaciones se refieren a una composición definida como única característica que comprenda una pleuromutilina, entonces su novedad está ligada únicamente a la novedad del compuesto. Así las cosas, entonces la "invención de la presente solicitud" ya era del estado de la técnica y se observa que la solución al problema técnico planteado no es nueva, no se observa ningún aporte nuevo al estado de la técnica.

-D6 describe compuestos derivados de ciertas pleuromutilinas, usado por su reconocida actividad antibacteriana en formulaciones antibacterianas, que comprenden agentes antibacterianos. Esta anterioridad comprende composiciones que comprenden pleuromutilinas, que demuestran que no es la primera vez que se usan en composiciones, tal y como se reivindica en la solicitud en estudio.

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Como consecuencia de todo lo expuesto anteriormente, la solicitud no cumple con el requisito de novedad, por lo tanto se recomienda negar el privilegio solicitado para las reivindicaciones 1 a 8, folio 133 a 137

Bogotá, D C , 15 de mayo de 2006

CONCEPTO TÉCNICO No 831	JEFE DE DIVISIÓN NUEVAS CREACIONES	EXAMINADOR TÉCNICO Código No 202012
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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

168

RADICACIÓN 0-85195

EDICTO No. 10629

LA SECRETARÍA GENERAL AD-HOC HACE SABER

Que esta Superintendencia proferió Resolución No 17289 de 29-JUN-2006. Que el contenido de la parte resolutive es como sigue. El Superintendente de Industria y Comercio

RESUELVE

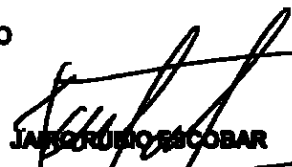
ARTICULO PRIMERO Negar el privilegio de patente de invención a la creación denominada. DERIVADOS DE PLEUROMUTILINA Y VALNEMULINA USADOS PARA LA FABRICACIÓN DE UN MEDICAMENTO PARA EL TRATAMIENTO TRANSDÉRMICO DE INFECCIONES BACTERIANAS EN HUMANOS Y ANIMALES Y COMPOSICIONES QUE LOS CONTIENE

ARTICULO SEGUNDO Notificar personalmente a la doctora Jimena Escobar Uribe en su calidad de apoderada de la sociedad Novartis Ag, o a quien haga sus veces, el contenido de la presente resolución entregándole copia de la misma advirtiéndole que contra ella procede el recurso de reposición ante el Superintendente de Industria y Comercio al momento de notificarse o dentro de los 5 días hábiles siguientes

NOTIFIQUESE Y CUMPLASE

Dada en Bogotá D C a los 29 JUN. 2006

EL SUPERINTENDENTE DE INDUSTRIA Y COMERCIO


JAIME RUBIO ESCOBAR

Para notificar a los interesados se fija el presente EDICTO en lugar visible al público en la SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO por el término de (10) diez días hábiles contados a partir de las 8.30 a.m de hoy

Secretaría General Ad-Hoc 14-JUL-2006
Secretaría General Ad-Hoc
EDICTO No 10629

Este edicto se desfilja hoy 28-JUL-2006 a las cinco (5.00 p.m)