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(12) # EUROPEAN PATENT SPECIFICATION

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GB-A- 2 035 800

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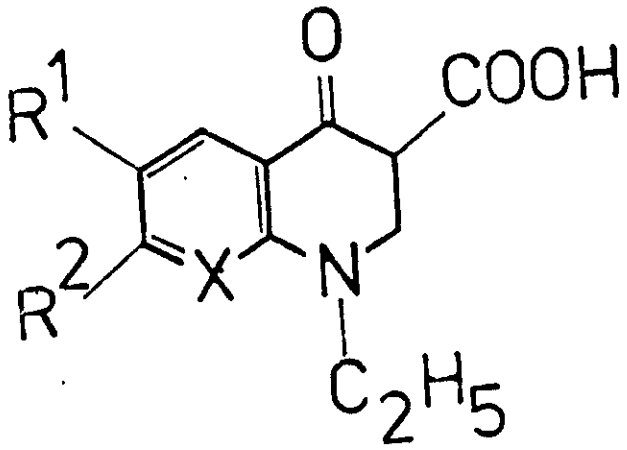
Description

This invention relates to synergistic, anti-microbial pharmaceutical compositions containing a quinolinecarboxylic acid derivative or a naphthyridine-carboxylic acid derivative of the general formula (I)

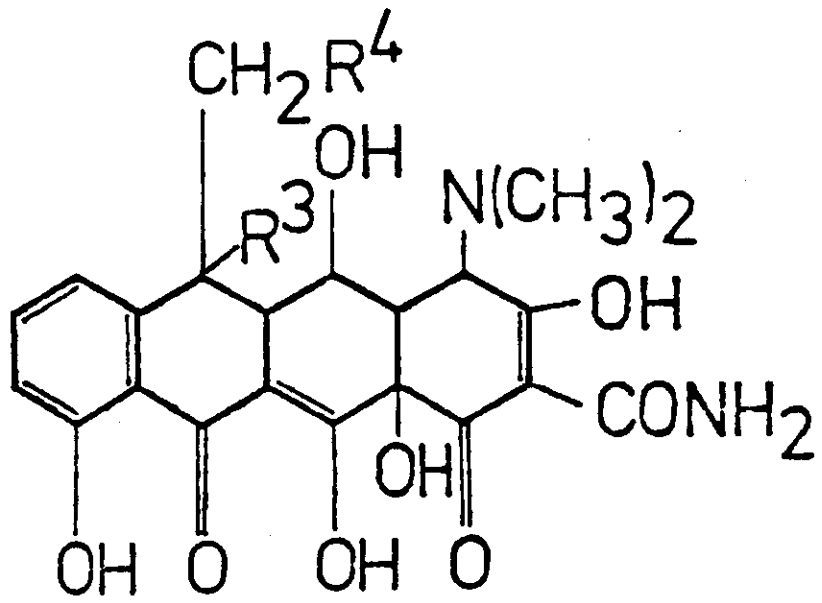


(I)

wherein

X is a carbon or nitrogen atom;
R^1 is a hydrogen or fluorine atom;
R^2 is a methyl, piperazino or methylpiperazino group; or
R^1 and R^2 together are a methylenedioxy group;

and a tetracycline derivative of the general formula (II)



(II)

wherein

R^3 and R^4 are each 2 hydrogen atom; or
R^3 and R^4 together represent an additional chemical bond,

as active ingredients.

In another aspect of the invention, there is provided a process for the preparation of these compositions.

In the antimicrobial therapy, a continuous combat exists between the adaptation capability of microorganisms (development of resistance) and the preparation of novel drugs.

In the case of novel drugs, the adaptation capability, i.e. the resistance, usually develops within a shorter or longer period. It can be expected that the development of the resistance becomes particularly

rapid when the new substance is a derivative of a drug previously used for a long time, since in this case the resistance developed to the starting compound will of course more rapidly be modified for the derivatives.

The development of the resistance can be delayed by the simultaneous administration of several active compounds whereby the metabolism of the microorganisms is attacked at several points at the same time. This results in the resistance of the microorganisms to the combination hardly developing or only long afterwards. Thus, the desired "microbicidal" (killing) effect is strengthened.

In antimicrobial therapy, nalidixic acid has been used for a long time as active ingredient. It is known that of its derivatives, norfloxacin (Belgian patent specification. No. 863,429) and pefloxacin (Belgian patent specifications Nos. 870,576 and 870,917) show a highly favourable effect on gram-negative pathogens whereas their effect on gram-positive pathogens is more moderate.

Tetracycline is also a long-known antimicrobial substance. Of its derivatives, doxicycline has a very favourable effect on gram-positive pathogens and a moderate effect on gram-negative ones.

GB-A-2 035 800 generally describes combinations of antibiotics and β-ketoacids, and FR-A-2 563 433 describes combinations of oxytetracycline and oxolinic or nalidixic acid.

The aim of the invention is to prepare broad-spectrum pharmaceutical compositions by combining these two types of active substances and thereby to inhibit the development of resistance.

When combining tetracycline derivatives with the quinoline-carboxylic acid derivatives or naphthyridinecarboxylic acid derivatives of the general, formula (I), it was surprisingly observed that, in addition to the realization of the aim of the invention, a high-level synergistic action of these two types of active substances occurred, whereby the effective doses could be significantly decreased with the important advantages of fewer side-effects and a cheaper therapy.

Thus, the present invention relates to the preparation of a synergistic, antimicrobial pharmaceutical composition containing a quinolinecarboxylic acid derivative or a naphthyridinecarboxylic acid derivative of the general formula (I) as defined above; and a tetracycline derivative of the general formula (II) as defined above as active ingredients, which comprises mixing together 0.01 to 50 % by weight of a derivative of the general formula (I) and 0.01 to 95 % by weight of a tetracycline derivative of the general formula (II), while maintaining the ratio of the compound of the general formula (I) to the compound of the general formula (II) as 1:1 to 1:20, and optionally inert, solid or liquid carriers, preferably magnesium carbonate, magnesium stearate, starch, talc, cyclodextrin or water as well as binding, disintegrating, emulsifying, sliding agents and lubricants as additives and formulating them in a known way to give a pharmaceutical composition suitable for therapeutical application.

In the process of the invention, preferably a compound of the general formula (I), wherein X, R^1 and R^2 are as defined above, suitably norfloxacin (1,4-dihydro-1-ethyl-6-fluoro-4-oxo-7-piperazinoquinoline-3-carboxylic acid) and doxicycline (4-dimethylamino-1,11-dioxo-6-methyl-1,4,4a,5,5a,6,11,12a-octahydro-3,5,10,12,12a-pentahydroxy-2-naphthacenecarboxamid) may be used as active ingredients of the combination.

Similarly, oxolinic acid (1,4-dihydro-1-ethyl-6,7-methylenedioxy-4-oxoquinoline-3-carboxylic acid) and methacycline (4-dimethylamino-1,11-dioxo-6-methylene-1,4,4a,5,5a,6,11,12a-octahydro-3,5,10,12,12a-pentahydroxy-2-naphthacenecarboxamide) may preferably be used in the combination according to the invention.

According to a preferred embodiment of the invention, the active ingredients are used in an 1:1 ratio. If desired, the compositions may contain also other active ingredients, (such as antibiotics or chemotherapeutics).

The pharmaceutical compositions according to the invention may be formulated in solid forms, such as granulates, tablets, capsules, dragées and suppositories, semisolid forms, such as ointments or liquid forms, such as injectable solutions, emulsions or suspensions. Preferably gels, ointments, dusting powders for wounds, injectable solutions and suspensions as well as the combinations of powder and solvent ampoules are prepared.

Depending on the formulation, magnesium carbonate, magnesium stearate, starch, talc and water as commonly used carriers, cyclodextrin as a novel carrier as well as other additives such as vehicles, disintegrating, sliding and emulsifying agents may be used.

The compositions according to the invention may be administered by the oral, parenteral or rectal route or may be used topically.

The orally useful compositions are e.g. granulates, tablets, capsules or dragées. Parenterally useful compositions are e.g. aqueous emulsions, suspensions or solutions. Ointments, aqueous or oily emulsions and suspensions as well as sprays may be applied topically.

The pharmaceutical compositions containing the synergistic active ingredient combination may also be

used in veterinary medicine, e.g. in the form of a powder mixed with the fodder, or in the form of a solution added to the drinking fluid of the animals. For this purpose, compositions containing a combination of oxolinic acid and methacycline are preferably used.

The in vitro biological activity of the compositions according to the invention are shown in Tables I to V.

The international resistant and/or polyresistant human-pathogenic and/or veterinary-pathogenic microorganisms used in these investigations were as follows.

1.) Vibrio parahaemolyticus	CCM.5938.
2.) Pseudomonas fluorescens	CCM.2115.
3.) Pseudomonas pictorum	CCM.284.
4.) Pseudomonas acidovorans	CCM.283.
5.) Proteus vulgaris	CCM.1799.
6.) Proteus mirabilis	CCM.1944.
7.) Shigella sonnei	CCM.1373.
8.) Salmonella typhimurium	CCM.5445
9.) Salmonella cholerae suis	CCM.5438.
10.) Escherichia coli	DSM.30038.
11.) Escherichia coli	CCM.5863.
12.) Escherichia coli	CCM.5172.
13.) Klebsiella pneumoniae	CCM.1848.
14.) Serratia marcescens	CCM.303.
15.) Pasteurella multocida	CCM.5419.
16.) Staphylococcus aureus	CCM.885.
17.) Staphylococcus aureus	CCM.2317.
18.) Staphylococcus aureus	CCM.2326.
19.) Streptococcus agalactiae	CCM.5534.
20.) Streptococcus disgalactiae	CCM.5548.
21.) Bacillus subtilis	ATCC.6633.
22.) Micrococcus flavus	ATCC.10240.
23.) Bacillus licheniformis	CCM.2182.
24.) Bacillus licheniformis	CCM.2205.
25.) Pseudomonas putrefaciens	Sz-III-156.
26.) Pseudomonas fluorescens putida	M-III-21.
27.) Pseudomonas fluorescens putida	K-I-86.

Abbreviations used hereinabove and hereinafter are as follows:

ATCC = The American Type Culture Collection

CCM = Czechoslovak Collection of Microorganisms

DSM = Deutsche Sammlung für Mikroorganismen

µg/ml = microgram/millilitre

The investigations were carried out on a Difco Bouillon medium (in the case of bacteria) or on a modified Difco Bouillon medium (in the case of vibrios).

The inoculation was made with a germ number of 5×10^5/ml. The incubation lasted 24 hours at 37 °C.

It is obvious from the data of the Tables that, due to the synergistic effect, from the combination a part and in some cases even a fraction of the amounts of the active ingredients, (as calculated for their individual activity), is sufficient to achieve an identical effect.

Table I

Combination of Nalidixic Acid with Doxicycline

		MIC value /ug/ml				Decrease of the MIC value by the combination %			Effect %	
				Combination						
		Nal	Dox	Nal	Dox	Nal	Dox	Nal + Dox	Additive	Synerg.
Vibrio p. haemolyticus	CCM.5938.	5	0.5	0.5	0.25	10	50	30	60	40
Pseudomonas pictorum	CCM.284.	25	0.75	2.5	0.075	10	10	10	20	80
Proteus vulgaris	CCM.1799.	50	10	5	2,5	10	25	16.5	35	65
Proteus mirabilis	CCM.1944.	10	25	2.5	5	25	20	22.5	45	55
Salmonella typhimurium	CCM.5445.	50	10	5	5	10	50	30	60	40
Salmonella cholerae suis	CCM.5438.	25	0.5	2,5	0,05	10	10	10	20	80
Escherichia coli	DSM.30038.	50	5	5	0,5	10	10	10	20	80
Escherichia coli	CCM.5863.	25	5	2.5	0.5	10	10	10	20	80
Escherichia coli	CCM.5172.	50	2.5	5	0.5	10	20	15	30	70
Pasteurella multocida	CCM.5419.	50	0.25	5	0.025	10	10	10	20	80
Staphylococcus aureus	CCM.2317.	100	0.25	10	0.05	10	20	25	30	70
Staphylococcus aureus	CCM.2326.	100	0.25	10	0.075	10	30	20	40	60
Streptococcus disgalactiae	CCM.5948.	75	0.5	10	0.25	13.3	50	31.6	63.3	36.7

Abbreviations: Nal = nalidixic acid

Dox = doxicycline

Table II

Combination of Oxolinic acid with Doxicycline

		MIC value /ug/ml				Decrease of the MIC value by the combination %		Effect, %		
				Combination						
		Ox	Dox	Ox	Dox	Ox	Dox	Ox + Dox	Additive	Synerg.
Vibrio p-Haemolyticus	CCM.5938.	1	0.5	0.1	0.25	10	50	30	60	40
Pseudomonas fluorescens	CCM.2115.	10	0.5	0.25	0.25	2.5	50	26.3	52.5	47.5
Pseudomonas acidovorans	CCM.283.	0.5	0.25	0.05	0.05	10	20	15	30	70
Pseudomonas pictorum	CCM.284.	5	0.75	0.5	0.075	10	10	10	20	80
Shigella sonnei	CCM.1373.	0.75	1	0.075	0.05	10	5	7,5	15	85
Escherchia coli	CCM.5863.	5	5	0.75	0.75	15	15	15	30	70
Escherichia coli	CCM.5172.	2.5	2.5	0.75	0.75	30	30	30	60	40
Staphylococcus aureus	CCM.885.	25	1	2.5	0.1	10	10	10	20	80
Staphylococcus Aureus	CCM.2317.	10	0.25	1	0.025	10	10	10	20	80
Bacillus subtilis	ATCC.6633.	0.75	0.05	0.1	0,025	13.3	50	31.6	63.3	36.7
Bacillus cereus	CCM.2010.	5	0.5	0.5	0.25	10	50	30	60	40

Abbreviations: Ox = oxolinic acid

Dox = doxicycline

Table III

Combination of Norfloxacin with Doxicycline

		MIC value /ug/ml				Decrease of the MIC value by the combination %			Effect %	
		Norf	Dox	Combination Norf	Combination Dox	Norf	Dox	Norf+ Dox	Additive	Synerg.
Vibrio p. haemolyticus	CCM.5938	0.5	0.5	0.25	0.1	50	20	35	70	30
Pseudomonas fluorescens	CCM.2115.	0.25	0.5	0,05	0.05	20	10	15	30	70
Pseudomonas pictor.	CCM.284.	0.75	0.75	0.1	0.25	13.3	33.3	23.3	46.6	53.4
Proteus vulg.	CCM.1799.	0.1	10	0.01	5	10	50	30	60	40
Shigella sonnei	CCM.1373.	0.1	1	0.01	0.5	10	50	30	60	40
Salmon. typhimus.	CCM.5445.	0.5	10	0.075	2.5	15	25	20	40	60
Salmon. Choleraesuis	CCM.5438.	0.5	0.5	0.05	0.05	10	10	10	20	80
Esch. Coli	DSM.30038.	0.1	5	0,025	0.75	25	15	20	40	60
Esch. coli	CCM.5863.	0.25	5	0.05	0,75	20	15	17.5	35	65
Past. multocida	CCM.5419.	0.5	0.25	0.05	0.025	10	10	10	20	80
Staph. aureus	CCM.885.	5	1	1	0.25	20	25	22.5	45	55
Strept. disgalact.	CCM.5548.	2,5	0,5	0,75	0,1	30	20	25	50	50

Abbreviations: Norf = Norfloxacin

Dox = doxicycline

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Table IV

Combination of Pefloxacin with Doxicycline

		MIC value /ug/ml				Decrease of the MIC value by the combination %			Effect %	
		Pefl	Dox	Combination Pefl	Combination Dox	Pefl	Dox	Pefl + Dox	Additive	Synerg.
Vibrio p. haemolyticus	CCM.5938.	0.5	0.5	0.75	0.25	15	50	32.5	65	35
Proteus vulgaris	CCM.1799.	0.5	10	0.1	0.05	20	0.5	10.2	20.5	79.5
Proteus mirabilib	CCM.1944.	0.5	25	0.075	2.5	15	10	12.5	25	75
Shigella sonnei	CCM.1373.	0.25	1	0.05	0.1	20	10	15	30	70
Salmon. typhimur	CCM.5445.	2.5	10	0.5	2.5	20	25	22.5	45	55
Salmon. choleraesuis	CCM.5438.	1	0.5	0.1	0.05	10	10	10	20	80
Esch. coli	DSM.30038.	1	5	0.1	0.5	10	10	10	20	80
Esch. coli	CCM.5863.	1	5	0.1	1	10	20	15	30	70
Klebs. pneumon.	CCM.1848.	0.75	2.5	0.075	1	10	40	25	50	50
Serratia marcesc.	CCM.303.	0.5	25	0.1	10	20	40	30	60	40
Past. multocida	CCM.5419.	0.25	0.25	0.05	0.05	20	20	20	40	60
Strept. disgalact.	CCM.5548.	10	0.5	1	0.25	10	50	30	60	40
Pseud. putrefac.	Sx-III-156.	0.25	0.5	0.05	0.075	20	15	17.5	35	65
Pseud. fluoresc. putida	M-III-21.	2.5	2.5	0.5	0.75	20	30	25	50	50
Pseud. flouresc. putida	K-I-86.	2.5	0.25	0.05	0.05	2	20	11	22	78

Abbreviations: Pefl = pefloxacin

Dox = doxicycline

Table V

Combination of Oxolinic acid with Methacycline

		MIC value /ug/ml				Decrease of the MIC value by the combination %			Effect %	
		Combination								
		Ox	Methac	Ox	Methac	Ox	Methac	Ox + Methac	Additive	Synerg.
Vibrio p. haemolyticus	CCM.5938.	1	1	0.25	0.1	25	10	17.5	35	65
Pseud. fluoresc.	CCM.2115.	2.5	0.5	0.75	0.1	30	20	25	50	50
Esch. coli	DSM.30038.	1	2.5	0.25	0.25	25	10	17.5	35	65
Esch. coli	CCM.5863.	5	2.5	0.25	0.25	5	10	7.5	15	85
Esch. coli	CCM.5172.	2.5	2.5	0.25	0.25	10	10	10	20	80

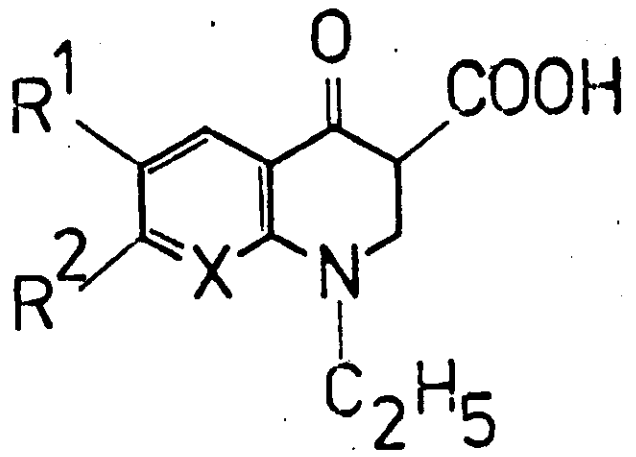
Abbreviations: Ox = oxolinic acid

Methac = methacycline

Claims

1. Synergistic, antimicrobial pharmaceutical compostion which comprises 0.01 to 50 % by weight of a quinolinecarboxylic acid derivative or a naphthyridinecarboxylic acid derivative of the general formula

(I)

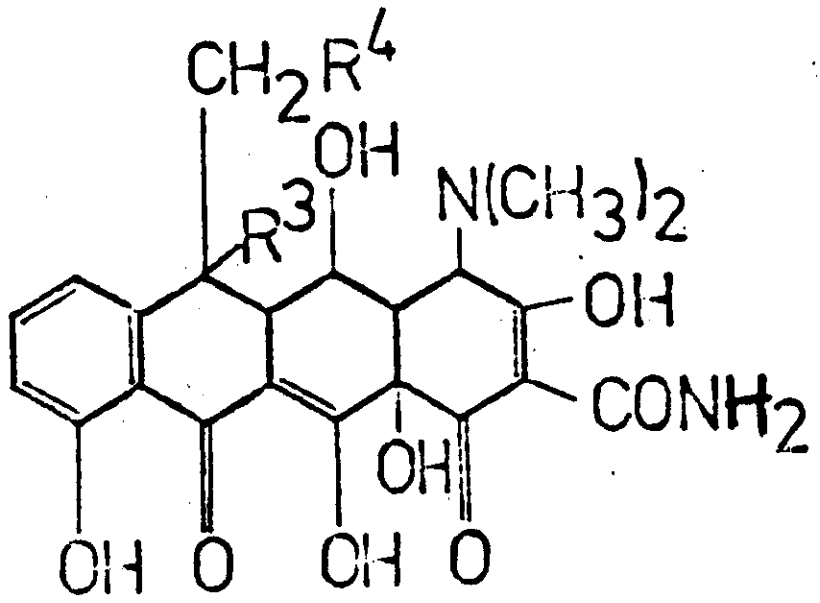


(I)

wherein

X	is a carbon or nitrogen atom;
R^1	is a hydrogen or fluorine atom;
R^2	is a methyl, piperazino or methylpiperazino group; or
R^1 and R^2	together are a methylenedioxy group;

and 0.01 to 95 % by weight of a tertracycline derivative of the general formula (II)



(II)

wherein

R^3 and R^4	are each a hydrogen atom; or
R^3 and R^4	together represent an additional Chemical bond,

in an 1:1 to 1:20 ratio of the compound of the general formula (I) to the compound of the general formula (II), optionally in an admixture with an inert, solid or liquid carrier. and other additives.

2. A composition as claimed in claim 1 which comprises doxicycline (4-dimethylamino-1,11-dioxo-6-methyl-1,4,4a,5,5a,6,11,12,12a-octahydro-3,5,10,12,12a-pentahydroxy-2-naphthacenecarboxamide) as active ingredient of formula (II).

3. A composition as claimed in claim 2, which comprises norfloxacin (1,4-dihydro-1-ethyl-6-fluoro-4-oxo-7-

piperazinoquinoline-3-carboxylic acid) and doxicycline as active ingredients.

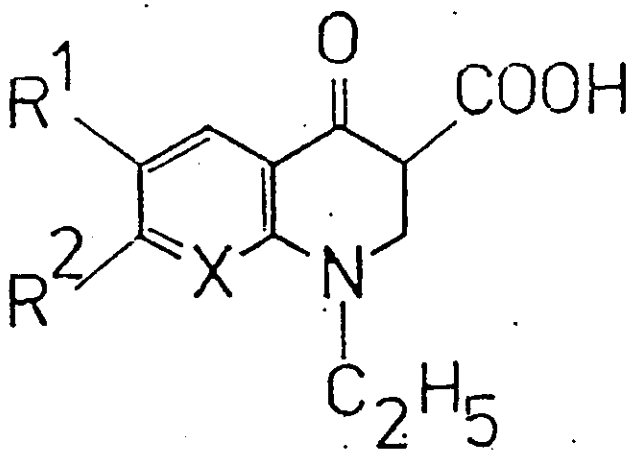
4. A composition as claimed in claim 1, which comprises oxolinic acid (1,4-dihydro-1-ethyl-6,7-methylenedioxy-4-oxoquinoline-3-carboxylic acid) and methacycline (4-dimethylamino-1,11-dioxo-6-methylene-1,4,4a,5,5a,6,11,12,12a-octahydro-3,5,10,12,12a-pentahydroxy-2-naphthacenecarboxamide) as active ingredients.

5. A composition as claimed in claim 1, which comprises the active ingredients in an 1:1 ratio.

6. Process for the preparation of a composition according to claim 1, which comprises mixing together 0.01 to 50 % by weight of a derivative of the general formula (I) and 0.01 to 95 % by weight of a tetracycline derivative of the general formula (II), while maintaining the ratio of the compound of the general formula (I) to the compound of the general formula (II) as 1:1 to 1:20, and optionally inert, solid or liquid carriers and additives.

Patentansprüche

1. Synergistische, antimikrobielle, pharmazeutische Komposition, dadurch gekennzeichnet, daß sie 0,01 bis 50 Gew.% eines Chinolincarbonsäure-derivats oder eines Naphthyridincarbonsäure-derivats der allgemeinen Formel I:

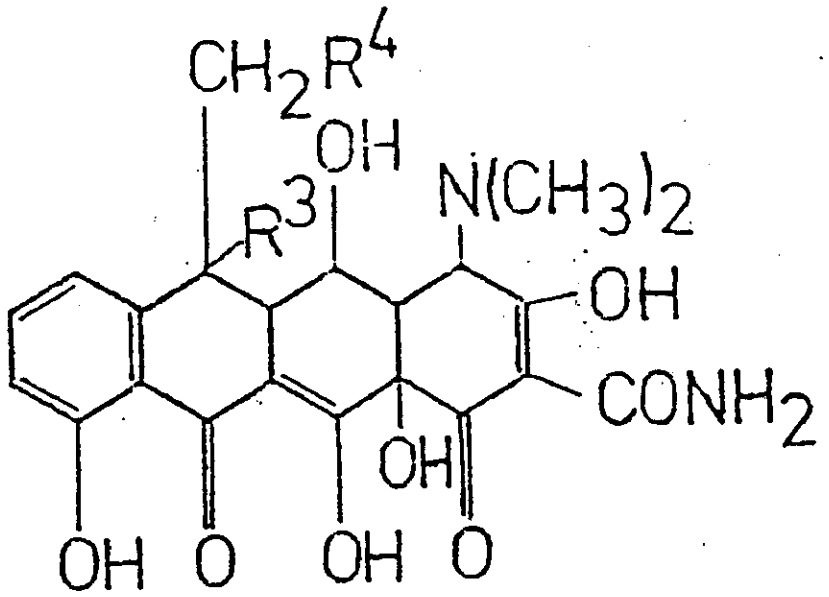


(I)

worin

X	ein Kohlenstoff- oder Stickstoffatom,
R^1	ein Wasserstoff- oder Fluoratom,
R^2	eine Methyl-, Piperazino- oder Methylpiperazino-gruppe bedeuten, oder
R^1 und R^2	gemeinsam eine Methylendioxy-gruppe bilden, und

0,01 bis 95 Gew.% eines Tetracyclin-derivats der allgemeinen Formal II:



(II)

worin

R^3 und R^4 je ein Wasserstoffatom bedeuten, oder

R^3 und R^4 gemeinsam eine zusätzliche chemische Bindung bilden,

wobei das Verhältnis der Verbindung der allgemeinen Formel I zur Verbindung der allgemeinen Formel II 1 : 1 bis 1 : 20 beträgt, gewünschtenfalls in Mischung mit einem inerten festen oder flüssigen Träger und weiteren Additiven enthält.

2. Komposition gemäß Anspruch 1, dadurch gekennzeichnet, daß sie Doxicyclin (4-Dimethylamino-1,11-dioxo-6-methyl-1,4,4a,5,5a,6,11,12,12a-octahydro-3,5,10,12,12a-pentyhadroxy-2-naphthacencarboxamid) als aktives Ingrediens der Formel II enthält.

3. Komposition gemäß Anspruch 2, dadurch gekennzeichnet, daß sie Norfloxacin (1,4-Dihydro-1-ethyl-6-fluor-4-oxo-7-piperazinochinolin-3-carbonsäure) und Doxicyclin als aktive Ingredientien enthält.

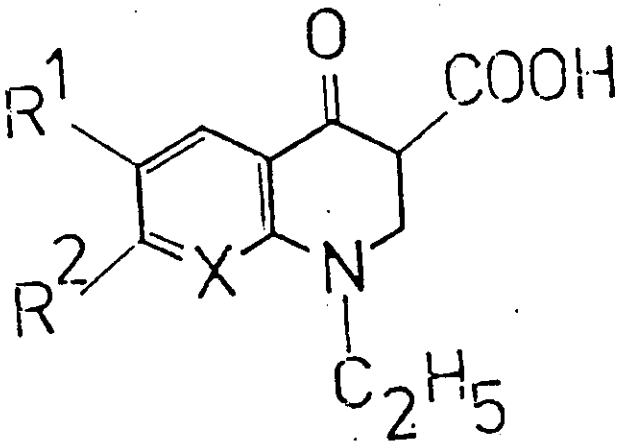
4. Komposition gemäß Anspruch 1, dadurch gekennzeichnet, daß sie oxolinsäure (1,4-Dihydro-1-ethyl-6,7-methylen-dioxy-4-oxochinolin-3-carbonsäure und Methacyclin (4-Dimethylamino-1,11-dioxo-6-methylen-1,4,4a,5,5a,6,11,12,12a-octahydro-3,5,10,12,12a-pentahydroxy-2-naphthacencarboxamid als aktive Ingredientien enthält.

5. Komposition gemäß Anspruch 1, dadurch gekennzeichnet, daß sie die aktiven Ingredientien im Verhältnis 1 : 1 enthält.

6. Verfahren zur Herstellung einer Komposition gemäß Anspruch 1, dadurch gekennzeichnet, daß man
0,01 bis 50 Gew.% eines Derivats der allgemeinen Formel I und
0,01 bis 95 Gew.% eines Tetracyclin-derivats der allgemeinen Formel II,
unter Aufrechterhaltung des Verhältnisses von Verbindung der allgemeinen Formel I zur Verbindung der allgemeinen Formel II von 1 : 1 bis 1 : 20 und gewünschtenfalls inerte feste oder flüssige Träger und Additive miteinander vermischt.

Revendications

1. Composition pharmaceutique antimicrobienne synergétique qui comprend de 0,01 à 50% en poids d'un dérivé d'acide quinolinecarboxylique ou d'un dérivé d'acide naphtyridinecarboxylique de la formule générale (I),

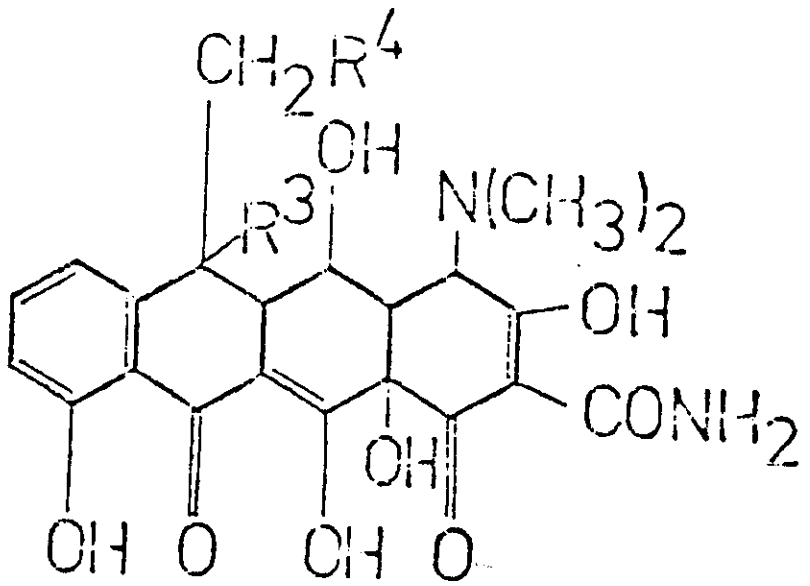


(I)

dans laquelle

X est un atome de carbone ou d'azote ;
R^1 est un atome d'hydrogène ou de fluor ;
R^2 est un groupement méthyle, pipérazine ou méthylepipérazine ; ou
R^1 et R^2 ensemble sont un groupement méthylènedioxy ;

et de 0,01 à 95% en poids d'un dérivé de tétracycline de formule générale (II)



(II)

dans laquelle

R^3 et R^4 sont chacun un atome d'hydrogène ; ou
R^3 et R^4 représentent ensemble une liaison chimique supplémentaire,

dans un rapport de 1:1 à 1:20 du composé de formule générale (I) au composé de formule générale (II), facultativement en une admixion avec un support inerte, solide ou liquide.

2. Une composition selon la revendication 1 qui comprend de la doxycycline (4-diméthylamino-1,11-dioxo-6-méthyle-1,4,4a,5,5a,6,11,12,12a-octahydro-3,5,10,12,12a-pentahydroxy-2-naphtacènecarboxamide) comme ingrédient actif de formule (II).

3. Une composition selon la revendication 2, qui comprend de la norfloxacine (acide 1,4-dihydro-1-éthyle-6-fluoro-4-oxo-7-pipérazinoquinoline-3-carboxylique) et de la doxicycline comme ingrédients actifs.

4. Une composition selon la revendication 1, qui comprend de l'acide oxolinique (acide 1,4-dihydro-1-

éthyle-6,7-méthylènedioxy-4-oxoquinoline-3-carboxylique) et de la méthacycline (4-diméthylamino-1,11-dioxo-6-méthylène-1,4,4a,5,5a,6,11,12,12a-octahydro-3,5,10,12,12a-pentahydroxy-2-naphtacènecarboxamide) comme ingrédients actifs.

5. Une composition selon la revendication 1, qui comprend les ingrédients actifs dans un rapport de 1:1.

6. Procédé pour la préparation d'une composition selon la revendication 1, qui comprend de mélanger ensemble de 0,01 à 50% en poids d'un dérivé de formule générale (I), et de 0,01 à 95% en poids d'un dérivé de tétracycline de formule générale (II), tout en maintenant le rapport du composé de formule générale (I) au composé de formule générale (II) entre 1:1 et 1:20, et facultativement des additifs et supports inertes, liquides ou solides.

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