Description

Technical Field

The present invention relates to a novel quinolone carboxylic acid derivative and a salt thereof which exhibit excellent antimicrobial activity against both Gram positive and Gram negative microorganisms.

Background Art

Quinolone carboxylic acid derivatives with diazepinyl substituents at position 7 are known from JP-A-63 132 885, JP-A-63 196 580 and J. Med.Chem Vol.33 Nr.1, 1990, p.142-146. Quinolone carboxylic acids with fluorine substituents at position 8 are known from EP-A-0 153 828. Quinolone carboxylic acids with hexahydro-1,4-oxazepin-4-yl substituents at position 7 are known from JP-A-2 115 181. Quinolone carboxylic acids with 3-oxo-1-piperazinyl substituents in position 7 are known from EP-A-0 166 939. Quinolone carboxylic acids with fluoro-methoxy substituents at position 8 are known from EP-A-0 352 123.

Synthetic antimicrobial agents such as nalidixic acid, piromidic acid, and the like are known as drugs for curing infectious diseases caused by Gram negative microorganisms. They exhibit, however, only deficient effects on intractable diseases such as pseudomoniasis and the like.

On the other hand, quinolone carboxylic acid derivatives substituted with a fluorine atom at 6 position, such as norfloxacin, ofloxacin, and cyprofloxacin, or quinolone carboxylic acid derivatives substituted with a chlorine atom at 8 position have been developed (Japanese Patent Laid-open (ko-kai) Nos. 225181/1986, 90813/1989) and clinically used because of their strong antimicrobial activity.

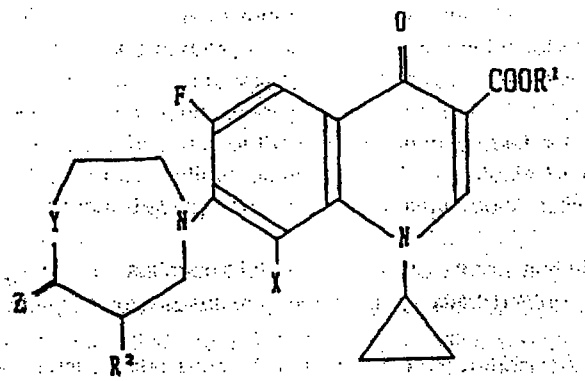
These conventional synthetic antimicrobial agents had defects of insufficient absorptivity in a living body, providing only low bioavailability, and of a low antimicrobial activity against Gram positive microorganisms.

Therefore, development of antimicrobial agents having strong antimicrobial activity against both Gram positive and Gram negative microorganisms, including resistant bacteria, and superior absorptivity in living bodies has been desired.

In view of such a situation, the present inventors have synthesized a number of quinolone derivatives and studied their antimicrobial activity and absorptivity in a living body, and found that quinolone carboxylic acid derivatives of the following formula (1) and their salts exhibited antimicrobial activities against Gram positive microorganisms much stronger than conventional quinolone carboxylic acid derivatives, while maintaining their strong antimicrobial activities against Gram negative microorganisms, as well as excellent absorptivity. Such findings have led to the completion of the present invention.

Disclosure of the Invention

The present invention provides a quinolone carboxylic acid derivative having the following formula (1),



(1)

wherein Z is an oxygen atom, Y is N-R^3, wherein R^3 is a hydrogen atom or a C_1-C_5 alkyl group, R^1 is a hydrogen atom, an alkyl group, an aralkyl group, an ester residual group which can be hydrolyzed in living bodies, R^2 is a hydrogen atom or an amino group which may be substituted by one or two C_1-C_5 alkyl groups and X is a hydrogen atom or a chlorine atom; or a salt thereof;

or wherein Z is two hydrogen atoms, Y is CH_2, SO or SO_2, R^1 is a hydrogen atom, an alkyl group, an

aralkyl group, an ester residual group which can be hydrolyzed in living bodies, R^2 is a hydrogen atom or an amino group which may be substituted by one or two C_1-C_5 alkyl groups, X is a hydrogen atom or a chlorine atom; or a salt thereof.

The present invention also provides an antimicrobial agent comprising a quinolone carboxylic acid derivative of formula (1) or a salt thereof as an effective component.

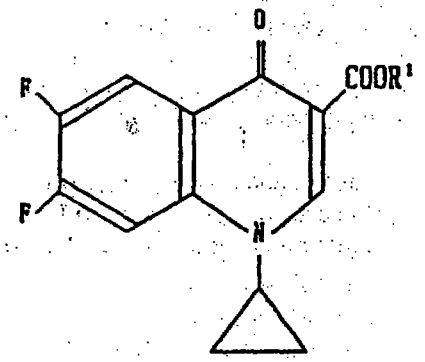
Best Mode for Carrying out the Invention

Given as examples of groups represented by R^1 in formula (1) are, as alkyl groups, linear or branched alkyl groups having 1-12 carbon atoms, e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, t-butyl, n-pentyl, n-hexyl, and the like; as aralkyl groups, benzyl, phenyl ethyl, methyl benzyl, naphtyl methyl, and the like; and as ester residual groups which can be hydrolyzed in living bodies, alkanoyloxyalkyl, alkoxycarbonyloxyalkyl, carbamoylalkyl, alkoxyalkyl, and the like; specifically, acetoxymethyl, 1-acetoxyethyl, ethoxycarbonyloxymethyl, carbamoylmethyl, carbamoylethyl, methoxymethyl, methoxyethyl, and the like. Examples of amino groups which may be substituted by one or two lower alkyl groups, represented by R^2, include amino, methylamino, ethylamino, isopropylamino, dimethylamino, diethylamino, diisopropylamino, and the like. Examples given of halogen atoms represented by X are chlorine, fluorine, bromine, iodine. Lower alkyl groups used in the present invention may be linear or branched alkyl groups having 1-5 carbon atoms, e.g., methyl, ethyl, i-propyl, sec-butyl, t-butyl, amyl, and the like.

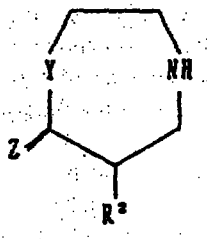
When R^2 in formula (1) is other than hydrogen, the carbon atom to which R^2 is bonded is asymmetrical, so that there are optical isomers; R and S compounds, for compounds (1) of the present invention. The present invention includes both the optical isomers and the racemate.

As examples of the salts of the compounds of formula (1) of the present invention, salts of alkali metal, inorganic acid, organic acid, and the like are given, and more specifically, lithium salts, sodium salts, potassium salts, and the like, as salts of alkali metal; hydrochloride, sulfate, nitrate, hydrobromide, phosphate, and the like, as salts of inorganic acids; and acetate, fumarate, maleate, lactate, citrate, tartarate, malate, oxalate, methanesulfonate, benzenesulfonate, p-toluenesulfonate, and the like, as salts of organic acid.

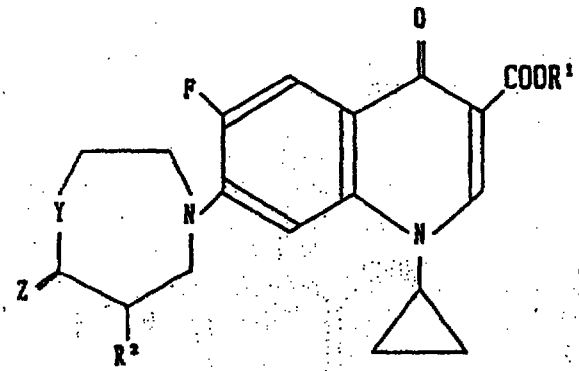
In the preparation of the compound of formula (1) of the present invention [Compounds (1a) and (1b)] Compound (2) and Compound (3), for example, are reacted according to the following reaction scheme to produce Compound (1a), and Compound (1a) is halogenated to produce Compound (1b).



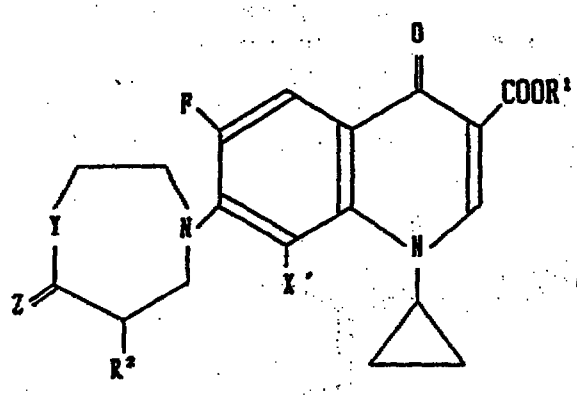
(2)



(3)



(1a)



(1b)

wherein X' is a halogen atom, and R^1, R^2, Y and Z are the same as those previously defined.

The raw material, Compound (2), is a known compound and can be prepared by the method described, for example, in Journal of Medicinal Chemistry, 31, 983 (1989). Compound (3) is also a known compound and can be prepared by the method described, for example, in Journal of American Chemical Society, 106, 630 (1984).

In order to prepare Compound (1a) from Compound (2) and Compound (3), 1 mol of Compound (2) is reacted with 1-5 mols of Compound (3) in a solvent such as acetonitrile, dimethylsulfoxide, or the like at room temperature to 100 °C for 1-7 days. After the reaction, precipitate is collected by filtration and washed with a suitable solvent, e.g., methanol, chloroform, ether, etc., to obtain a crude product. The crude product is purified by silica gel column chromatography or by recrystallization to obtain Compound (1a).

The preparation of Compound (1b) from Compound (1a) can be carried out by a method described, for example, in Japanese Patent Laid-open 90183/1989; that is, 1 mol of Compound (1a) is reacted with 1-10 mols of a halogenizing agent, such as sulfuryl chloride, chlorine, bromine, iodine, N-chlorosuccinic acid imide, N-bromosuccinic acid imide, or the like, in a suitable solvent, such as chloroform, dichloromethane, acetic acid, methanol, ethanol, or the like, at 0-100 °C for 1-48 hours. After the reaction, water is added to collect precipitate by filtration and the precipitate is washed with water to produce a crude product. This crude product is purified by silica gel column chromatography or by the recrystallization to obtain Compound (1b).

If necessary, Compound (1) thus obtained is converted into a salt, such as a salt of alkali metal, inorganic acid, organic acid, or the like, according to a conventional method.

When Compound (1) of this invention thus prepared is used as an antimicrobial agent, it is administered orally at a dose of 200 to 800 mg per day or parenterally at a dose of 5 to 40 mg per day, depending on the weight, the age, the sex, the physical conditions, or the symptom of the patient or the manner of administration.

Compound (1) can be formed into various antimicrobial preparations, such as tablets, granules, powders, capsules, suspensions, injections, suppositories, or the like, according to conventional methods. When solid preparations are produced, compound (1) is mixed with excipients, and as required, with binders, disintegrators, lubricants, coloring agents, sweetening agents, flavoring agents, fillers, coating agents, sugar-coating agents, and the like, and formed into preparations such as tablets, granules, powders, capsules, suppositories, or the like according to known methods. When compound (1) is made into a preparation for injection, it is dissolved, suspended, or emulsified into an aqueous medium such as distilled water, or made into powder which is dissolvable when it is injected. Intravenous, intraarterial, intraportal, intraperitoneal, intramuscular, or subcutaneous injection are applicable.

Examples

The present invention is hereinafter described in more detail by way of examples and test examples, which are not intended to be limiting thereof.

Example 1

1-Cyclopropyl-6-fluoro-7-(2,3,4,5,6,7-hexahydro-1H-1,4-diazepin-5-one-1-yl)-4-oxoquinoline-3-carboxylic acid (Compound No. 1)

0.265 g of 1-cyclopropyl-6,7-difluoro-4-oxoquinoline-3-carboxylic acid and 0.200 g of 2,3,4,5,6,7-hexahydro-1H-1,4-diazepin-5-one dissolved into 20 ml of acetonitrile and refluxed for 3 days. After cooling, the precipitate was collected by filtration, washed with chloroform, methanol, and ether in this order to obtain 0.300 g of colorless crystals of the target compound (yield: 83%).

$$IR\ \nu_{max}^{KBr}\ cm^{-1}:\ 1720,\ 1660,\ 1620$$

^{1}H-NHR δ ppm(NaOD + D_2O): 0.76-1.48(m, 4H), 2.50-3.80(m, 9H), 7.10(d, J = 7.7Hz, 1H), 7.56(d, J = 14.1Hz, 1H), 8.48(s, 1H) m.p.: 300 °C or above

Example 2

8-Chloro-1-cyclopropyl-6-fluoro-7-(2,3,4,5,6,7-hexahydro-1H-1,4-diazepin-5-one-1-yl)-4-oxoquinoline-3-carboxylic acid (Compound No. 2)

0.84 ml of sulfuryl chloride was added dropwise to a suspension of 1.50 g of 1-cyclopropyl-6-fluoro-7-(2,3,4,5,6,7-hexahydro-1H-1,4-diazepin-5-one-1-yl)-4-oxoquinoline-3-carboxylic acid in 30 ml of chloroform, and the mixture was stirred for 12 hours at room temperature. After an addition of ice water, the precipitate was collected by filtration, washed with water, dried in air, and recrystallized in ethanol-chloroform to obtain 0.87 g pale yellow crystals of the target compound (yield: 53.0%).

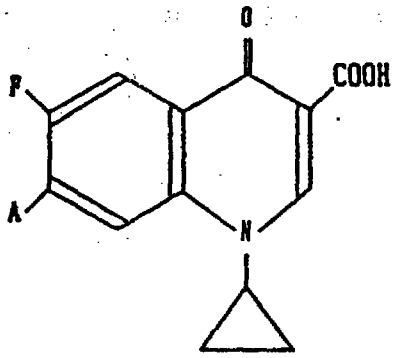
IRν_{max}^{KBr} cm^{-1}: 1720, 1660, 1620

^{1}H-NHR δ ($CD_3OD + CDCl_3$): 0.80-1.50(m, 4H), 2.50-3.00(m, 2H), 3.30-3.64(m, 7H), 7.52(s, 1H), 8.10(d, J = 11.6Hz, 1H), 9.02(s, 1H) m.p.: 282-284 °C (decomposed)

Examples 3-9

Compound Nos. 3-9 listed in Table 1 were prepared in the same manner as in Example 1. Physicochemical data of these compounds are given in Table 2.

Table 1



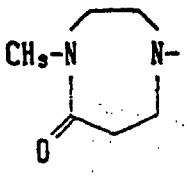
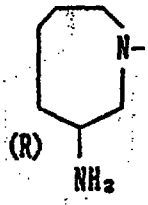
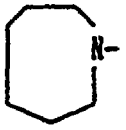
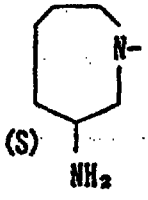
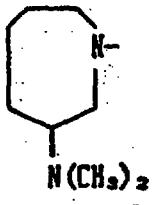
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4		8	
5		9	
6			

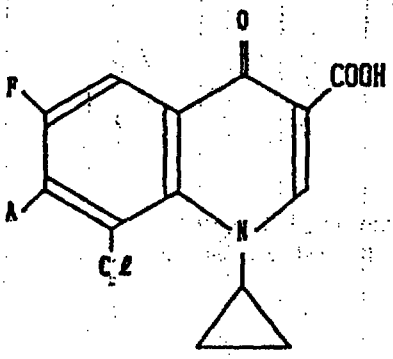
TABLE 2

Compound No.	Melting Point(°C),	Property	IR (KBr, cm^{-1})	^{1}H-NMR (δ ppm)
3	268-271(decomposed)	light yellow powder	1720, 1650, 1625	1.10-1.60(m, 4H), 2.80-3.15(m, 5H), 3.40-3.85(m, 7H), 7.44(d, J=7.7Hz, 1H), 7.98(d, J=14.1Hz, 1H), 8.76(s, 1H). ($CDCl_3$+CD_3OD).
4	205-209	colorless powder	1630	1.00-2.20(m, 10H), 3.00-4.00(m, 6H), 7.28(d, J=9.0Hz, 1H), 7.96(d, J=15.4Hz, 1H), 8.76(s, 1H). ($CDCl_3$+CD_3OD).
5	228-230.5	light yellow powder	1720, 1620	1.10-1.40(m, 4H), 1.40-2.10(m, 8H), 3.05-3.30(m, 1H), 3.30-3.80(m, 4H), 7.18 (d, J=9.0Hz, 1H), 7.90(d, J=15.4Hz, 1H), 8.70(s, 1H). ($CDCl_3$).
6	184-187	light yellow powder	1720, 1625	1.00-1.65(m, 4H), 1.65-2.20(m, 6H), 2.32(s, 6H), 2.68-3.05(m, 1H), 3.10-3.75 (m, 4H), 3.75-4.05(m, 1H), 7.25(d, J=9.6Hz, 1H), 7.90(d, J=15.4Hz, 1H), 8.68 (s, 1H). ($CDCl_3$).
8	215-217	colorless powder	1625	1.00-2.20(m, 10H), 3.00-4.00(m, 6H), 7.28(d, J=7.7Hz, 1H), 7.96(d, J=15.4Hz, 1H), 8.75(s, 1H). ($CDCl_3$+CD_3OD).
9	218-221	colorless powder	1725, 1620	1.00-2.20(m, 10H), 2.60-4.00(m, 6H), 7.25(d, J=7.7Hz, 1H), 7.85(d, J=15.4Hz, 1H), 8.75(s, 1H). ($CDCl_3$+CD_3OD).

Examples 10-16

Reactions were carried out in the same manner as in Example 2 to prepare Compound Nos. 10-16 listed in Table 3. Physicochemical data of these compounds are given in Table 4.

Table 3



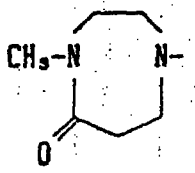
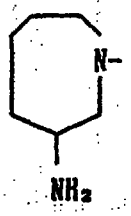
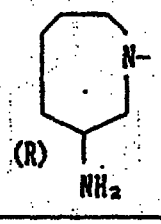
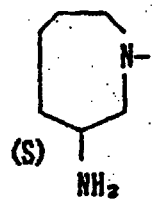
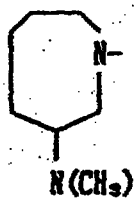
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11		15	
12		16	
13			

TABLE 4

Compound No.	Melting Point(°C),	Property	IR (KBr, cm^{-1})	^{1}H-NMR (δ ppm)
10	136-140	light yellow powder	1720, 1640, 1610	0.80-1.50(m, 4H), 2.80-3.00(m, 2H), 3.08(s, 3H), 3.30-3.80(m, 6H), 4.20-4.50 (m, 1H), 8.15(d, J=11.6Hz, 1H), 9.00(s, 1H). ($CDCl_3$).
11	275-278(decomposed)	colorless powder	1610-1640	0.55-2.30(m, 4H), 1.40-1.95(m, 6H), 2.75-3.45(m, 5H), 4.00-4.30(m, 1H), 7.90 d, J=11.6Hz, 1H), 8.75(s, 1H). (NaOD+D_2O).
12	163-165	light yellow powder	1720, 1620	0.80-1.50(m, 4H), 1.55-2.00(m, 8H), 3.20-3.70(m, 4H), 4.24-4.55(m, 1H), 8.05 (d, J=11.6Hz, 1H), 8.96(s, 1H). ($CDCl_3$).
13	210-215(decomposed)	light yellow powder	1720, 1610	1.00-1.45(m, 4H), 1.60-2.20(m, 6H), 2.60-2.80(m, 6H), 3.00-3.60(m, 4H), 3.80 -4.00(m, 1H), 4.15-4.30(m, 1H), 8.15(d, J=7.7Hz, 1H), 8.98(s, 1H). ($CDCl_3$).
15	255-257(decomposed)	colorless powder	1600-1640	0.50-1.30(m, 4H), 1.40-2.00(m, 6H), 2.75-3.50(m, 5H), 4.00-4.30(m, 1H), 7.90 (d, J=11.6Hz, 1H), 8.65(s, 1H). (NaOD+D_2O).
16	241-244(decomposed)	colorless powder	1600-1640	0.50-1.30(m, 4H), 1.40-2.00(m, 6H), 2.80-3.50(m, 5H), 4.10-4.40(m, 1H), 7.90 (d, J=11.6Hz, 1H), 8.65(s, 1H). (NaOD+D_2O).

Test Example 1

Antimicrobial Activity

Antimicrobial activities against bacteria listed in Tables 5-7 were measured according to the MIC measurement method of The Japan Chemotherapeutic Association. Ofloxacin was used as a control. The results are shown in Tables 5-7.

Medium: Mueller Hinton Medium

Sample dilution: A 1,000 μg/ml solution in 25% dimethylsulfoxide was prepared. A series of solutions with various concentrations (100 μg/ml to 0.006 μg/ml) were prepared by successively diluting the solution with sterilized water by a factor of 1/2.

Amount of inoculated bacteria: 10^6/ml

Cultivation conditions: 37 °C, 48 hours

Determination: after 24 hours

TABLE 5

Tested Bacteria	MIC (μg/ml)		
	Compound Number 2	Compound Number 15	Ofloxacin
Gram-positive bacteria 1. Bacillus subtilis ATCC 6633	0.024	0.024	0.098
2. Staphylococcus aureus FDA 209P	0.012	0.012	0.195
3. Staphylococcus aureus Terajima	0.098	0.195	0.78
4. Staphylococcus aureus Smith	0.012	0.024	0.39
5. Staphylococcus epidermidis ATCC 12228	0.049	0.049	0.78
6. Sarcina lutea ATCC 9341	0.195	0.098	3.12
7. Streptococcus faecalis IFO 12964	0.195	0.195	1.56
8. Micrococcus lysodeikticus IFO 3333	0.049	0.195	1.56

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TABLE 6

Tested Bacteria	MIC (μg/ml)		
	Compound Number 2	Compound Number 15	Ofloxacin
Gram-negative bacteria			
9. Escherichia coli 0-1	0.195	0.098	0.098
10. Escherichia coli K-12	0.39	0.098	0.098
11. Salmonella typhi TD	0.098	0.049	0.024
12. Shigella flexneri 2b	0.003	0.006	0.012
13. Pseudomonas aeruginosa IFO 13736	6.25	1.56	1.56
14. Pseudomonas aeruginosa P2	12.5	1.56	0.78
15. Pseudomonas aeruginosa IFO 12582	6.25	0.78	3.12
16. Klebsiella pneumoniae ATCC 10031	0.012	0.012	0.024
17. Klebsiella pneumoniae IFO 13541	0.098	0.049	0.024
18. Proteus vulgaris OXK	0.024	0.049	0.049
19. Proteus rettgeri	0.78	0.195	0.098
20. Serratia marcescens NHL	0.78	0.195	0.049

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TABLE 7

Tested Bacteria	MIC (μg/ml)		
	Compound Number 2	Compound Number 15	Ofloxacin
Gram-positive bacteria			
21. M.R.Staphylococcus aureus 395	0.049	0.049	0.39
22. M.R.Staphylococcus aureus 415	0.024	0.024	0.39
23. M.R.Staphylococcus aureus 419	0.024	0.024	0.39
24. M.R.Staphylococcus aureus 420	0.024	0.049	0.39
25. M.R.Staphylococcus aureus 421	0.024	0.049	0.39

(The abreviation M.R. stands for methicillin-resistant)

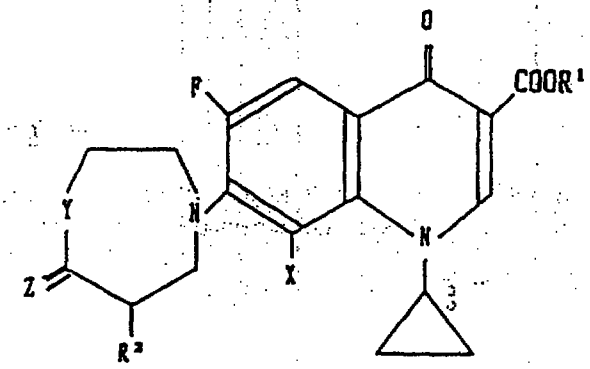
Industrial Applicability

The compound (1) and its salt of this invention exhibit a superior antimicrobial activity, especially against Gram positive microorganisms, and are thus useful for the treatments and prevention of various infectious diseases in clinics.

Claims

Claims for the following Contracting States : AT, BE, CH, LI, DE, DK, FR, GB, IT, LU, NL, SE

1. A quinolone carboxylic acid derivative having the formula (I),



(I)

wherein Z is an oxygen atom, Y is N-R^3, wherein R^3 is a hydrogen atom or a C_1-C_5 alkyl group, R^1 is a hydrogen atom, an alkyl group, an aralkyl group, an ester residual group which can be hydrolyzed in living bodies, R^2 is a hydrogen atom or an amino group which may be substituted by one or two C_1-C_5 alkyl groups and X is a hydrogen atom or a chlorine atom; or a salt thereof;

or wherein Z is two hydrogen atoms, Y is CH_2, SO or SO_2, R^1 is a hydrogen atom, an alkyl group, an aralkyl group, an ester residual group which can be hydrolyzed in living bodies, R^2 is a hydrogen atom or an amino group which may be substituted by one or two C_1-C_5 alkyl groups, X is a hydrogen atom or a chlorine atom; or a salt thereof.

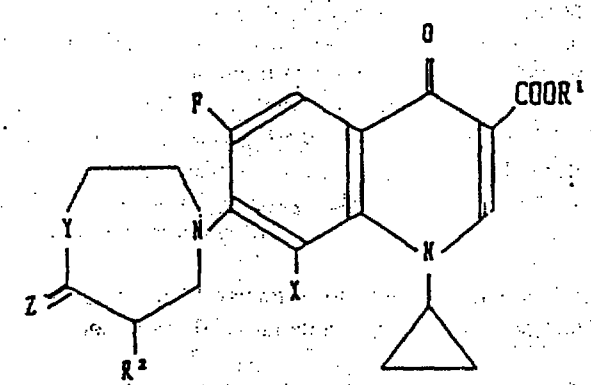
2. The quinolone carboxylic acid derivative of Claim 1, wherein Z is two hydrogen atoms, Y is CH_2, SO or SO_2, R^1 is a hydrogen atom, R^2 is an amino group, and X is a hydrogen atom or a chlorine atom.

3. The quinolone carboxylic acid derivative of Claim 1, wherein Z is an oxygen atom, Y is N-R^3, wherein R^3 is a hydrogen atom or a C_1-C_5 alkyl group, R^1 is a hydrogen atom, R^2 is a hydrogen atom, and X is a hydrogen atom or a chlorine atom; or a salt thereof.

4. An antimicrobial agent comprising the quinolone carboxylic acid derivative or a salt thereof defined Claim 1 as an effective component.

Claims for the following Contracting States : ES, GR

1. A process for preparing a quinolone carboxylic acid derivative having the formula (I),



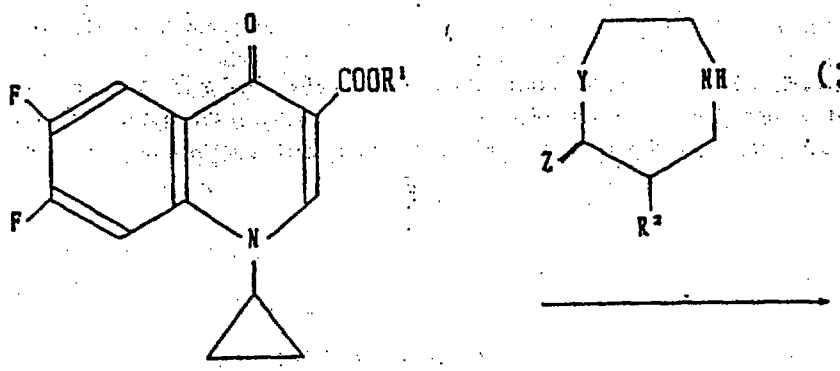
(I)

wherein Z is an oxygen atom, Y is N-R^3, wherein R^3 is a hydrogen atom or a C_1-C_5 alkyl group, R^1 is a hydrogen atom, an alkyl group, an aralkyl group, an ester residual group which can be hydrolyzed in living bodies, R^2 is a hydrogen atom or an amino group which may be substituted by one or two C_1-C_5

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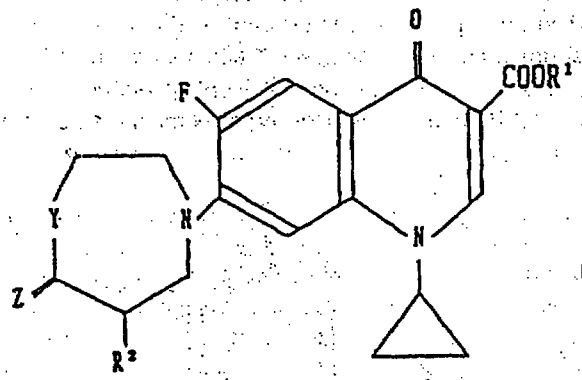
alkyl groups and X is a hydrogen atom or a chlorine atom; or a salt thereof;

or wherein Z is two hydrogen atoms, Y is CH_2, SO or SO_2, R^1 is a hydrogen atom, an alkyl group, an aralkyl group, an ester residual group which can be hydrolyzed in living bodies, R^2 is a hydrogen atom or an amino group which may be substituted by one or two C_1-C_5 alkyl groups, X is a hydrogen atom or a chlorine atom; or a salt thereof, said process comprising a reaction of a Compound (2) with a Compound (3) according to the following reaction scheme to produce Compound (1a) and optionally Compound (1a) is halogenated to produce Compound (1b):

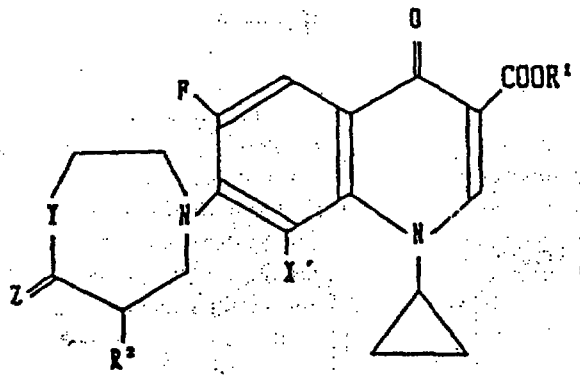


(2)

(3)



(1a)



(1b)

wherein X' is a halogen atom, and R^1, R^2, Y and Z are as defined above by reacting one mol of Compound (2) with 1-5 mols of Compound (3) in a solvent at room temperature to 100 °C for 1-7 days to prepare Compound (1a) and optionally 1 mol of Compound (1a) is reacted with 1-10 mols of a

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halogenizing agent in a solvent at 0-100 °C for 1-48 hours to obtain Compound (1b).

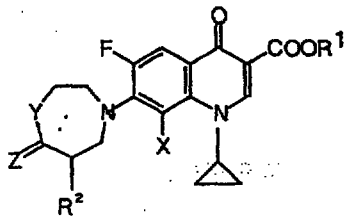
2. The process according to Claim 1, wherein Z is two hydrogen atoms, Y is CH_2, SO or SO_2, R^1 is a hydrogen atom, R^2 is an amino group, and X is a hydrogen atom or a chlorine atom.

3. The process according to Claim 1, wherein Z is an oxygen atom, Y is N-R^3, wherein R^3 is a hydrogen atom or a C_1-C_5 alkyl group, R^1 is a hydrogen atom, R2 is a hydrogen atom, and X is a hydrogen atom or a chlorine atom; or a salt thereof.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, LI, DE, DK, FR, GB, IT, LU, NL, SE

1. Chinoloncarbonsäurederivat der Formel (I)



(I)

worin Z ein Sauerstoffatom, Y N-R^3 ist, worin R^3 ein Wasserstoffatom oder eine C_1-C_5-Alkylgruppe ist, R^1 ein Wasserstoffatom, eine Alkylgruppe, eine Aralkylgruppe, eine Esterrest-Gruppe ist, die in lebenden Körpern hydrolysiert werden kann, R^2 ein Wasserstoffatom oder eine Aminogruppe ist, die durch ein oder zwei C_1-C_5-Alkylgruppen substituiert sein kann und X ein Wasserstoffatom oder ein Chloratom ist, oder ein Salz davon,
oder worin Z zwei Wasserstoffatome sind, Y CH_2, SO oder SO_2 ist, R^1 ein Wasserstoffatom, eine Alkylgruppe, eine Aralkylgruppe, eine Esterrest-Gruppe ist, die in lebenden Körpern hydrolysiert werden kann, R^2 in Wasserstoffatom oder eine Aminogruppe ist, die durch ein oder zwei C_1-C_5-Alkylgruppen substituiert sein kann und X ein Wasserstoffatom oder ein Chloratom ist, oder ein Salz davon.

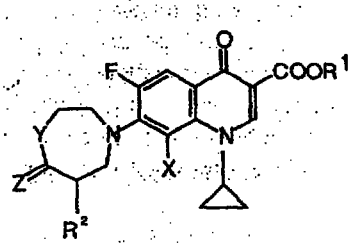
2. Chinoloncarbonsäurederivat nach Anspruch 1, worin Z zwei Wasserstoffatome sind, Y CH_2, SO oder SO_2 ist, R^1 ein Wasserstoffatom, R^2 eine Aminogruppe ist und X ein Wasserstoff- oder ein Chloratom ist.

3. Chinoloncarbonsäurederivat nach Anspruch 1, worin Z ein Sauerstoffatom, Y N-R^3 ist, worin R^3 ein Wasserstoffatom oder eine C_1-C_5-Alkylgruppe ist, R^1 ein Wasserstoffatom, R^2 ein Wasserstoffatom ist und X ein Wasserstoff- oder ein Chloratom ist, oder ein Salz davon.

4. Antimikrobielles Mittel, umfassend das Chinoloncarbonsäurederivat oder ein Salz davon, wie in Anspruch 1 definiert, als eine wirksame Komponente.

Patentansprüche für folgende Vertragsstaaten : ES, GR

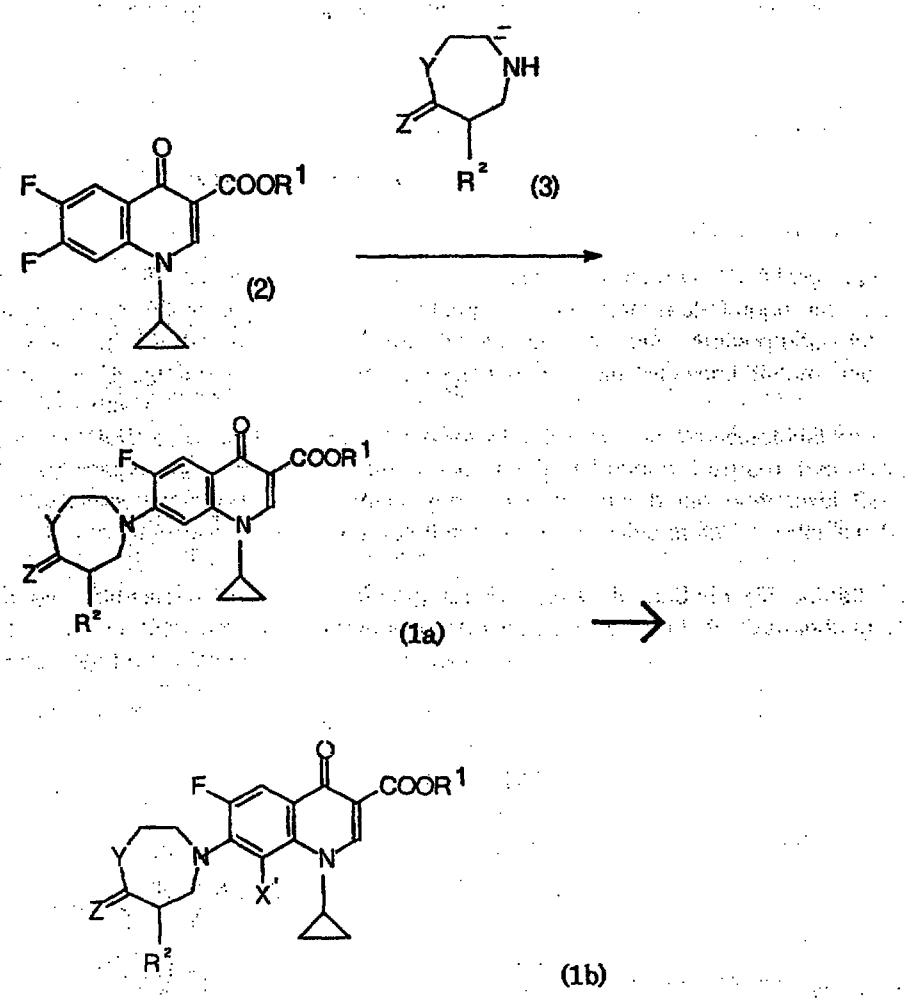
1. Verfahren zum Herstellen eines Chinoloncarbonsäurederivates der Formel (I)



(I)

* C L M S *

worin Z ein Sauerstoffatom, Y N-R^3 ist, worin R^3 ein Wasserstoffatom oder eine C_1-C_5-Alkylgruppe ist, R^1 ein Wasserstoffatom, eine Alkylgruppe, eine Aralkylgruppe, eine Esterrest-Gruppe ist, die in lebenden Körpern hydrolysiert werden kann, R^2 in Wasserstoffatom oder eine Aminogruppe ist, die durch ein oder zwei C_1-C_5-Alkylgruppen substituiert sein kann und X ein Wasserstoffatom oder ein Chloratom ist, oder ein Salz davon,
oder worin Z zwei Wasserstoffatome sind, Y CH_2, SO oder SO_2 ist, R^1 ein Wasserstoffatom, eine Alkylgruppe, eine Aralkylgruppe, eine Esterrest-Gruppe ist, die in lebenden Körpern hydrolysiert werden kann, R^2 in Wasserstoffatom oder eine Aminogruppe ist, die durch ein oder zwei C_1-C_5-Alkylgruppen substituiert sein kann und X ein Wasserstoffatom oder ein Chloratom ist, oder ein Salz davon,
wobei das Verfahren eine Umsetzung einer Verbindung (2) mit einer Verbindung (3) gemäß dem folgenden Reaktionsschema umfaßt, um eine Verbindung (1a) herzustellen und die Verbindung (1a) gegebenenfalls zur Herstellung einer Verbindung (1b) halogeniert wird,



worin X' ein Halogenatom ist, R^1, R^2, Y und Z die obige Bedeutung haben, durch Umsetzen von 1 Mol der Verbindung (2) mit 1 bis 5 Molen der Verbindung (3) in einem Lösungsmittel bei Raumtemperatur bis 100 °C für 1 bis 7 Tage, um Verbindung (1a) herzustellen und gegebenenfalls 1 Mol der Verbindung (1a) mit 1 bis 10 Molen eines Halogenierungsmittels in einem Lösungsmittel bei 0 bis 100 °C für 1 bis 48 Stunden umgesetzt wird, um Verbindung (1b) zu erhalten.

2. Verfahren nach Anspruch 1, worin Z zwei Wasserstoffatome sind, Y CH_2, SO oder SO_2 ist, R^1 ein Wasserstoffatom, R^2 eine Aminogruppe ist und X ein Wasserstoff- oder ein Chloratom ist.

3. Verfahren nach Anspruch 1, worin Z ein Sauerstoffatom, Y N-R^3 ist, worin R^3 ein Wasserstoffatom oder eine C_1-C_5-Alkylgruppe ist, R^1 ein Wasserstoffatom, R^2 ein Wasserstoffatom ist und X ein Wasserstoff-

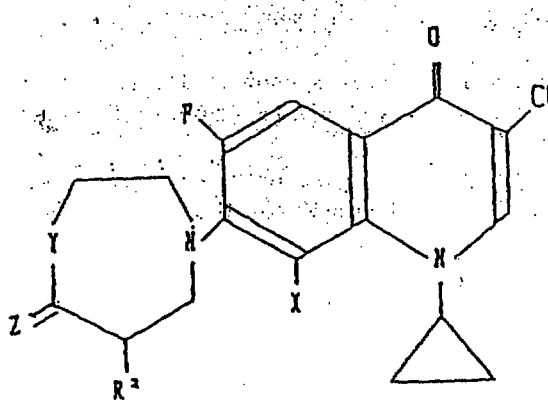
* C L M S *

oder ein Chloratom ist, oder ein Salz davon.

Revendications

Revendications pour les Etats contractants suivants : AT, BE, CH, LI, DE, DK, FR, GB, IT, LU, NL, SE

1. Dérivé de l'acide quinolone carboxylique de formule (I),



(I)

dans laquelle Z est un atome d'oxygène, Y est N-R^3 où R^3 est un atome d'hydrogène ou un groupe alkyle en C_1 à C_5, R^1 est un atome d'hydrogène, un groupe alkyle, un groupe aralkyle, un groupe résiduel d'ester, pouvant être hydrolysé dans les organismes vivants, R^2 est un atome d'hydrogène ou un groupe amino pouvant être substitué par un ou deux groupes alkyle en, C_1 à C_5, et X est un atome d'hydrogène ou un atome de chlore ; ou un sel de celui-ci ;

ou dans laquelle Z représente deux atomes d'hydrogène, Y est CH_2, SO ou SO_2, R^1 est un atome d'hydrogène, un groupe alkyle, un groupe aralkyle, un groupe résiduel d'ester, pouvant être hydrolysé dans les organismes vivants, R^2 est un atome d'hydrogène ou un groupe amino pouvant être substitué par un ou deux groupes alkyle en C_1 à C_5, X est un atome d'hydrogène ou un atome de chlore ; ou un sel de celui-ci.

2. Dérivé de l'acide quinolone carboxylique selon la revendication 1, dans lequel Z représente deux atomes d'hydrogène, Y est CH_2, SO ou SO_2, R^1 est un atome d'hydrogène, R^2 est un groupe amino et X est un atome d'hydrogène ou un atome de chlore.

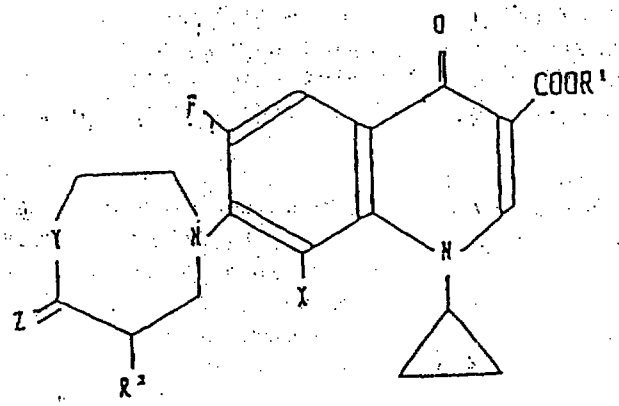
3. Dérivé de l'acide quinolone carboxylique selon la revendication 1, dans lequel Z est un atome d'oxygène, Y est N-R^3, où R^3 est un atome d'hydrogène ou un groupe alkyle en C_1 à C_5, R^1 est un atome d'hydrogène, R^2 est un atome d'hydrogène et X est un atome d'hydrogène ou un atome de chlore ; ou un sel de celui-ci.

4. Agent antimicrobien comprenant comme principe actif le dérivé d'acide quinolone carboxylique ou un sel de celui-ci selon la revendication 1.

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Revendications pour les Etats contractant suivants : ES, GR

1. Procédé pour préparer un dérivé de l'acide quinolone carboxylique de formule (I)



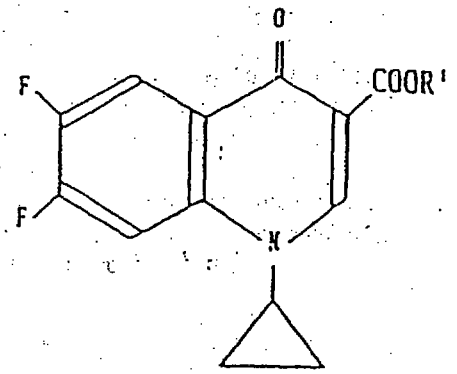
(I)

dans laquelle Z est un atome d'oxygène, Y est N-R^3 où R^3 est un atome d'hydrogène ou un groupe alkyle en C_1 à C_5, R^1 est un atome d'hydrogène, un groupe alkyle, un groupe aralkyle, un groupe résiduel d'ester, pouvant être hydrolysé dans les organismes vivants, R^2 est un atome d'hydrogène ou un groupe amino pouvant être substitué par un ou deux groupes alkyle en C_1 à C_5, et X est un atome d'hydrogène ou un atome de chlore ; ou un sel de celui-ci ;

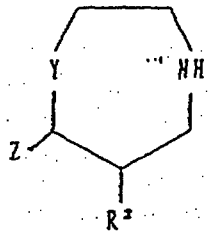
ou dans laquelle Z représente deux atomes d'hydrogène, Y est CH_2, SO ou SO_2, R^1 est un atome d'hydrogène, un groupe alkyle, un groupe aralkyle, un groupe résiduel d'ester, pouvant être hydrolysé dans les organismes vivants, R^2 est un atome d'hydrogène ou un groupe amino pouvant être substitué par un ou deux groupes alkyle en C_1 à C_5, X est un atome d'hydrogène ou un atome de chlore ; ou un sel de celui-ci,

ce procédé comprenant une réaction d'un composé (2) avec un composé (3) selon le schéma réactionnel ci-après pour donner le composé (1a), et éventuellement une halogénation du composé (1a) pour produire le composé (1b):

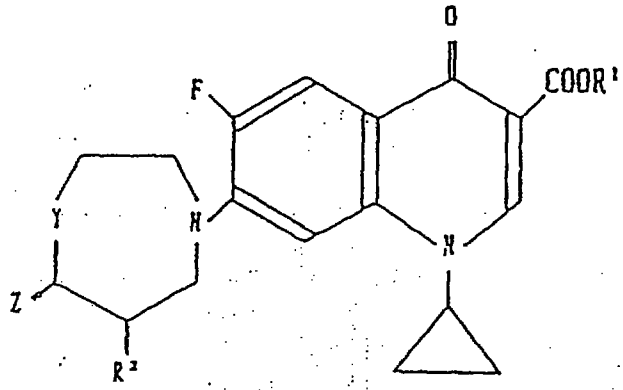
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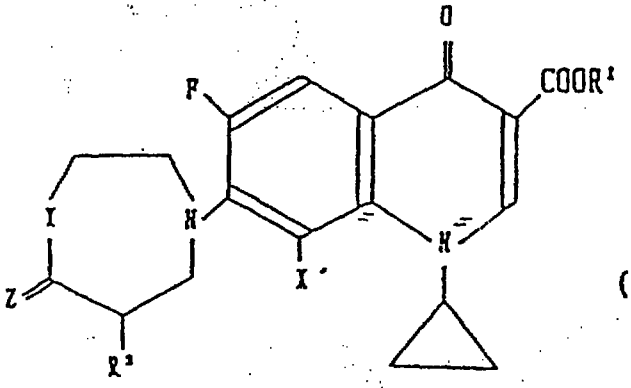
(2)



(3)



(1a)



(1b)

où X' est un atome d'halogène, et R^1, R^2, Y et Z sont tels que définis ci-dessus, par la réaction d'une mole du composé (2) avec 1 à 5 moles du composé (3) dans un solvant, à une température comprise dans la plage allant de la température ambiante à 100 °C, pendant 1 à 7 jours pour préparer le composé (1a), et on fait éventuellement réagir 1 mole du composé (1a) avec 1 à 10 moles d'un agent d'halogénation dans un solvant à une température de 0 à 100 °C pendant 1 à 48 heures pour obtenir le composé (1b).

2. procédé selon la revendication 1, dans lequel Z représente deux atomes d'hydrogène, Y est CH_2, SO ou SO_2, R^1 est un atome d'hydrogène, R^2 est un groupe amino et X est un atome d'hydrogène ou un atome de chlore.

3. Procédé selon la revendication 1, dans lequel Z est un atome d'oxygène Y est N-R^3, où R^3 est un atome d'hydrogène ou un groupe alkyle en C_1 à C_5, R^1 est un atome d'hydrogène, R^2 est un atome d'hydrogène et X est un atome d'hydrogène ou un atome de chlore ; ou l'un de ses sels.

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