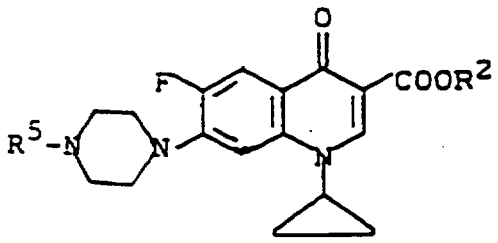
The present invention relates to formulations which contain quinolonecarboxylic acids and derivatives thereof, for use in the drinking water against mycoplasmas and bacterial diseases in poultry.

It has already been disclosed that quinolonecarboxylic acids and their derivatives have bactericidal properties (DE-OS (German Published Specification) 3,033,157). However, nothing has been disclosed about their wide and universal applicability for livestock or about formulations which are especially suitable for applicability for livestock.

Veterinary medicine encounters particular problems in treating infections which are caused by Escherichia coli, salmonellae or mycoplasmas, particularly when these pathogens have now become resistant to known agents.

The present invention relates to formulations which contain quinolonecarboxylic acids and derivatives thereof of the formula



(I)

in which

R^2 represents hydrogen, alkyl with 1 to 4 carbon atoms

R^5 represents hydrogen, methyl or ethyl, as well as the pharmaceutically utilizable salts thereof, which can be administered in the drinking water against mycoplasmoses and bacterial diseases in poultry.

The following quinolonecarboxylic acids and derivatives thereof may be especially mentioned as active compounds:

1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl or 4-methyl- or 4-ethyl-1-piperazinyl-)-quinoline-3-carboxylic acid, and the methyl and ethyl esters of this compound.

Pharmaceutically utilizable salts which may be mentioned are salts with acids and bases which form physiologically tolerated salts. The salts are known or can be prepared in analogy to known processes.

Acids which may be mentioned are: hydrochloric acid, sulphuric acid, phosphoric acid, organic acids such as formic acid, acetic acid, lactic acid, malic acid, fumaric acid, citric acid, ascorbic acid, succinic acid, tartaric acid, malonic acid, maleic acid and embonic acid.

Hydrochloric acid, acetic acid, lactic acid and embonic acid may be mentioned as preferred.

Embonic acid may be mentioned as particularly preferred.

Bases which may be mentioned are inorganic bases such as NaOH, KOH, $Ca(OH)_2$, ammonia, and organic bases such as amines, such as mono-, di- and trialkylamines, substituted amines such as ethanolamine, cyclic amines such as morpholine and piperazine, basic amino acids such as arginine, lysine, choline and N-methylglucamine.

The following bases are preferred: NaOH, KOH, ethanolamine, lysine and N-methylglucamine.

The following bases are particularly preferred: NaOH and KOH.

The active compounds are known or can be prepared in analogy to known processes.

The active compounds are used in the form of formulations which are administered in the drinking water.

Concentrates for oral administration after dilution are prepared by dissolution of the active compound in a suitable solvent and possibly addition of additives such as solubilizers, acids, bases, buffer salts, antioxidants and preservatives,

Solvents which may be mentioned are: physiologically tolerated solvents such as water, alcohols such as ethanol, butanol, benzyl alcohols, glycerol, propylene glycol, polyethylene glycols, N-methyl-pyrrolidone, and mixtures thereof.

Solubilizers which may be mentioned are: solvents which promote the dissolution of the active compound in the main solvent or prevent its precipitation. Examples are polyvinylpyrrolidone, polyoxyethylated castor oil and polyoxyethylated sorbitan esters.

Preservatives are: benzyl alcohol, trichlorobutanol, p-hydroxybenzoic esters and n-butanol.

Concentrates for administration in the drinking water must be formulated so that a clear solution or a stable homogeneous suspension is produced on mixing with the drinking water.

Thus, suitable vehicles are substances which are soluble in water (feed additives) such as sugars or salts (for example citrates, phosphates, sodium chloride and Na carbonate).

They may likewise contain antioxidants and preservatives.

The active compounds can be present in the formulations alone or mixed with other active compounds, mineral salts, trace elements, vitamins, proteins, pigments, fats or flavourings.

The active compounds are active against microorganisms pathogenic to livestock.

The microorganisms pathogenic to livestock include:

1. Spirochaetaceae
2. Micrococcaceae (for example Staphylococci)
3. Streptococcaceae (for example Streptococci of Lancefield types A-N)
4. Pseudomonaceaea (for example Ps. aeruginosa), Bordetella such as Bordetella bronchiseptica.
5. Enterobacteriaceae (for example Salmonella, E. coli, Klebsiella, Proteus, Citrobacter, Edwardsiella, Haemophilus, Providencia and Yersina)

6. Vibrionaceae (for example Vibrio such as Vibrio cholerae, Pasteurella such as Pasteurella multocida, Aeromonas, Actinobacillus and Streptobacillus)
7. Bacetroidaceae (for example Bacteroides and Fusobacterium)
8. Lactobacillaceae (Erysiphylothrix, Listeria such as Listeria monocytogenes)
9. Bacillaceae (for example Clostridium types A-D, such as Clostridium perfringens)
and anaerobic Cocci such as, for example, Peptostreptococci and Peptococci
10. Coryneform bacteria (for example Corynebacterium pyogenes)
11. Mycobacteriaceae (for example Mycobacterium avium and M. tuberculosis)
12. Nocardiaceaea (for example Norcardia asteroides)
13. Chlamydiaceae (for example Chlamydia psittaci)
14. Mycoplasmataceae (for example M. gallisepticum).

Microorganisms pathogenic for livestock can cause, as single or mixed infections, manifestations of disease in the following organ systems of the livestock:

Lung and trachial space, digestive system, genital system, soft tissues, active and passive locomotor system, urogenital system, nervous system, auditory apparatus and eyes.

As already mentioned, the active compounds are used to combat bacterial diseases in poultry.

The bacterial diseases include, for example in poultry (chickens, turkeys, guineafowl, quail, pigeons, ornamental birds etc.) mycoplasmosis, E. coli infection, chronic respiratory disease, salmonellosis, contagious avian influenza, pasteurellosis, Campylobacter infection, and psittacosis-ornithosis; and infections or mixed infections with, for example, Escherichia coli, Salmonella spp., Klebsielle spp., Proteus spp., Haemophilus spp., Pasteurella spp., Actinobacillus spp., Pseudomonas spp., Brucella spp., ordetella spp., Moraxella spp., Campylobacter spp., Staphylococcus spp., Streptococcus spp., Listeria spp., Erysipelothrix spp., Cornynebacterium

spp., Fusobacterium spp., Borellia spp., Treponema spp., Leptospira spp., Clostridium spp., Mycoplasma spp., Nocardia spp., Rickettsia spp., Mycobacterium spp., and Yersinia spp.

Poultry diseases, especially caused by E. coli, Mycoplasmas, Salmonellae, Pasteurellae and Campylobacters are treated by oral therapy in the drinking water, 10 to 500 mg/l, preferably 2.5 to 100 mg/l, for 1 to 20, preferably 3 to 10, days, where appropriate repeated (prophylaxis programme).

Formulations which contain the abovementioned active compounds are particularly suitable for the treatment of infections caused by E. coli, Salmonellae and/or Mycoplasmas. They are particularly suitable for use against those pathogens of infectious diseases which have become resistant to agents currently known.

Particular mention may be made of the suitability of formulations which contain the abovementioned active compounds for the treatment of salmonelloses and Mycoplasma infections in poultry, especially in chickens and broilers.

Particular attention is drawn to the simple and beneficial treatment of salmonelloses and mycoplasmoses of poultry, especially of chickens, via the drinking water. The active compounds are dissolved in the drinking water either in the form of salts thereof with water-soluble acids or in the form of salts thereof with water-soluble bases.

For the salt formation, the bases or acids are added to the active compounds preferably in above equimolar amounts so that the aqueous solution ready for use has a basic or acidic reaction.

The solutions ready for use preferably contain 10 - 50 ppm, preferably 25 - 100 ppm, very particularly preferably 50 - 100 ppm of active compound.

The pH of the acidic solution ready for use is between 2 and 5, preferably between 3 and 5.

The pH of the basic solution ready for use is between 8 and 11, preferably between 9 and 10.

Examples

The active compounds used in the following examples are 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7(4-ethyl-1-piperazinyl-)quinoline-3-carboxylic acid (I) and 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperaziyl)quinoline-3-carboxylic acid (II).

A. General procedure for the preparation of concentrates with a basic reaction for use in the drinking water:

The active compound and the auxiliaries are suspended in the major amount of the water. The alkali is cautiously added, while stirring, until the active compound has dissolved. Stirring is continued until a clear, low-viscosity gel without lumps has been produced.

Example 1

Active compound I	2.500 g
Benzyl alcohol	1.400 g
Methyl-hydroxypropyl-cellulose	3.500 g
Potassium hydroxide to pH 11 about	0.004 g
Demineralized water	95.996 g
	100 ml ≙ 100.900 g

Example 2

Active compound II	2.00 g
Polyacrylic acid Na salt	0.62 g
1 N sodium hydroxide solution	12.00 g
Benzyl alcohol	1.00 g
Dimineralized water	85.08 g
	100 ml ≙ 100.70 g

Example 3

Active compound I	20.00 g
Benzyl alcohol	1.00 g
10% potassium hydroxide solution	30.56 g
Demineralized water	55.94 g
	100 ml ≙ 107.50 g

B. General procedure for the preparation of concentrates with an acidic reaction for use in the drinking water:

Example 4

Active compound I	10.0 kg
Acetic acid	2.5 kg
Benzyl alcohol	1.0 kg
Demineralized water	89.7 kg
	100 l ≙ 103.2 kg

Water is initially introduced into a vessel, and the other substances are added, with stirring.

Example 5

Active compound II	5.0 kg
20% lactic acid	10.0 kg
Demineralized water	ad 100 l

Preparation is carried out as in Example 4.

The examples of use which follow show the outstanding suitability of the abovementioned active compounds for the treatment of diseases of poultry via the drinking water.

Example A

Treatment of mycoplasmoses in poultry

Groups of 40 chicks which were free of Mycoplasma gallisepticum and Mycoplasma synoviae were infected on the second day of life with a pathogenic wild strain of Mycoplasma gallisepticum. The treatment started 24 hours after the infection. One group of 40 chicks was not treated, as a control. Treatment was via the drinking water on 5 consecutive days after the infection. 19 days after the infection the birds were sacrificed, weighed and examined. The results of this were as follows:

Table 1

Drinking water treatment with	Average weight of the birds after 0	14	19	Clinical symptoms
Compound I 250 ppm	47.3	355.7	463.8	None
Comparison substance tylosin 500 ppm	48.4	311.9	426.3	Marked, no dead birds
Untreated	48.2	269.6	347.4	Marked, 18 dead birds

It was not possible to isolate Mycoplasmas from any of the treated birds after sacrifice.

Example B

Mycoplasmas/inhibitory concentration test

Serial concentrations of the active compounds in 0.01 N sodium carbonate solution were prepared. The concentrations were from 256 µg/ml at 0.0156 µg/ml.

0.5 ml of an active compound solution was placed in each well of the microtitre plate. To this was added 0.5 ml of an inoculum of Mycoplasmas containing about 10^6 organisms per ml.

The inoculum consisted of a modified Mycoplasma broth (PPLO) which contained about 20% horse serum and in which Mycoplasmas were used up to a titre of about 10^7 organisms per ml (determined by the MacCrady method).

The microtitre plate was then incubated at 37°C, and the growth was determined in each case after 48, 72 and 96 hours. The MIC value has been reported as the active compound concentration which prevented growth of the inoculated Mycoplasmas.

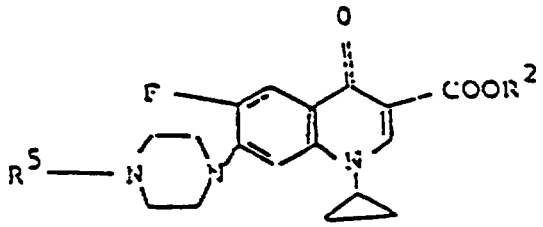
Table II

Mycoplasmas/inhibitory concentration

Active compound	MIC values for Mycoplasma strains Nos.					
	348	7981	6442	4587	81115	8008
Compound I	0.5	0.5	0.15	0.5	0.5	0.25
Comparison:						
Nalidixic acid	128	128	128	128	128	128
Flumequine	256	256	256	256	256	256

Patent claim

1. Use of quinolonecarboxylic acids and derivatives thereof of the formula I



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R^2 represents hydrogen or alkyl with 1 to 4 carbon atoms,

R^5 represents hydrogen, methyl or ethyl, as well as the pharmaceutically utilizable salts thereof, for the preparation of agents, which can be administered in the drinking water, against mycoplasmoses and bacterial diseases in poultry.

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