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(54) Title: USE OF QUINOLONE DERIVATIVES FOR THE TREATMENT OF MYCOPLASMAL PNEUMONIA IN PIGS

(57) Abstract

A method of treating mycoplasmal pneumonia in pigs comprising administration of an antimycoplasmally effective amount of a quinolone derivative of formula (I) or a pharmaceutically acceptable salt or ester thereof; wherein Y is an optionally substituted aromatic six membered ring containing up to two nitrogen atoms; R₁ is C₁₋₄ alkyl optionally substituted by halogen, hydroxy or aryl; C₃₋₆ cycloalkyl; allyl or vinyl; or R₁ together with a substituent on the ring Y located at the position adjacent to the bridgehead from an optionally substituted six membered ring containing 0, 1 or 2 additional heteroatoms selected from oxygen, nitrogen and sulphur; R₂ is hydrogen or R₂ together with R₁ forms an optionally substituted thiazolidinyl ring. The use of compounds of formula (I) or a pharmaceutically acceptable salt or ester thereof in the manufacture of a medicament for the treatment or prophylaxis of mycoplasmal pneumonia in pigs is also included.
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USE OF QUINOLONE DERIVATIVES FOR THE TREATMENT OF MYCOPLASMAL PNEUMONIA IN PIGS

The present invention relates to a method of treating mycoplasmal pneumonia in pigs and to compounds for use in that method.

A number of specific quinolone antibacterial agents have been found to have activity against human mycoplasma, for example M. pneumoniae (see Japanese patent application No. J.59116217A).

Mycoplasmal infections in animals are widespread and have been found to be very difficult to treat. For example, enzootic pneumonia in pigs is probably the most widespread and economically important pig disease in any swine-producing country in the world. (Switzer W.P. and Ross R.F. (1975) 'Diseases of Swine' 4th Ed. p 749-58.) Mycoplasma hyopneumoniae is now well established as the principal causative agent of this disease. (Whittlestone P. (1973) Advances in Veterinary Science and Comparative Medicine 17, 1-55 and Switzer W.P. and Ross R.F. (1975) as above).

The applicants have found that many quinolone derivatives have surprisingly high activities against strains of Mycoplasma hyopneumoniae and furthermore are mycoplasmacidal in action.

According to the present invention there is provided a method of treating pigs for the therapy and/or prophylaxis of mycoplasmal pneumonia which method comprises administration to a pig in need thereof, an antimycoplasmally effective amount of a quinolone derivative of formula (I)
or a pharmaceutically acceptable salt or ester thereof;

wherein Y is an optionally substituted aromatic six membered ring containing up to two nitrogen atoms;

R₁ is C₁⁻₄ alkyl optionally substituted by halogen, hydroxy or aryl; C₃⁻₆ cycloalkyl; allyl or vinyl; or R₁ together with a substituent on the ring Y located at the position adjacent to the bridgehead form an optionally substituted six membered ring containing 0,1 or 2 additional heteroatoms selected from oxygen, nitrogen and sulphur;

R₂ is hydrogen or R₂ together with R₁ forms an optionally substituted thiazolidinyl ring.

Further according to the present invention there is provided the use of compound of formula (I) as hereinbefore defined in the manufacture of a medicament for the treatment or prophylaxis of mycoplasmal pneumonia in pigs.

As used herein the term 'aryl' includes phenyl.

Suitably Y is an optionally substituted benzene, azine or diazine ring, preferably an optionally substituted benzene or azine ring.
Suitable substituents for Y include up to three members selected from C₁₋₄ alkyl, C₁₋₄ alkoxy, halogen, dioxyethylene, or an optionally substituted heterocyclic group having 5 or 6 ring atoms one or two of which may be selected from nitrogen, oxygen and sulphur.

Suitable substituents for the above mentioned heterocyclic groups include hydroxy, C₁₋₄ alkyl such as methyl, or C₁₋₄ alkyl substituted by amino or C₁₋₄ alkylamino such as ethylamino-methyl.

Preferred substituents for Y include fluorine, methyl, pyridinyl, 2,5-dimethyl-pyridinyl, pyrrolidinyl, 3-hydroxy-pyrrolidinyl, piperazinyl, 3[(ethylamino)methyl]pyrrolidinyl, N-methyl piperazinyl and thiomorpholinyl.

When a substituent on Y forms a 5 or 6 membered ring with R₁, suitable substituents for that ring include oxo and C₁₋₄ alkyl such as methyl. Preferably the ring contains one oxygen atom. It is however preferred that when this ring contains an oxygen atom and is substituted by C₁₋₆ alkyl at the carbon atom adjacent the nitrogen atom, that Y is not a benzene ring substituted by N-alkyl piperazinyl.

Suitably R₁ is ethyl, cyclopropyl or 2-fluoroethyl.

Suitably X is CR₂ wherein R₂ is hydrogen or together with R₁ forms a thiazolidinyl ring optionally substituted with C₁₋₄ alkyl such as methyl.

Suitable pharmaceutically acceptable salts of the compounds of formula (I) include acid addition salts, metal salts, in particular alkali metal salts such as
sodium or potassium, or salts with strong organic bases for example those with lower alkylamines such as triethylamine, or with guanidine or tetramethyl-guanidine, or quaternary ammonium salts such as t-butyl ammonium salts.

Suitable acid addition salts of compounds of formula (I) include pharmaceutically acceptable inorganic salts such as the sulphate, nitrate, phosphate, hydrochloride and hydrobromide and pharmaceutically acceptable organic acid addition salts such as tartrate, maleate, citrate, methane-sulphonate, p-toluene-sulphonate, α-glycerophosphate, and glucose-1-phosphate.

Examples of suitable pharmaceutically acceptable ester groups include those which are in-vivo hydrolysable in that they break down readily in the human or animal body to leave the parent acid or its salt. An example of such an ester group is pivaloyloxymethyl.

Further examples of pharmaceutically acceptable esters include C\textsubscript{1-6} alkyl esters and amino C\textsubscript{3-8} alkyl esters.

A preferred sub group of compounds of formula (I) are compounds of formula (II)

\[
\text{(II)}
\]

or a salt thereof.
wherein

X is nitrogen or CH;
R₃ is C₁₋₄ alkyl or vinyl;
R₄ is halogen such as fluorine, chlorine or bromine; and
R₅ and R₆ are each independently C₁₋₅ alkyl or R₅ and R₆ together form a pyrrolidino, optionally substituted with hydroxy or C₁₋₄ alkylaminoC₁₋₄ alkyl; piperidino, morpholino or piperazino optionally 4-substituted by R₇(CH₂)ᵣ where r is 0-3 and R₇ is hydrogen, hydroxy (if r is 2 or 3) optionally substituted phenyl, benzyl, vinyl (if r = 1, 2 or 3) or lower acyl.

Suitable compounds of formula (II) are described in Belgium Patent Nos. 870,576 and 863,429, European Patent No. 9425 and Austrian Patent Application No. 8318698A.

In particular R₃ is vinyl, R₄ is halogen and R₅ and R₆ together form an unsubstituted piperazino group. Such compounds are described in European Published Patent Application No. 9425A.

A further preferred sub group of compounds of formula (I) are compounds of formula (III)
or a salt thereof

wherein

- $R_9$ is hydrogen or halogen,
- $R_9$ is optionally substituted piperaziny1,
- $R_{10}$ is hydrogen, halogen, or C$_{1-4}$ alkoxy,
- $R_{11}$ is hydrogen;
- $R_{12}$ is C$_{1-4}$ alkyl such as methyl.

Compounds of formula (III) are described in European Published Patent Application 0058392A.

A further preferred sub-group of compounds of formula (I) are compounds of formula (IV)

![Chemical Structure](image)

or a salt thereof.

Wherein $R_{13}$ is methyl, n-propyl, allyl, vinyl, 2-fluoroethyl or 2-hydroxyethyl and $R_{14}$ is piperizino; or

- $R_{13}$ is 2-fluoroethyl and $R_{14}$ is 4-(allyl, ethyl, or 2-hydroxylethyl)piperizino, 3-or 4-hydroxy-piperidino, 1-pyrolidino, morpholino or 4-dimethylaminopiperidino.

Suitable compounds of formula (IV) are described in Belgium Patent No. 887574.
Yet a further preferred sub-group of compounds of formula (I) are compounds of formula (V)

\[
\begin{align*}
\text{\text{O}} \\
\text{\text{N}} \\
\text{\text{R}_{16}} \\
\text{\text{R}_{15}} \\
\text{\text{\text{S} \ (O)_{n}}}}
\end{align*}
\]

(V)

or a salt or ester thereof;

wherein \( R_{15} \) is \( C_{1-4} \) alkyl optionally substituted with halogen or vinyl;
\( R_{16} \) and \( R_{17} \) are independently selected from hydrogen or halogen;
\(-N\text{S}\) is thiazolidine or thiomorpholine; and
\( n \) is 0 to 2.

Suitable compounds of formula (V) are described in US Patent No. 4473568.

Yet a further preferred sub-group of compounds of formula (I) are compounds of formula (VI)

\[
\begin{align*}
\text{\text{O}} \\
\text{\text{N}} \\
\text{\text{R}_{18}} \\
\text{\text{R}_{19}} \\
\text{\text{R}_{20}} \\
\text{\text{\text{R}_{21}}} \\
\text{\text{\text{\text{N} \ (C)_{3}}}}
\end{align*}
\]

(VI)

or a salt thereof.
wherein $R_{18}$ is N or $CR_{22}$ in which $R_{22}$ is hydrogen, halogen, nitrile, carboxamide, carboxyl or an ester group;

$R_{19}$ is N or CH provided that $R_{19}$ is not N when $R_{18}$ is N;

$R_{20}$ and $R_{21}$ are hydrogen, optionally substituted $C_{1-12}$ alkyl, optionally substituted alkenyl or optionally substituted alkynyl; or

$R_{20}$ and $R_{21}$ together form an optionally substituted 3 to 7 membered ring which may contain additional heteroatoms.

Suitable compounds of formula (VI) we described in German Offenlegungsschrift No. 3033 157.

A further sub-group of compounds of formula (I) are compounds of formula (VII)

![Chemical Structure](image)

(VII)

or a salt thereof

wherein $R_{23}$ is hydrogen or $C_{1-6}$ alkyl;

$R_{24}$ is halogen, and

$R_{25}$ is mono or disubstituted amino, or optionally substituted cyclic amino.

It is preferred that $R_{23}$ is not $C_{1-6}$ alkyl when $R_{25}$ is $N$-alkyl substituted piperazinyl.
Compounds of formula (VII) we described in European Published Patent Application No. 47005 A.

Suitable examples of compounds of formula (I) include:

1-ethyl-6-fluoro-1,4-dihydro-7-(4-methyl-1-piperazinyl)-4-oxoquinoline-3-carboxylic acid;

1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-piperazinoquinoline-3-carboxylic acid;

6-chloro-1-ethyl-1,4-dihydro-4-oxo-7-piperazinoquinoline-3-carboxylic acid;

1-ethyl-6,8 difluoro-1,4-dihydro-4-oxo-7-(3-ethylaminomethyl-1-pyrrolidinyl)quinoline-3-carboxylic acid;

9-fluoro-10-(3-hydroxy-1-pyrrolidinyl)-3-methyl-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid;

9-fluoro-2,3-dihydro-3-methyl-7-oxo-10-(4-thiomorpholinyl)-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid;

1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-piperazinequinoline-3-carboxylic acid;

1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-piperazino-1,8-naphthylidine-3-carboxylic acid and the sesquihydrate thereof;

1-(2-fluoroethyl)-7-(1-piperazinyl)-6,8-difluoro-4-quinolone-3-carboxylic acid;
l-ethyl-1,4-dihydro-4-oxo-7-(4-pyridyl)quinoline-3-carboxylic acid;

l-ethyl-1,4-dihydro-7-(2,6-dimethyl-4-pyridyl)-4-oxo-quinoline-3-carboxylic acid;

7-fluoro-1-methyl-8-(4-methyl-1-piperazinyl)-5-oxo-5H-thiazolo[3,2-a]quinoline-4-carboxylic acid;

7-fluoro-1-methyl-5-oxo-8-(1-piperazinyl)-5H-thiazolo[3,2-a]quinoline-4-carboxylic acid;

9-fluoro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-d,e][1,4]benzoxazine-6-carboxylic acid;

and pharmaceutically acceptable salts thereof.

Compounds of formula (I) are known compounds or can be produced from known compounds by known methods.


As has been stated hitherto the infection in which these compounds of formula (I) particularly useful is enzootic pneumonia of pigs, also known as mycoplasmal pneumonia of swine, this infection being attributable to Mycoplasma hyopneumoniae.
The compound of formula (I) may be administered to the animal as part of the total dietary intake. In this case the amount of compound employed may be less than 0.1% by weight of the diet. The diet for animals may consist of normal foodstuffs to which the compound of formula (I) may be added or the compound of formula (I) may be included in a premix for admixture with the foodstuff.

A suitable method administration of the compound of formula (I) to animals is to add it to the animals' drinking water, for example at a concentration of about 5 to 500µg/ml.

The compound of formula (I) is suitably administered in this way for a period of up to eight weeks depending upon the seriousness of the infection being treated.

Alternatively the compound of formula (I) can be applied in the form of a pharmaceutical composition. Further according to the present invention there is provided a composition for use in the treatment or prophylaxis of mycoplasma pneumonia in pigs which composition comprises a compound of formula (I) as hereinbefore defined and a pharmaceutically acceptable carrier.

The composition may be formulated for administration by any suitable route, such as oral or parenteral.

For oral administration the composition may be in the form of a dispersion or a solution of the drug in a suitable vehicle for use with an oral doser (this is a well known item of farm equipment, basically comprising a liquid reservoir, a mouthpiece adapted for insertion into animals mouths, and a pump mechanism whereby unit doses can be ejected from the reservoir through the
mouthpiece). Conveniently the drug may be administered from an oral doser as an aqueous solution. Alternatively, the vehicle will be an oil or water based cream to ensure homogeneity of the unit doses administered.

The invention, therefore, also provides an oral doser containing a multi-dose of the drug in a veterinarily acceptable vehicle.

For parenteral administration either short-acting or long-acting formulations can be employed. Fluid unit dosage forms are prepared utilizing the compound and a sterile vehicle, water being preferred. The compound, or pharmaceutically acceptable salt thereof depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions the compound can be dissolved in water for injection and filter sterilised before filling into a suitable vial or ampoule and sealing. Advantageously, agents such as a local anaesthetic, preservative and buffering agents can be dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum.

The dry lyophilized powder is then sealed in the vial and an accompanying vial of water for injection may be supplied to reconstitute the liquid prior to use. Parenteral suspensions are prepared in substantially the same manner except that the compound is suspended in the vehicle instead of being dissolved and sterilization cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene
oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The dosage of the compound will depend upon the nature of the infection being treated, as well as the severity of the condition. Generally the dosage will be within the range of from 5 to 50 mg/kg per day.

The following biological data illustrates the invention.
Compounds Tested

Compound of general formula (A)

![Chemical Structure](image)

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<td>F</td>
<td>-N (N)CH₃</td>
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<td>CH₂CH₃</td>
<td>CH</td>
<td>F</td>
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<td>CF</td>
<td>F</td>
<td>-N (CH₂-N)CH₂CH₃</td>
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<tr>
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<td>F</td>
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<td>N</td>
<td>F</td>
<td>(\text{N-NH})</td>
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<tr>
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<td>CH$_2$CH$_2$F</td>
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<td>8</td>
<td>CH$_2$CH$_3$</td>
<td>CH</td>
<td>H</td>
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<tr>
<td>9</td>
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Compounds of general formula (B)

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Compounds of general formula (C)

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<td>F</td>
<td>N_NH</td>
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METHOD

Minimal Inhibitory Concentration (MIC)

MIC's were determined by incorporating the compounds in Friis' medium (Friis 1975) supplemented with 1-cysteine hydrochloride (0.012% w/v) and nicotinamide - adenine dinucleotide (NAD) (0.012% w/v) and solidified with 0.65% agarose (Miles Laboratories Ltd) or in solidified SP4 medium (Tully et al 1977), and inoculating the surface of the plates with 0.001 ml of thawed aliquots of mycoplasmal cultures containing $10^6$cfu (colony forming units) per ml and incubating them aerobically in moist conditions at 37°C for 6 days. The concentration of the compounds tested ranged from 10µg/ml to 0.00025 µg/ml. The MIC was taken as the lowest concentration of compound to cause a 50% reduction in mycoplasmal growth.

References.

Friis M.F. (1973) Nordisk Veterinaer medicin 27, 337-339

The results obtained for compounds 1 to 14 against three strains of M.hyopneumoniae and against M.bovis by way of comparison are given in the following table.
**Mycoplasmacidal Test**

**Method**

A stock culture of *M. hyopneumoniae* strain UCD4 was maintained in Friis broth in 1 ml amounts at -70°C. For the test, one vial was thawed, diluted 1:40 in Friis broth and incubated at 37°C for 72 hours. 1.0 ml of neat culture was then added to 48 ml of Friis broth in 100 ml bottles. The bottles were incubated at 37°C for 2 hours. To each was then added 1.0 ml of drug solution at 50x the desired concentration (1 x agar MIC, 5 x agar MIC and 10 x agar MIC). A control culture containing no antibiotic was also prepared. The cultures were incubated at 37°C. Immediately on addition of drug solution, and periodically thereafter, samples of culture were withdrawn for viable count determinations. These were performed by preparing serial 10-fold dilutions of the drug-containing Friis broth in drug-free Friis broth (down to 1:106) and then plating 0.02 ml amounts of the dilutions on to Friis agarose plates. Colony counts were performed after 7 days incubation at 37°C. The number of survivors was determined in this way for up to 96 hours.

Results are shown graphically in the attached Figure 1 in which the number of survivors are shown (as log_{10} cfu/ml) plotted against hours.
KILLING CURVES VERSUS M. HYOPNEUMONIAE STRAIN UCD4† IN FRIIS BROTH

- Control
- Example 3 (0.5 µg/ml)
- Example 10 (0.25 µg/ml)
- Example 2 (0.5 µg/ml)

Log10 cfu/ml

99.99% Kill

Time (Hours)

Example 2 UCD4 Strain

<table>
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<tr>
<th>Example</th>
<th>MIC's (µg/ml)</th>
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<td>0.1</td>
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†MIC's vs.
Claims

1. The use of a quinolone derivative of formula (I)

\[
\begin{align*}
\text{Y} & \quad \text{COOH} \\
\text{R}_1 & \quad \text{R}_2
\end{align*}
\]

or a pharmaceutically acceptable salt or ester thereof;

wherein \( Y \) is an optionally substituted aromatic six membered ring containing up to two nitrogen atoms;

\( R_1 \) is \( \text{C}_{1-4} \) alkyl optionally substituted by halogen, hydroxy or aryl; \( \text{C}_{3-6} \) cycloalkyl, allyl or vinyl; or \( R_1 \) together with a substituent on the ring \( Y \) located at the position adjacent to the bridgehead form an optionally substituted six membered ring containing 0, 1 or 2 additional heteroatoms selected from oxygen, nitrogen and sulphur;

\( R_2 \) is hydrogen or \( R_2 \) together with \( R_1 \) forms an optionally substituted thiazolidinyl ring:

for the manufacture of a medicament for the treatment or prophylaxis of mycoplasmal pneumonia in pigs.

2. The use according to claim 1 wherein \( Y \) is an optionally substituted benzene, azine or diazine ring.
3. The use according to claim 2 wherein \( Y \) has up to three substituents selected from \( C_{1-4} \) alkyl, \( C_{1-4} \) alkoxy, halogen, dioxymethylene or an optionally substituted heterocyclic group having 5 or 6 ring atoms, one or two of which may be selected from nitrogen, oxygen and sulphur.

4. The use according to any preceding claim wherein the quinolone derivative is a compound of formula (II)

\[
\begin{align*}
\text{O} & \\
\text{R}_4 & \\
\text{R}_5 & \text{N} \\
\text{R}_6 & \\
\text{R}_3 & \\
\text{COOH} & \\
\end{align*}
\]

(II)

or a salt thereof

wherein

- \( X \) is nitrogen or CH;
- \( R_3 \) is \( C_{1-4} \) alkyl or vinyl;
- \( R_4 \) is halogen such as fluorine, chlorine or bromine; and
- \( R_5 \) and \( R_6 \) are each independently \( C_{1-5} \) alkyl or \( R_5 \) and \( R_6 \) together form a pyrrolidino, optionally substituted with hydroxy or \( C_{1-4} \) alkylamino\( C_{1-4} \) alkyl; piperidino, morpholino or piperazino optionally 4-substituted by \( R_7(CH_2)_n \) where \( n \) is 0-3 and \( R_7 \) is hydrogen, hydroxy (if \( n \) is 2 or 3) optionally substituted phenyl, benzyl, vinyl (if \( n \) is 1, 2 or 3) or lower acyl.
5. The use according to any one of claims 1 to 3 wherein the quinolone derivative is a compound of formula (III)

\[
\begin{align*}
\text{R}_{10} & \quad \text{R}_{11} \\
\text{R}_{9} & \quad \text{R}_{8} \\
\text{N} & \quad \text{S} \\
\text{R}_{12} & \\
\end{align*}
\] (III)

or a salt thereof

wherein

- \( \text{R}_{8} \) is hydrogen or halogen,
- \( \text{R}_{9} \) is optionally substituted piperazinyl,
- \( \text{R}_{10} \) is hydrogen, halogen, or \( \text{C}_{1-4}\) alkoxy,
- \( \text{R}_{11} \) is hydrogen;
- \( \text{R}_{12} \) is \( \text{C}_{1-4} \) alkyl such as methyl.

6. The use according to any one of claims 1 to 3 wherein the quinolone derivative is a compound of formula (IV)

\[
\begin{align*}
\text{F} & \quad \text{N} \\
\text{R}_{14} & \quad \text{F} \\
\text{R}_{13} & \\
\end{align*}
\] (IV)
or a salt thereof.

Wherein \( R_{13} \) is methyl, n-propyl, allyl, vinyl, 2-fluoroethyl or 2-hydroxyethyl and \( R_{14} \) is piperizino; or
\( R_{13} \) is 2-fluoroethyl and \( R_{14} \) is 4-(allyl, ethyl, or 2-hydroxylethyl)piperizino, 3-or 4-hydroxy-piperidino, 1-pyrrolidino, morpholino or 4-dimethylaminopiperidino.

7. The use according to any one of claims 1 to 3 wherein the quinolone derivative is a compound of formula (V)

\[ \text{Formula (V)} \]

or a salt or ester thereof;

wherein \( R_{15} \) is C\(_{1-4}\) alkyl optionally substituted with halogen or vinyl;
\( R_{16} \) and \( R_{17} \) are independently selected from hydrogen or halogen;
\(-N\_S\) is thiazolidine or thiormorpholine; and
\( n \) is 0 to 2.

8. The use according to any one of claims 1 to 3 wherein the quinolone derivative is a compound of formula (VI)
wherein R₁₈ is N or CR₂₂ in which R₂₂ is hydrogen, halogen, nitrile, carboxamide, carboxyl or an ester group;
R₁₉ is N or CH provided that R₁⁹ is not N when R₁₈ is N;
R₂₀ and R₂₁ are hydrogen, optionally substituted C₁–₁₂ alkyl, optionally substituted alkenyl or optionally substituted alkynyl; or
R₂₀ and R₂₁ together form an optionally substituted 3 to 7 membered ring which may contain additional heteroatoms.

9. The use according to any one of claims 1 to 3 wherein the quinolone derivative is a compound of formula (VII)
or a salt thereof

wherein $R_{23}$ is hydrogen or $C_{1-6}$ alkyl;
$R_{24}$ is halogen, and
$R_{25}$ is mono or disubstituted amino, or optionally substituted cyclic amino.

10. The use of a quinolone derivative of formula I

\[ \text{O} \quad \text{COOH} \]

or a pharmaceutically acceptable salt or ester thereof;

wherein $Y$ is an optionally substituted aromatic six membered ring containing up to two nitrogen atoms;

$R_{1}$ is $C_{1-4}$ alkyl optionally substituted by halogen, hydroxy or aryl; $C_{3-6}$ cycloalkyl; allyl or vinyl; or $R_{1}$ together with a substituent on the ring $Y$ located at the position adjacent to the bridgehead form an optionally substituted six membered ring containing 0,1 or 2 additional heteroatoms selected from oxygen, nitrogen and sulphur;

$R_{2}$ is hydrogen or $R_{2}$ together with $R_{1}$ forms an optionally substituted thiazolidinyl ring with the proviso that when $Y$ is a benzene ring substituted by $N$-alkyl piperazinyl and $R_{1}$ together with a substituent on $Y$ form a six membered ring containing one oxygen atom, that this ring is not substituted by $C_{1-6}$ alkyl.
at the carbon atom adjacent the nitrogen atom; for the manufacture of a medicament for the treatment or prophylaxis of mycoplasmal pneumonia in pigs.

11. The use according to claim 10 wherein the quinolone derivative is a compound of formula (VII)

![Chemical Structure](image)

(VII)

or a salt thereof

wherein R\textsubscript{23} is hydrogen or C\textsubscript{1-6} alkyl
R\textsubscript{24} is halogen and
R\textsubscript{25} is mono or disubstituted amino or optionally substituted cyclic amino

with the proviso that R\textsubscript{23} is not C\textsubscript{1-6} alkyl when R\textsubscript{25} is N-alkyl substituted piperazinyl.

12. The use according to claim 1 of a compound selected from:

1-ethyl-6-fluoro-1,4-dihydro-7-(4-methyl-1-piperazinyl)-4-oxoquinoline-3-carboxylic acid;

1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-piperazino-quinoline-3-carboxylic acid;

6-chloro-1-ethyl-1,4-dihydro-4-oxo-7-piperazino-quinoline-3-carboxylic acid;
1-ethyl-6,8 difluoro-1,4-dihydro-4-oxo-7-(3-ethylaminomethyl-1-pyrrolidinyl)quinoline-3-carboxylic acid;

9-fluoro-10-(3-hydroxy-1-pyrrolidinyl)-3-methyl-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid;

9-fluoro-2,3-dihydro-3-methyl-7-oxo-10-(4-thiomorpholiny1)-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid;

1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-piperazine-quinoline-3-carboxylic acid;

1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-piperazino-1,8-naphthyridine-3-carboxylic acid and the sesquihydrate thereof;

1-(2-fluoroethyl)-7-(1-piperazinyl)-6,8-difluoro-4-quinolone-3-carboxylic acid;

1-ethyl-1,4-dihydro-4-oxo-7-(4-pyridyl)quinoline-3-carboxylic acid;

1-ethyl-1,4-dihydro-7-(2,6-dimethyl-4-pyridyl)-4-oxo-quinoline-3-carboxylic acid;

7-fluoro-1-methyl-8-(4-methyl-1-piperazinyl)-5-oxo-5H-thiazolo[3,2-a]quinoline-4-carboxylic acid;

7-fluoro-1-methyl-5-oxo-8-(1-piperazinyl)-5H-thiazolo [3,2-a]-quinoline-4-carboxylic acid;

9-fluoro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-d,e][1,4]benzoxazine-6-carboxylic acid;
and pharmaceutically acceptable salts thereof.

13. A method of treating pigs for the therapy and/or prophylaxis of mycoplasmal pneumonia which method comprises administration to a pig in need thereof an antimycoplasmally effective amount of a quinolone derivative of formula I

\[
\text{(I)}
\]

or a pharmaceutically acceptable salt or ester thereof;

wherein \(Y\) is an optionally substituted aromatic six membered ring containing up to two nitrogen atoms;

\(R_1\) is \(C_1-4\) alkyl optionally substituted by halogen, hydroxy or aryl; \(C_3-6\) cycloalkyl; allyl or vinyl; or \(R_1\) together with a substituent on the ring \(Y\) located at the position adjacent to the bridgehead form an optionally substituted six membered ring containing 0, 1 or 2 additional heteroatoms selected from oxygen, nitrogen and sulphur;

\(R_2\) is hydrogen or \(R_2\) together with \(R_1\) forms an optionally substituted thiazolidinyl ring.

14. A method of treating pigs for the therapy and/or prophylaxis of mycoplasmal pneumonia which method comprises administration to a pig in need thereof an antimycoplasmally effective amount of a quinolone derivative of formula I
or a pharmaceutically acceptable salt or ester thereof;

wherein Y is an optionally substituted aromatic six
membered ring containing up to two nitrogen atoms;

R₁ is C₁-₄ alkyl optionally substituted by halogen,
hydroxy or aryl; C₃-₆ cycloalkyl; allyl or vinyl; or R₁
together with a substituent on the ring Y located at
the position adjacent to the bridgehead form an
optionally substituted six membered ring containing 0,1
or 2 additional heteroatoms selected from oxygen,
nitrogen and sulphur;

R₂ is hydrogen or R₂ together with R₁ forms an
optionally substituted thiazolidinyl ring, with the
proviso that when Y is a benzene ring substituted by
N-alkyl piperazinyl and R₁ together with a substituent
on Y form a six membered ring containing one oxygen
atom, that this ring is not substituted by C₁-₆ alkyl
at the carbon atom adjacent the nitrogen atom.

15. A method of treatment according to claim 13
wherein the quinolone derivative is selected from:-
1-ethyl-6-fluoro-1,4-dihydro-7-(4-methyl-1-piperazinyl)-4-oxoquinoline-3-carboxylic acid;

1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-piperazinoquinoline-3-carboxylic acid;

6-chloro-1-ethyl-1,4-dihydro-4-oxo-7-piperazinoquinoline-3-carboxylic acid;

1-ethyl-6,8 difluoro-1,4-dihydro-4-oxo-7-(3-ethylaminomethyl-1-pyrrolidinyl)quinoline-3-carboxylic acid;

9-fluoro-10-(3-hydroxy-1-pyrrolidinyl)-3-methyl-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid;

9-fluoro-2,3-dihydro-3-methyl-7-oxo-10-(4-thiomorpholinyl)-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid;

1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-piperazinoquinoline-3-carboxylic acid;

1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-piperazino-1,8-naphthyridine-3-carboxylic acid and the sesquihydrate thereof;

1-(2-fluoroethyl)-7-(1-piperazinyl)-6,8-difluoro-4-quinolone-3-carboxylic acid;

1-ethyl-1,4-dihydro-4-oxo-7-(4-pyridyl)quinoline-3-carboxylic acid;

1-ethyl-1,4-dihydro-7-(2,6-dimethyl-4-pyridyl)-4-oxoquinoline-3-carboxylic acid;
7-fluoro-1-methyl-8-(4-methyl-1-piperazinyl)-5-oxo-5H-thiazolo[3,2-a]-quinoline-4-carboxylic acid;

7-fluoro-1-methyl-5-oxo-8-(1-piperazinyl)-5H-thiazolo[3,2-a]-quinoline-4-carboxylic acid;

9-fluoro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-d,e][1,4]benzoxazine-6-carboxylic acid;

and pharmaceutically acceptable salts thereof.
**INTERNATIONAL SEARCH REPORT**

International Application No PCT/GB 86/00258

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) 4

According to International Patent Classification (IPC) or to both National Classification and IPC

**IPC**

A 61 K 31/47; A 61 K 31/535; A 61 K 31/44

II. FIELDS SEARCHED

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Documentation Searched other than Minimum Documentation to the extent that such Documents are included in the Fields Searched 9

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<th>Category 5</th>
<th>Citation of Document, 10 with indication, where appropriate, of the relevant passages 12</th>
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<td>X</td>
<td>Antimicrobial Agents and Chemotherapy, volume 14, no. 2, August 1978, (American Society for Microbiology, US), P.P. Williams: &quot;In vitro susceptibility of Mycoplasma hyopneumoniae and Mycoplasma hyorhinis to fifty-one antimicrobial agents&quot;, pages 210-213 see the whole article</td>
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<td>X</td>
<td>Chemotherapy, volume 32, supplement 3, April 1984, (Tokyo, JP), pages 70-85 see the abstract; pages 73,76</td>
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| * Special categories of cited documents: 16 |
| "A" document defining the general state of the art which is not considered to be of particular relevance |
| "E" earlier document but published on or after the international filing date |
| "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) |
| "O" document referring to an oral disclosure, use, exhibition or other means |
| "P" document published prior to the international filing date but later than the priority date claimed |
| "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention |
| "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step |
| "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. |
| "Z" document member of the same patent family |

IV. CERTIFICATION

Date of the Actual Completion of the International Search
29th September 1986

Date of Mailing of this International Search Report
07 NOV 1986

International Searching Authority
EUROPEAN PATENT OFFICE

Signature of Authorized Officer
M. VAN MOL

Form PCT/ISA/210 (second sheet) (January 1985)
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<td>Inn. Med., volume 12, May 1985, (R. Pflaum Verlag), F. Gutzler: &quot;Gyrasehemmer - eine neue Klasse von Antibiotika&quot;, pages 139-146 see the whole article</td>
<td>1-8,10,12</td>
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<td>X,P</td>
<td>J. Antimicrob. Chemother., volume 15, no. 6, June 1985, M. Bakhtiar et al.: &quot;In-vitro sensitivity of legionellas, meningococci and mycoplasmas to ciprofloxacin and enoxacin&quot;, pages 787-789 see the whole article</td>
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<td>X</td>
<td>EP, A, 0049355 (BAYER AG) 14 April 1982 see claims 1-2,8-10; pages 13-17 &amp; DE, A, 3033157 (cited in the application)</td>
<td>1-8,10,12</td>
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<td>BE, A, 870576 (LABORATOIRE ROGER BELLON) 19 March 1979 see pages 2,34-43; claims 1-31 (cited in the application)</td>
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<td>A</td>
<td>BE, A, 863429 (KYORIN SEIYAKU K.K.) 16 May 1978 see pages 6-7; claims 1-4 (cited in the application)</td>
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| A        | US, A, 3753993 (G.Y. LESHER et al.)  
21 August 1973  
see column 6, lines 50-66  
(cited in the application) | 1-8,10,12 |
| A        | US, A, 4473568 (HUTT, Jr.) 25 September 1984  
see column 3, lines 63-68, claims 1-10  
(cited in the application) | 1-8,10,12 |
| A        | US, A, 4398029 (IRIKURA et al.)  
9 August 1983, see column 20  
(cited in the application) | 1-8,10,12 |
| A        | BE, A, 887574 (KYORIN SEIYAKU K.K.)  
15 June 1981  
see pages 18-20; claims 1-15  
(cited in the application) | 1-8,10,12 |
| A        | EP, A, 0058392 (NIPPON SHINYAKU COMPANY)  
25 May 1982  
see pages 10,11,50-52; claims  
(cited in the application) | 1-8,10,12 |
FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

VI. OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. Claim numbers ..., because they relate to subject matter not required to be searched by this Authority, namely:
   §§ Claims 13-15
   See Rule 39.1(iv):
   Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

2. Claim numbers ..., because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. Claim numbers ..., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This International Searching Authority found multiple inventions in this international application as follows:

claims 5-7 and partly 1-4,8,10 and 12: Use of compounds of formula (I)
wherein Y is an optionally substituted benzene ring, which does not form part of a peri-condensed system.

See attached annex

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers 5-7, and partly 1-4,8,10 and 12.

4. As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest
☐ The additional search fees were accompanied by applicant's protest.
☐ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (supplemental sheet (2)) (January 1985)
2. Partly Claims 1-4, 8, 10 and 12:
Use of compounds of formula (I) wherein Y is an optionally substituted azine ring, which does not form part of a peri-condensed system.

3. Partly Claims 1-3, and 10:
Use of compounds of formula (I) wherein Y is an optionally substituted diazine ring, which does not form part of a peri-condensed system.

4. Claims 9 and 11, and partly 1-3, 10 and 12:
Use of compounds of formula (I) wherein Y does not form part of a peri-condensed system.

The lack of unity a posteriori is based on the following documents:

a) Antimicrobial Agents and Chemotherapy, Vol.14, Nr.2, August 1978; Pages 210-213; P.P. Williams: "In Vitro Susceptibility of Mycoplasma hyopneumoniae and Mycoplasma hyorhinis to Eighty-One Antimicrobial Agents".


c) Chemotherapy (Tokyo) Vol.32, Suppl. 3; April 1984, Pages 70-85; S.Nakamura et al: "In vitro and in vivo antibacterial activity of AT-2266".
This Annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 08/10/86.

The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

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