

Señor

Superintendente de Industria y Comercio

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REF: EXPEDIENTE 00-058-178

TÍTULO SOLICITADO: "FORMULACIÓN DE SAL COMÚN Y MOXIFLOXACINA"

PUBLICACIÓN: Gaceta 519 de 29-08-2002, número de publicación 677

SOLICITANTE: BAYER AKTIENGESELLSCHAFT

APODERADO: EMILIO FERRERO

TRÁMITE: REMISIÓN DE INFORMACIÓN

JOSÉ LUIS REYES VILLAMIZAR, mayor de edad, identificado como aparece al pie de mi firma, abogado en ejercicio, titular de la tarjeta profesional número 44655 del Consejo Superior de la Judicatura, obrando en calidad de apoderado de la sociedad **LAFRANCOL S.A.**, con el propósito de coadyuvar en la negación de la solicitud colombiana 00-058-178 en trámite, por este escrito me refiero a la contestación de la oposición presentada por el solicitante el 20 de junio de 2003 para manifestar:

1. En cuanto a la pretendida ausencia de legítimo interés en la opositora

Muy respetuosamente me permito reiterar al Despacho y al solicitante que el cumplimiento del requisito en cuestión por parte de mi cliente, es un hecho notorio que, en esa condición, no requiere de demostración adicional:

Es evidente que a mi poderdante le asiste legítimo interés en la presentación y sustentación de escritos de oposición, pues la eventual concesión de esta clase de solicitudes de patente restringiría injustificadamente el empleo de ciertas sustancias, derivados, procesos y formulaciones carentes de nivel inventivo, en

detrimento de sus legítimos intereses comerciales. De igual manera mi cliente está interesado, por su misma condición de industria farmacéutica, en evitar la concesión de privilegios de patente que incumplan los requisitos materiales de patentabilidad establecidos en las normas vigentes, y que supongan un riesgo para la libre competencia.

2. En cuanto a la carencia de nivel inventivo de la solicitud en curso

Si bien es cierto en el estado del arte no se encuentra una revelación textual de la supuesta invención, es decir, de una solución de Moxifloxacino y sal común tal como se describe en la solicitud que nos ocupa, no se puede desconocer que en la práctica farmacéutica el uso de la sal común como medio o como agente isotonizante en la formulación de medicamentos es muy amplio.

Es claro, en efecto, que dentro de los principales vehículos para los productos farmacéuticos estériles se encuentran agua inyectable, algunos aceites vegetales o ésteres de ácidos grasos de peso molecular elevado, mono o diglicéridos sintéticos y otros compuestos en funciones de alcoholes libres o esterificados, empleados solos o mezclados. La solución inyectable de cloruro de sodio o la solución de Ringer se pueden usar total o parcialmente, en lugar del agua inyectable y en suficiente cantidad para hacerlas isotónicas.

Del mismo modo, numerosas preparaciones inyectables necesitan de ciertas sustancias para tener isotonicidad, estabilizar el pH, aumentar la solubilidad, prolongar el tiempo de conservación del principio activo, modificar la tensión superficial de una suspensión o asegurar la acción bacteriostática.

En cualquier caso, los compuestos utilizados deben ser inocuos en las cantidades administradas, no deben interferir con la eficacia terapéutica, ni causar toxicidad o irritación local a la concentración usada, ni entorpecer las pruebas y ensayos prescritos.

Además, cabe resaltar que, para un formulador no sólo es indispensable escoger la materia prima cuyas características farmacotécnicas sean más adecuadas en la elaboración de un medicamento, sino también debe poseer un conocimiento cabal de las propiedades fisicoquímicas y del comportamiento farmacocinética y biofarmacéutico de cada medicamento que se desarrolle.

En la etapa de preformulación se realiza la caracterización fisicoquímica del principio activo en cuestión, de igual manera, se evalúan parámetros como tamaño y forma de los cristales, perfil pH-solubilidad, perfil pH-estabilidad, polimorfismo, efecto de partición, permeabilidad y comportamiento de disolución; también se consideran las posibles interacciones con diversos componentes inertes destinados a usar en la forma posológica final.

Por esta razón, no resulta un avance el hecho que el solicitante *“encuentre de forma sorprendente que puedan prepararse formulaciones aceptables de clorhidrato de moxifloxacin con isotonicación con sal común, si se mantiene un estrecho intervalo de concentración determinado para la sustancia activa y el agente isotonizante”*; además y contrario a lo señalado por el mismo solicitante, la obtención de una solución parenteral estable que pueda suministrar la cantidad farmacológicamente necesaria de clorhidrato de moxifloxacin es evidente e indiscutiblemente posible para una persona versada en la materia y dedicada a la formulación.

De otro lado, me permito llamar la atención a ese Despacho en cuanto a lo revelado en FDA (Electronic Orange Book- Moxifloxacin):

Appl No	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
021277	Moxifloxacin Hydrochloride	Injectable; IV (Infusion)	160mg/100mL	AVELOX IN SODIUM CHLORIDE 0.8% IN PLASTIC CONTAINER	BAYER PHARMS
021598	Moxifloxacin Hydrochloride	Solution/Drops; Ophthalmic	0.5%	VIGAMOX	ALCON
021085	Moxifloxacin Hydrochloride	Tablet; Oral	EQ 400mg Base	AVELOX	BAYER PHARMS

Estos tres productos tienen como soporte de aprobación, algunas patentes americanas, las cuales se señalan en la columna azul como vemos a continuación:

MOXIFLOXACIN HYDROCHLORIDE – INJECTABLE (AVELOX®)			
Appl No	Prod No	Patent No	Patent Expiration
021277	001	4990517	JUN 30,2009
021277	001	5607942	MAR 04,2014
021277	001	5849752	DEC 05,2016

MOXIFLOXACIN HYDROCHLORIDE – SOLUTION/ DROPS; OPHTHALMIC (VIGAMOX®)			
Appl No	Prod No	Patent No	Patent Expiration
021598	001	4990517	JUN 30,2009
021598	001	5607942	MAR 04,2014
021598	001	6716830	SEP 20,2019

207

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MOXIFLOXACIN HYDROCHLORIDE – TABLET; ORAL (AVELOX®)			
Appl No	Prod No	Patent No	Patent Expiration
021085	001	4990517	JUN 30,2009
021085	001	5607942	MAR 04,2014
021085	001	5849752	DEC 05,2016

Tanto Moxifloxacin clorhidrato inyectable- AVELOX®, como Moxifloxacin clorhidrato tabletas- AVELOX® y Moxifloxacin clorhidrato solución/gotas oftálmicas- VIGAMOX®, tienen como referencia común de aprobación al menos dos patentes, la US 4,990,517 y la US5,607,942, -las cuales son equivalentes puesto que invocan las mismas prioridades-. Esto significa que la FDA ha reconocido como fundamento de aprobación estos documentos, independientemente del tipo de producto a comercializar.

La **US 4,990,517** publicada en febrero 5 de 1991, revela 7 -(1-pirrolidinil) -3-quinolona y derivados del ácido naftiridoncarboxílicos como agentes antibacteriales, dentro de los cuales se encuentra **MOXIFLOXACINA** y que además, puede ser incluida en diferentes formulaciones farmacéuticas como tabletas, tabletas cubiertas, cápsulas, gránulos, supositorios, soluciones, suspensiones, emulsiones, ungüentos, geles, cremas, lociones; entre otros. (ver columna 57, líneas 53 a 57).

Del mismo modo, este documento revela en la columna 58, líneas 50 a 53 que, "para la administración parenteral, las soluciones y emulsiones también pueden estar en la forma estéril, y que deben ser isotónicas con la sangre".- subrayado fuera del texto.

Más adelante, en la columna 59, líneas 11 a 19, se describe claramente que: "las formulaciones mencionadas pueden ser usadas en humanos y animales oralmente, rectalmente, parenteralmente (intravenosa, intramuscular o subcutáneamente), intravaginalmente, intraperitonealmente o localmente (polvos, ungüentos, gotas) para la terapia de infecciones en espacios huecos y cavidades de cuerpo"- subrayado fuera del texto.

Adicionalmente, la patente US 5,849,752 publicada en diciembre 15 de 1998, describe la modificación cristalina de CDCH (Clorhidrato de Moxifloxacin monohidrato), un proceso para su preparación y formulaciones farmacéuticas de la misma, que pueden ser de administración oral, parenteral o rectal. (ver columna 4, líneas 28 y 29 y líneas 35 y 36).

Por último me permito citar lo revelado en el *abstract* del artículo: "Absolute bioavailability of moxifloxacin" publicado en el *Clin Ther.* 1999 Mar; 21(3): 513-22; el cual se refiere a Moxifloxacin (BAY 12-8039) y donde se hace un estudio farmacocinético comparativo de la administración de una dosis simple de 100mg oral o intravenosa de la misma, con el fin de determinar su biodisponibilidad absoluta.

Por lo tanto, queda demostrado que el supuesto fundamento de invención "una formulación acuosa de clorhidrato de Moxifloxacin y sal común para administración parenteral", carece por completo de nivel inventivo, puesto que con anterioridad a la publicación de la presente solicitud de patente, ya se revelaba la posibilidad de encontrar al principio activo Moxifloxacin en formulaciones para administración parenteral en forma estéril e isotónicas con la sangre.

Así las cosas, y con fundamento en los argumentos expuestos a lo largo del presente escrito y en los escritos de oposición y sustentación de la misma, respetuosamente reitero la solicitud para que su despacho se abstenga de conceder el privilegio de patente solicitado, y ordene en consecuencia el archivo del expediente respectivo.

PRUEBAS

Además de las solicitadas en el escrito de oposición y sustentación, y de aquellas que oficiosamente considere el despacho, ruego que se tengan como tales las siguientes:

- Apartes de la patente americana US 4,990,517 del 5 de febrero de 1991.
- Copia de la página frontal de la patente americana US 5,607,942 del 4 de marzo de 1997.

- Apartes de la patente americana US 5,849,752 del 15 de diciembre de 1998.
- Ballow C, Lettieri J, Agarwal V, Liu P, Stass H, Sullivan JT. "Absolute bioavailability of moxifloxacin" - Abstract. Clin Ther. 1999 Mar;21(3): 513-22.

Señor Superintendente,



José Luis Reyes Villamizar

C.C. 79'152.473 de Usaquén

T.P.A., 44655 del C.S.J.

United States Patent [19]

Petersen et al.

[11] **Patent Number:** 4,990,517[45] **Date of Patent:** Feb. 5, 1991

[54] **7-(1-PYRROLIDINYL)-3-QUINOLONE- AND -NAPHTHYRIDONECARBOXYLIC ACID DERIVATIVES AS ANTIBACTERIAL AGENTS AND FEED ADDITIVES**

[75] **Inventors:** Uwe Petersen, Leverkusen; Thomas Schenke, Bergisch-Gladbach; Andreas Krebs, Odenthal-Holz; Klaus Grohe; Michael Schriewer, both of Odenthal; Ingo Haller, Wuppertal; Karl G. Metzger, Wuppertal; Rainer Endermann, Wuppertal; Hans-Joachim Zeiler, Velbert, all of Fed. Rep. of Germany

[73] **Assignee:** Bayer Aktiengesellschaft, Leverkusen, Fed. Rep. of Germany

[21] **Appl. No.:** 375,434

[22] **Filed:** Jun. 30, 1989

[30] **Foreign Application Priority Data**

Jul. 15, 1988 [DE] Fed. Rep. of Germany 3824072

Mar. 1, 1989 [DE] Fed. Rep. of Germany 3906365

[51] **Int. Cl.⁵** A61K 31/44; A61K 31/47; C07D 471/04; C07D 215/56

[52] **U.S. Cl.** 514/300; 514/224.5; 514/230.2; 514/230.5; 514/312; 544/32; 544/63; 544/91; 544/101; 546/100; 546/113; 546/123; 546/156

[58] **Field of Search** 544/32, 101, 63, 91; 546/100, 113, 123, 156; 514/224.5, 230.2, 230.5, 300, 312

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,777,175 10/1988 Culbertson et al. 546/123

FOREIGN PATENT DOCUMENTS

1056673 3/1989 Japan 546/123

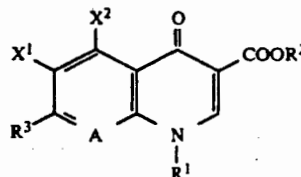
Primary Examiner—Mary C. Lee

Assistant Examiner—Bernard I. Dentz

Attorney, Agent, or Firm—Sprung Horn Kramer & Woods

[57] **ABSTRACT**

7-(1-Pyrrolidinyl)-3-quinolone- and -naphthyridonecarboxylic acid derivatives as antibacterial agents and feed additives, of the formula



in which

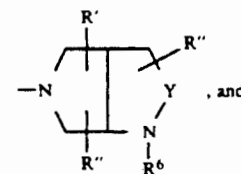
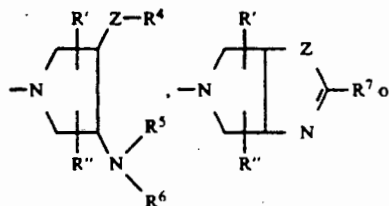
X¹ is halogen,

X² is hydrogen, halogen, amino or other radical,

R¹ is alkyl, cycloalkyl, optionally substituted phenyl or other radical,

R² is hydrogen, alkyl or a dioxolymethyl radical,

R³ is



A is N, CH, C-halogen, or the like, or forms a bridge with R¹,

and addition products thereof.

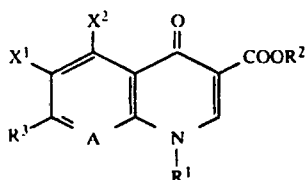
14 Claims, No Drawings

**7-(1-PYRROLIDINYL)-3-QUINOLONE- AND
-NAPHTHYRIDONECARBOXYLIC ACID
DERIVATIVES AS ANTIBACTERIAL AGENTS
AND FEED ADDITIVES**

The invention relates to new 7-(1-pyrrolidinyl)-3-quinolone- and -naphthyridonecarboxylic acid derivatives, processes for their preparation and antibacterial agents and feed additives containing them.

A number of 3-quinolone- and naphthyridonecarboxylic acids which are substituted in the 7-position by a pyrrolidinyl ring have already been disclosed. German Patent Application 3,318,145 and European Patent Applications 106,489 and 153,826.

It has been found that the 7-(1-pyrrolidinyl)-3-quinolone- and naphthyridonecarboxylic acid derivatives of the formula (I)



in which

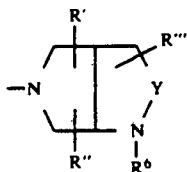
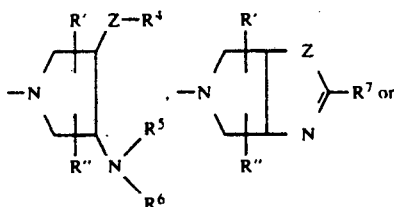
X¹ represents halogen,

X² represents hydrogen, amino, alkylamino having 1 to 4 carbon atoms, dialkylamino having 1 to 3 carbon atoms per alkyl group, hydroxyl, alkoxy having 1 to 4 carbon atoms, mercapto, alkylthio having 1 to 4 carbon atoms, arylthio or halogen,

R¹ represents alkyl having 1 to 4 carbon atoms, alkyl having 2 to 4 carbon atoms, cycloalkyl having 3 to 6 carbon atoms, 2-hydroxyethyl, 2-fluoroethyl, methoxy, amino, methylamino, ethylamino, dimethylamino or phenyl which is optionally substituted by 1 or 2 fluorine atoms,

R² represents hydrogen, alkyl having 1 to 4 carbon atoms or (5-methyl-2-oxo-1,3-dioxol-4-yl)-methyl,

R³ represents a radical of the structure



wherein

R⁴ can represent H, C₁-C₄-alkyl, aryl or C₁-C₄-acyl,

R⁵ can represent H, C₁-C₄-alkyl, OH or OCH₃, it also being possible for R⁴ and R⁵ together to denote a C₁-C₃-alkylene bridge which is optionally mono- or disubstituted by methyl,

R⁶ can represent H, optionally hydroxyl-substituted C₁-C₄-alkyl, as well as aryl, heteroaryl, benzyl, C₁-C₄-alkoxycarbonyl, C₁-C₄-acyl, (5-methyl-2-oxo-1,3-dioxol-4-yl)-methyl, or C₃-C₆-cycloalkyl,

R⁷ can represent H or C₁-C₄-alkyl,

R' can represent H, CH₃ or phenyl,

R'' can represent H, CH₃ or phenyl,

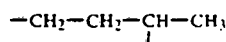
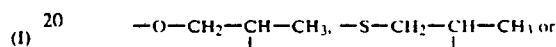
R''' can represent H or CH₃,

Y can represent O, CH₂, CH₂CH₂ or CH₂—O, it being possible for the CH₂—O group to be linked to the nitrogen either via O or via CH₂, and

Z can represent O or S, and

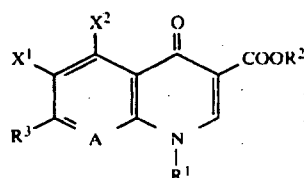
A represents N or C—R⁸, wherein

R⁸ represents H, halogen, methyl, cyano, nitro, hydroxyl or methoxy or, together with R¹, can form a bridge having the structure



and pharmaceutically usable hydrates and acid addition salts thereof and the alkali metal, alkaline earth metal, silver and guanidinium salts of the underlying carboxylic acids, have a high antibacterial action, in particular in the Gram-positive region.

Preferred compounds are those of the formula (I)



in which

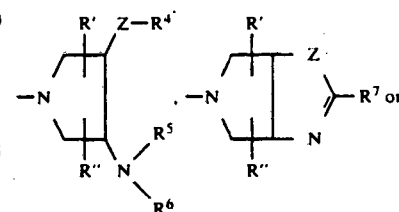
X¹ represents fluorine or chlorine,

X² represents hydrogen, amino, alkylamino having 1 or 2 carbon atoms, dimethylamino, hydroxyl, methoxy, mercapto, methylthio, phenylthio, fluorine or chlorine,

R¹ represents alkyl having 1 to 3 carbon atoms, alkyl having 2 or 3 carbon atoms, cycloalkyl having 3 to 5 carbon atoms, 2-hydroxyethyl, 2-fluoroethyl, methoxy, amino, methylamino, ethylamino, dimethylamino or phenyl which is optionally substituted by 1 or 2 fluorine atoms,

R² represents hydrogen, alkyl having 1 to 3 carbon atoms or (5-methyl-2-oxo-1,3-dioxol-4-yl)-methyl,

R³ represents a radical having the structure



wounds, infections in the oral region, infections following dental operations, osteomyelitis, septic arthritis, cholecystitis, peritonitis with appendicitis, cholangitis, intraabdominal abscesses, pancreatitis, sinusitis, mastoiditis, mastitis, tonsillitis, typhoid, meningitis and infections of the nervous system, salpingitis, endometritis, genital infections, pelveoperitonitis and eye infections.

As well as in humans, bacterial infections can also be treated in other species. Examples which may be mentioned are:

Pigs: colidiarrhoea, enterotoxaemia, sepsis, dysentery, salmonellosis, mastitis-metritis-agalactia syndrome and mastitis;

Ruminants (cattle, sheep and goats): diarrhoea, sepsis, bronchopneumonia, salmonellosis, pasteurellosis, mycoplasmosis and genital infections;

Horses: bronchopneumonias, joint ill, puerperal and postpuerperal infections and salmonellosis;

Dogs and cats: bronchopneumonia, diarrhoea, dermatitis, otitis, urinary tract infections and prostatitis;

Poultry (chickens, turkeys, quail pigeons, ornamental birds and others): mycoplasmosis, *E. coli* infections, chronic respiratory tract infections, salmonellosis, pasteurellosis and psittacosis.

Bacterial diseases in the rearing and keeping of stock and ornamental fishes can also be treated, the antibacterial spectrum extending beyond the abovementioned pathogens to further pathogens, such as, for example, *Pasteurella*, *Brucella*, *Campylobacter*, *Listeria*, *Erysipelothrix*, *Corynebacteria*, *Borrelia*, *Treponema*, *Nocardia*, *Rickettsia* and *Yersinia*.

The present invention includes pharmaceutical formulations which contain, in addition to non-toxic, inert pharmaceutically suitable excipients, one or more compounds according to the invention or consist of one or more active compounds according to the invention, and processes for the preparation of these formulations.

The present invention also includes pharmaceutical formulations in dosage units. This means that the formulations are present in the form of individual parts, for example tablets, coated tablets, capsules, pills, suppositories and ampoules, the active compound content of which corresponds to a fraction or a multiple of an individual dose. The dosage units can contain, for example, 1, 2, 3 or 4 individual doses or $\frac{1}{2}$, $\frac{1}{3}$ or $\frac{1}{4}$ of an individual dose. An individual dose preferably contains the amount of active compound which is administered in one application and which usually corresponds to a whole, one half, one third or a quarter of a daily dose.

Non-toxic inert pharmaceutically suitable excipients are to be understood as solid, semi-solid or liquid diluents, fillers and formulation auxiliaries of all types.

Preferred pharmaceutical formulations which may be mentioned are tablets, coated tablets, capsules, pills, granules, suppositories, solutions, suspensions and emulsions, pastes, ointments, gels, creams, lotions, dusting powders and sprays.

Tablets, coated tablets, capsules, pills and granules can contain the active compound or compounds in addition to the customary excipients, such as (a) fillers and extenders, for example starches, lactose, sucrose, glucose, mannitol and silicic acid, (b) binders, for example carboxymethylcellulose, alginates, gelatine and polyvinylpyrrolidone, (c) humectants, for example glycerol, (d) disintegrating agents, for example agar-agar, calcium carbonate and sodium carbonate, (e) solution retarders, for example paraffin, and (f) absorption accelerators, for example quaternary ammonium com-

pounds, (g) wetting agents, for example cetyl alcohol and glycerol monostearate, (h) adsorbents, for example kaolin and bentonite, and (i) lubricants, for example talc, calcium stearate, magnesium stearate and solid polyethylene glycols, or mixtures of the substances listed under (a) to (i).

The tablets, coated tablets, capsules, pills and granules can be provided with the customary coatings and shells, optionally containing opacifying agents, and can also be of a composition such that they release the active compound or compounds only or preferentially in a certain part of the intestinal tract, if appropriate in a delayed manner, examples of embedding compositions which can be used being polymeric substances and waxes.

If appropriate, the active compound or compounds can also be present in microencapsulated form with one or more of the abovementioned excipients.

Suppositories can contain, in addition to the active compound or compounds, the customary water-soluble or water-insoluble excipients, for example polyethylene glycols, fats, for example cacao fat, and higher esters (for example C_{14} -alcohol with C_{16} -fatty acid) or mixtures of these substances.

Ointments, pastes, creams and gels can contain, in addition to the active compound or compounds, the customary excipients, for example animal and vegetable fats, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures of these substances.

Dusting powders and sprays can contain, in addition to the active compound or compounds, the customary excipients, for example lactose, talc, silicic acid, aluminum hydroxide, calcium silicate and polyamide powder, or mixtures of these substances. Sprays can additionally contain the customary propellants, for example chlorofluorohydrocarbons.

Solutions and emulsions can contain, in addition to the active compound or compounds, the customary excipients, such as solvents, solubilizing agents and emulsifiers, for example water, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils, in particular cottonseed oil, groundnut oil, corn germ oil, olive oil, castor oil and sesame oil, glycerol, glycerol formal, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, or mixtures of these substances.

For parenteral administration, the solutions and emulsions can also be in a sterile form which is isotonic with blood.

Suspensions can contain, in addition to the active compound or compounds, the customary excipients, such as liquid diluents, for example water, ethyl alcohol and propylene glycol, and suspending agents, for example ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, or mixtures of these substances.

The formulation forms mentioned can also contain colouring agents, preservatives and additives which improve the smell and taste, for example peppermint oil and eucalyptus oil, and sweeteners, for example saccharin.

The therapeutically active compounds should preferably be present in the abovementioned pharmaceutical formulations in a concentration of about 0.1 to 99.5,

preferably about 0.5 to 95% by weight of the total mixture.

The abovementioned pharmaceutical formulations can also contain other pharmaceutical active compounds in addition to the compounds according to the invention.

The abovementioned pharmaceutical formulations are prepared in the customary manner by known methods, for example by mixing the active compound or compounds with the excipient or excipients.

The formulations mentioned can be used on humans and animals either orally, rectally, parenterally (intravenously, intramuscularly or subcutaneously), intracisternally, intravaginally, intraperitoneally or locally (dusting powder, ointment, drops) and for the therapy of infections in hollow spaces and body cavities. Possible suitable formulations are injection solutions, solutions and suspensions for oral therapy and gels, infusion formulations, emulsions, ointments or drops. Ophthalmological and dermatological formulations, silver salts and other salts, eardrops, eye ointments, dusting powders or solutions can be used for local therapy. In the case of animals, intake can also be in suitable formulations via the feed or drinking water. Gels, powders, dusting powders, tablets, delayed release tablets, premixes, concentrates, granules, pellets, boli, capsules, aerosols, sprays and inhalants can furthermore be used on humans and animals. The compounds according to the invention can moreover be incorporated into other carrier materials, such as, for example, plastics (chains of plastic for local therapy), collagen or bone cement.

In general, it has proved advantageous both in human and in veterinary medicine to administer the active compound or compounds according to the invention in total amounts of about 0.5 to about 500, preferably 5 to 100 mg/kg of body weight every 24 hours, if appropriate in the form of several individual doses, to achieve the desired results. An individual dose preferably contains the active compound or compounds according to the invention in amounts of about 1 to about 80, in

particular 3 to 30 mg/kg of body weight. However, it may be necessary to deviate from the dosages mentioned, and in particular to do so as a function of the nature and body weight of the object to be treated, the nature and severity of the disease, the nature of the formulation and of the administration of the medication and the period or interval within which administration takes place.

Thus in some cases it can suffice to manage with less than the abovementioned amount of active compound, while in other cases the abovementioned amount of active compound must be exceeded. The particular optimum dosage and mode of administration required for the active compounds can easily be determined by any expert on the basis of his expert knowledge.

The new compounds can be administered in the customary concentrations and formulations together with the feed or with feed formulations or with the drinking water. Infection by Gram-negative or Gram-positive bacteria can in this way be prevented, alleviated and/or cured and promotion of growth and an improvement in feed utilization can in this way be achieved.

The minimum inhibitory concentrations (MIC) were determined by the series dilution method on Iso-Sensitest agar (Oxoid). For each test substance, a series of agar plates which contained concentrations of the active compound which decreased by a dilution factor of two each time was prepared. The agar plates were inoculated with a multipoint inoculator (Denley). Overnight cultures of the pathogens which had first been diluted so that each inoculation point contained about 10^4 colony-forming particles were used for the inoculation. The inoculated agar plates were incubated at 37° C. and the germ growth was read off after about 20 hours. The MIC value ($\mu\text{g/ml}$) indicates the lowest active compound concentration at which no germ growth was to be detected with the naked eye.

The MIC values of some of the compounds according to the invention are shown in comparison with ciprofloxacin in the following table.

MIC values (mg/l) determined by the agar dilution test (Denley multipoint inoculator; Iso-sensitest agar)								
Test strain	Example							
	1	2	3	4	5	8	9	10
<i>Escherichia coli</i> Neumann	≤ 0.015	≤ 0.015	≤ 0.015	≤ 0.015	≤ 0.015	≤ 0.015	0.25	0.125
<i>Proteus mirabilis</i> 8223	1	4	1	0.5	2	2	8	16
<i>Proteus vulgaris</i> 1017	≤ 0.015	0.125	≤ 0.015	≤ 0.015	0.03	0.06	0.5	1
<i>Morganella morganii</i> 932	≤ 0.015	0.03	0.03	≤ 0.015	≤ 0.015	0.06	0.5	0.5
<i>Providencia stuartii</i> 12052	1	4	2	0.5	4	4	32	64
<i>Staphylococcus aureus</i> FK								
422	0.06	0.125	0.06	≤ 0.015	0.125	0.03	0.06	0.125
1756	0.06	0.125	0.06	≤ 0.015	0.125	0.03	0.06	0.125
133	0.06	0.125	0.03	≤ 0.015	0.125	0.03	0.06	0.125
<i>Enterococcus faecalis</i>								
27101	0.125	—	0.125	0.06	0.25	0.125	0.25	2
9790	0.125	0.5	0.25	0.06	0.25	0.125	0.25	2
Test strain	Example						Ciprofloxacin	
	13	14	15	16	17	18		
<i>Escherichia coli</i> Neumann	0.06	0.06	≤ 0.015	0.06	0.125	0.03	≤ 0.015	
<i>Proteus mira-</i>	1	4	0.5	4	8	1	1	



US005607942A

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United States Patent [19]**Petersen et al.**[11] **Patent Number:** **5,607,942**[45] **Date of Patent:** **Mar. 4, 1997**

[54] **7-(1-PYRROLIDINYL)-3-QUINOLONE- AND -NAPHTHYRIDONE-CARBOXYLIC ACID DERIVATIVES AS ANTIBACTERIAL AGENTS AND FEED ADDITIVES**

[75] **Inventors:** Uwe Petersen, Leverkusen; Thomas Schenke, Bergisch-Gladbach; Andreas Krebs, Odenthal-Holz; Klaus Grohe; Michael Schriewer, both of Odenthal; Ingo Haller, Wuppertal; Karl G. Metzger, Wuppertal; Rainer Endermann, Wuppertal; Hans-Joachim Zeiler, Velbert, all of Germany

[73] **Assignee:** Bayer Aktiengesellschaft, Leverkusen, Germany

[21] **Appl. No.:** 406,448

[22] **Filed:** Mar. 20, 1995

Related U.S. Application Data

[62] Division of Ser. No. 737,631, Jul. 30, 1991, Pat. No. 5,416,096, which is a division of Ser. No. 580,906, Sep. 10, 1990, Pat. No. 5,059,597, which is a division of Ser. No. 375,434, Jun. 30, 1989, Pat. No. 4,990,517.

[30] **Foreign Application Priority Data**

Jul. 15, 1988 [DE] Germany 38 24 072.6
Mar. 1, 1989 [DE] Germany 39 06 365.8

[51] **Int. Cl.⁶** A61K 31/47; C07D 471/04

[52] **U.S. Cl.** 546/200; 546/113

[58] **Field of Search** 546/113; 514/300

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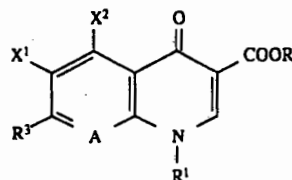
John M. Domagala, Quinolone activity and side-effect relationships, Journal of Antimicrobial Chemotherapy (1994) 33, 685-706.

(List continued on next page.)

Primary Examiner—Richard L. Raymond
Attorney, Agent, or Firm—Sprung Horn Kramer & Woods

[57] **ABSTRACT**

7-(1-Pyrrolidinyl)-3-quinolone- and -naphthyridone-carboxylic acid derivatives as antibacterial agents and feed additives, of the formula



in which

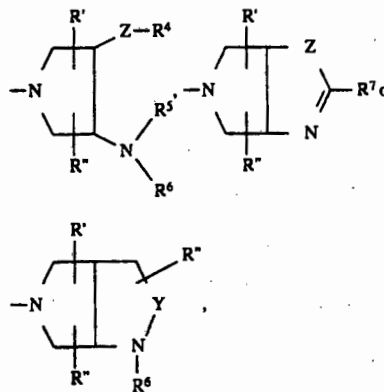
X¹ is halogen,

X² is hydrogen, halogen, amino or other radical,

R¹ is alkyl, cycloalkyl, optionally substituted phenyl or other radical,

R² is hydrogen, alkyl or a dioxolymethyl radical,

R³ is



and

A is N, CH, C-halogen, or the like, or forms a bridge with R¹, and addition products thereof.

8 Claims, No Drawings



US(00)5849752A

275
152

United States Patent [19]
Grunenberg et al.

[11] **Patent Number:** **5,849,752**
[45] **Date of Patent:** ***Dec. 15, 1998**

[54] **CRYSTAL MODIFICATION OF CDCH A
PROCESS FOR ITS PREPARATION AND
PHARMACEUTICAL FORMULATIONS
COMPRISING THIS MODIFICATION**

[75] **Inventors:** **Alfons Grunenberg**, Dormagen;
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[73] **Assignee:** **Bayer Aktiengesellschaft**, Leverkusen,
Germany

[*] **Notice:** This patent issued on a continued prosecution application filed under 37 CFR 1.53(d), and is subject to the twenty year patent term provisions of 35 U.S.C. 154(a)(2).

[21] **Appl. No.:** **760,543**

[22] **Filed:** **Dec. 5, 1996**

[30] **Foreign Application Priority Data**

Dec. 12, 1995 [DE] Germany 195 46 249.1

[51] **Int. Cl.** **A61K 31/47; C07D 47/04**

[52] **U.S. Cl.** **514/300; 546/113**

[58] **Field of Search** **514/300; 546/113**

[56] **References Cited**

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5,480,879 1/1996 Petersen et al.

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0 629 621 A1 12/1994 European Pat. Off.
0 643 058 A1 3/1995 European Pat. Off.

Primary Examiner—Patricia L. Morris

Attorney, Agent, or Firm—Sprung Kramer Schaefer &
Briscoe

[57] **ABSTRACT**

The invention relates to the new monohydrate of 1-cyclopropyl-7-([S,S]-2,8-diazabicyclo-[4:3:0]non-8-yl)-6-fluoro-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid hydrochloride (CDCH), a process for its preparation and pharmaceutical formulations which comprise this monohydrate as the active compound.

10 Claims, 8 Drawing Sheets

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CRYSTAL MODIFICATION OF CDCH A PROCESS FOR ITS PREPARATION AND PHARMACEUTICAL FORMULATIONS COMPRISING THIS MODIFICATION

BACKGROUND OF THE INVENTION

1. Field of the Invention

The invention relates to the new monohydrate of 1-cyclopropyl-7-([S,S]-2,8-diazabicyclo-[4.3.0]non-8-yl)-6-fluoro-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid hydrochloride (CDCH), a process for its preparation and pharmaceutical formulations which comprise this monohydrate as the active compound.

2. Description of Related Art

CDCH is a chemotherapeutic for humans and animals which has a broad spectrum of antibacterial action. The active compound can also be employed in the preservation of materials. CDCH shows a low toxicity and is particularly effective against Enterobacteriaceae, and especially against antibiotic resistant strains: *S. aureus*, *Ps. aeruginosa*, *Enterococcus faecalis* and *E. coli*. CDCH and its preparation as a betaine is described in EP-A-550 903 and EP-A-591 808.

An anhydrous form of CDCH is the only crystal modification known to date. However, this crystal modification is not entirely satisfactory in the preparation of various medicament forms. CDCH is hygroscopic and absorbs water under adverse storage conditions and during pharmaceutical processing of the active compound to medicament forms. This impairs the dosing accuracy and quality of the preparations. Subsequent changes in the crystal structure of the anhydrous form when CDCH is stored in aqueous suspensions or at ambient humidity are the reason for the physical instability of CDCH. It is therefore of great importance to use a crystal form which is as stable as possible for the preparation of medicament forms comprising CDCH.

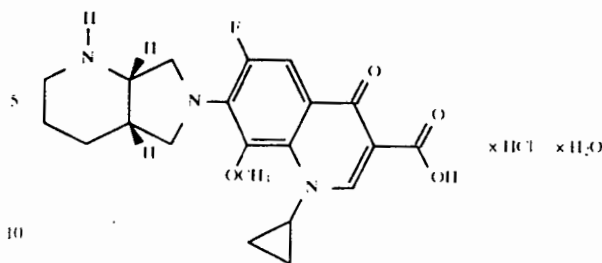
SUMMARY OF THE INVENTION

It has now been found that CDCH can be converted into a new water-containing crystalline modification which is distinguished by an increased stability, in particular during storage at high humidities, compared with the known anhydrous form and is particularly suitable for the preparation of stable pharmaceutical preparations.

During preparation of the monohydrate from aqueous media, the active compound crystallizes in the form of needles which become severely matted. Surprisingly, the crystal habit can be modified in a controlled manner under certain crystallization conditions. The prisms thus formed represent a preferred embodiment of the present invention, since they do not mat and are significantly more free-flowing than the monohydrate in the form of needles. This has considerable advantages in the preparation of medicament forms. By using a non-hygroscopic, free-flowing active compound, a satisfactory dosing accuracy is achieved during the preparation of medicaments, which increases safety and therefore minimizes the risk to the patient.

The invention accordingly relates to the new monohydrate of CDCH of the formula I

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and to a process for its preparation, which is characterized in that anhydrous, crystalline CDCH is treated with an amount of water sufficient for thorough mixing and for formation of the monohydrate at temperatures below 80° C. until the stoichiometric content of water of crystallization has been absorbed and conversion of the crystals is complete, and the crystals thus obtained are separated off and dried to the constant weight of the monohydrate in order to remove the adsorbed water present. To avoid the formation of the anhydrous form, the humidity during drying should be not less than 30% relative humidity. The monohydrate crystallizes in the form of needles from water-containing media with a water content of more than 10%.

BRIEF DESCRIPTION OF THE DRAWINGS

The invention will now be described in further detail with reference to the drawings, wherein:

FIG. 1 consists of two IR spectra, wherein FIG. 1A is the IR spectrum of CDCH anhydrous form, and FIG. 1B is the IR spectrum of CDCH monohydrate;

FIG. 2 consists of two graphs depicting thermogravimetric weight loss, wherein FIG. 2A shows the weight loss for CDCH anhydrous form, and FIG. 2B shows the weight loss for CDCH monohydrate;

FIG. 3 consists of two thermograms, wherein FIG. 3A is the thermogram for CDCH anhydrous form, and FIG. 3B is the thermogram for CDCH monohydrate;

FIG. 4 consists of two X-ray diffractograms, wherein FIG. 4A is the X-ray diffractogram for CDCH anhydrous form, and FIG. 4B is the X-ray diffractogram for CDCH monohydrate;

FIG. 5 consists of two ¹³C-NMR spectra, wherein FIG. 5A is the ¹³C-NMR spectra for CDCH anhydrous form, and FIG. 5B is the ¹³C-NMR spectra for CDCH monohydrate;

FIG. 6 consists of two Raman spectra, wherein FIG. 6A is the Raman spectra for CDCH anhydrous form, and FIG. 6B is the Raman spectra for CDCH monohydrate;

FIG. 7 consists of two FIR spectra, wherein FIG. 7A is the FIR spectra for CDCH anhydrous form, and FIG. 7B is the FIR spectra for CDCH monohydrate; and

FIG. 8 consists of four photographs of microscopic CDCH, wherein FIGS. 8A and 8B are photographs of CDCH needles, and FIGS. 8C and 8D are photographs of CDCH prisms.

DESCRIPTION OF PREFERRED EMBODIMENTS

The preferred monohydrate form which crystallizes as prisms can be obtained by suspending anhydrous crystalline CDCH in ethanol/water mixtures, especially preferably in ethanol/water with a maximum of 10% of water, thorough mixing of the solid contents with the amount of water added being ensured until the required content of water of crys-

tallization has been absorbed and conversion of the crystals is complete, for example by stirring the suspension or shaking, swirling, rotating the reaction vessel and the like. If the water content in the ethanol/water mixture is a maximum of 10%, the monohydrate crystallizes in the form of prisms.

Provided that the amount of water is sufficient for formation of a stoichiometric monohydrate and for thorough mixing of the amount of CDCH employed with the water, any desired amount of water can be used for formation of the monohydrate in the form of needles, since the absorption of water of crystallization, which proceeds with conversion of the crystals, ends with the formation of the monohydrate, and furthermore no further hydrates are obtained. The amount of water is expediently limited such that although thorough mixing can take place, no or low solubility losses occur. The preparation of the monohydrate is preferably carried out at room temperature, but can also be carried out at elevated temperature, for example 30° C. to 60° C., or a low temperature, for example 5° C. to 20° C. The preparation of the monohydrate from the anhydrous form also takes place successfully at humidities greater than 30% relative humidity. However, this process is not suitable for the preparation of the preferred monohydrate which crystallizes as prisms.

The crystals of the monohydrate are separated off from the excess solvent by customary methods, for example by filtering, decanting, centrifuging and the like. The crystals of the monohydrate which have been separated off are advantageously dried at room temperature or at elevated temperature up to 50° C. at humidities of at least 30% relative humidity.

The CDCH monohydrate according to the invention has a characteristic IR spectrum (FIG. 1), which shows characteristic absorption bands of the water of crystallization in the region of the OH valency vibrations (3600–3100 cm⁻¹), which are absent in the anhydrous crystal modification. It also differs from the anhydrous CDCH in other frequency ranges, so that a completely different arrangement of the molecules in the crystal lattices of the two modifications can be concluded.

The determination of the water content confirms the presence of a stoichiometric monohydrate of CDCH. The thermogravimetric weight loss determined in several samples of the monohydrate is 1 mol of water (3.9%, FIG. 2). The thermogram of the monohydrate (FIG. 3) recorded by means of DSC (Differential Scanning Calorimetry) under atmospheric pressure shows, in agreement with the thermogravimetric measurements, the release of water by a broad endothermal peak which indicates the rearrangement of the crystal lattice of the monohydrate analysed, the dissociation of CDCH and water and the enthalpy of vaporization of the liberated water of crystallization. The X-ray diffractograms and ¹³C-NMR, Raman and FIR spectra of the anhydrous form and of the monohydrate show characteristic differences (FIGS. 4–7, Tables 2–5): thus, for example, the ¹³C-NMR spectrum has a characteristic peak at 168.1 ppm and the X-ray diffractogram a line at 2θ=26.7.

The DSC and TGA thermograms were obtained using thermoanalysers (DSC 7 and TGA 7) from Perkin-Elmer. The X-ray diffractograms were recorded with a Stoe transmission diffractometer. The IR, FIR and Raman spectra were recorded with Fourier-IR spectrometers IFS 66 (IR), IFS 66v (FIR) and IFS 88 (Raman) from Bruker. The ¹³C-solid-NMR spectra were recorded with a Bruker MSI 300. The microscopic photographs were taken with a Laborlux S microscope from Leitz.

During storage, the CDCH monohydrate according to the invention shows a higher physical stability compared with the anhydrous crystal modification, and is therefore more suitable for the preparation of various medicament forms. The preferred monohydrate, which crystallizes in the form of prisms, furthermore imparts to CDCH excellent trickling and flow properties, which is of great advantage in the preparation of pharmaceutical formulations (FIG. 8). The invention therefore also relates to liquid and solid pharmaceutical formulations which comprise the CDCH monohydrate according to the invention, such as, for example, suspensions, emulsions, tablets, coated tablets, coated tablet cores, suppositories, hard or soft gelatin capsules and the like. Aqueous suspensions and tablets for oral administration preferably comprise the monohydrate according to the invention, particularly preferably in the prismatic crystal form.

CDCH can be present in these pharmaceutical formulations as the only active compound or can be combined with other antibacterially active substances.

Pharmaceutical formulations can comprise the CDCH monohydrate according to the invention by itself or in combination with several other active compounds, or be formulated together with auxiliaries and additives usually employed in pharmacy, such as tablet binders, fillers, preservatives, tablet disintegrating agents, flow regulating agents, plasticizers, wetting agents, dispersing agents, emulsifiers, solvents, flavourings and the like, to give presentation forms for oral, parenteral or rectal administration.

The pharmaceutical formulations are prepared in a manner known per se, for example by mixing, stirring, suspending, dispersing, emulsifying, and the like, the active compounds with or in the pharmaceutical auxiliaries and processing the components to pharmaceutically suitable presentation forms for oral, parenteral or rectal administration.

PREPARATION OF CRYSTALLINE CDCH (NEEDLES, PRISMS)

Example 1 (Prisms)

1 g of anhydrous CDCH is dissolved in 150 ml of absolute ethanol and the solution is filtered. The solution is heat treated at 60° C. until the solvent has evaporated completely. The crystals which have precipitated out are dried at room temperature/ambient humidity.

Example 2 (Prisms)

0.1 g of anhydrous CDCH is dissolved in 10 ml of ethanol (10% water content). The solution is heat treated at 60° C. until the solvent has evaporated completely. The crystals which have precipitated out are dried at room temperature/ambient humidity.

Example 3 (Prisms)

4 g of anhydrous CDCH are dissolved in 300 ml of ethanol (96%). The solvent is distilled off in a rotary evaporator at 60° C. under 120 mbar. The crystals are dried in a vacuum drying cabinet under 80 mbar at 105° C. for 2 hours and then exposed to ambient humidity.

Example 4 (Needles)

0.3 g of anhydrous CDCH is dissolved in 6 ml of water:ethanol (1:1). The solution is heat treated at 70° C. until the solvent has evaporated completely. The crystals

217 154

218 155

1: Clin Ther. 1999 Mar;21(3):513-22.

Related Articles, Links

[FULL-TEXT ARTICLE](#)**Absolute bioavailability of moxifloxacin.****Ballow C, Lettieri J, Agarwal V, Liu P, Stass H, Sullivan JT.**

State University of New York at Buffalo School of Pharmacy, USA.

Moxifloxacin (BAY 12-8039) is an investigational 8-methoxy-fluoroquinolone with broad-spectrum gram-positive and gram-negative activity. To determine the absolute bioavailability of moxifloxacin, this open-label, randomized, crossover study compared the pharmacokinetic characteristics of a single 100-mg dose administered either orally or intravenously as a 60-minute infusion in 10 healthy male volunteers (mean age [$\pm$ SD], 29.3 $\pm$ 7.1 years; mean weight [$\pm$ SD], 77.7 $\pm$ 8.7 kg). Geometric mean values for oral/IV moxifloxacin were as follows: peak serum concentration, 1.15/1.34 mg/L, and area under the concentration-time curve over 48 hours, 9.86/10.89 mg $\times$ h/L. The geometric mean absolute bioavailability of oral moxifloxacin was 91.8%. Mean renal clearance was approximately 2.3 L/h after administration of both the single oral and IV formulations, which suggests lack of active tubular secretion of moxifloxacin. Both the oral and IV formulations were well tolerated, with 5 reported possible or probable drug-related adverse events; they included headache, nausea, and localized urticaria. In summary, a single oral dose of moxifloxacin was extensively absorbed in healthy young men. Further studies are necessary in actual patients to confirm the viability of IV to oral conversion at the same dose of moxifloxacin.

Publication Types:

- Clinical Trial
- Randomized Controlled Trial

PMID: 10321420 [PubMed - indexed for MEDLINE]

United States Patent [19]

Petersen et al.

[11] Patent Number: 4,990,517

[45] Date of Patent: Feb. 5, 1991

[54] 7-(1-PYRROLIDINYL)-3-QUINOLONE- AND -NAPHTHYRIDONECARBOXYLIC ACID DERIVATIVES AS ANTIBACTERIAL AGENTS AND FEED ADDITIVES

[75] Inventors: Uwe Petersen, Leverkusen; Thomas Schenke, Bergisch-Gladbach; Andreas Krebs, Odenthal-Holz; Klaus Grohe; Michael Schriewer, both of Odenthal; Ingo Haller, Wuppertal; Karl G. Metzger, Wuppertal; Rainer Endermann, Wuppertal; Hans-Joachim Zeiler, Velbert, all of Fed. Rep. of Germany

[73] Assignee: Bayer Aktiengesellschaft, Leverkusen, Fed. Rep. of Germany

[21] Appl. No.: 375,434

[22] Filed: Jun. 30, 1989

[30] Foreign Application Priority Data

Jul. 15, 1988 [DE] Fed. Rep. of Germany 3824072

Mar. 1, 1989 [DE] Fed. Rep. of Germany 3906365

[51] Int. Cl.⁵ A61K 31/44; A61K 31/47; C07D 471/04; C07D 215/56

[52] U.S. Cl. 514/300; 514/224.5; 514/230.2; 514/230.5; 514/312; 544/32; 544/63; 544/91; 544/101; 546/100; 546/113; 546/123; 546/156

[58] Field of Search 544/32, 101, 63, 91; 546/100, 113, 123, 156; 514/224.5, 230.2, 230.5, 300, 312

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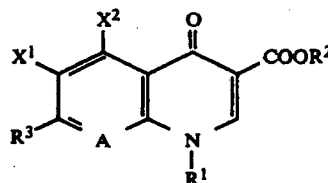
Primary Examiner—Mary C. Lee

Assistant Examiner—Bernard I. Dentz

Attorney, Agent, or Firm—Sprung Horn Kramer & Woods

[57] ABSTRACT

7-(1-Pyrrolidinyl)-3-quinolone- and -naphthyridonecarboxylic acid derivatives as antibacterial agents and feed additives, of the formula



in which

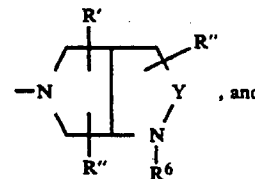
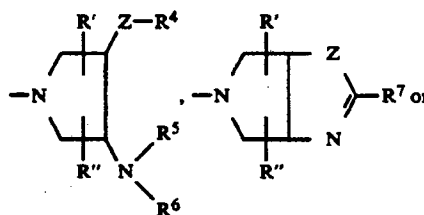
X¹ is halogen,

X² is hydrogen, halogen, amino or other radical,

R¹ is alkyl, cycloalkyl, optionally substituted phenyl or other radical,

R² is hydrogen, alkyl or a dioxolymethyl radical,

R³ is



A is N, CH, C-halogen, or the like, or forms a bridge with R¹,

and addition products thereof.

14 Claims, No Drawings

wounds, infections in the oral region, infections following dental operations, osteomyelitis, septic arthritis, cholecystitis, peritonitis with appendicitis, cholangitis, intraabdominal abscesses, pancreatitis, sinusitis, mastoiditis, mastitis, tonsillitis, typhoid, meningitis and infections of the nervous system, salpingitis, endometritis, genital infections, pelveoperitonitis and eye infections.

As well as in humans, bacterial infections can also be treated in other species. Examples which may be mentioned are:

Pigs: colidiarrhoea, enterotoxaemia, sepsis, dysentery, salmonellosis, mastitis-metritis-agalactia syndrome and mastitis;

Ruminants (cattle, sheep and goats): diarrhoea, sepsis, bronchopneumonia, salmonellosis, pasteurellosis, mycoplasmosis and genital infections;

Horses: bronchopneumonias, joint ill, puerperal and postpuerperal infections and salmonellosis;

Dogs and cats: bronchopneumonia, diarrhoea, dermatitis, otitis, urinary tract infections and prostatitis;

Poultry (chickens, turkeys, quail pigeons, ornamental birds and others): mycoplasmosis, *E. coli* infections, chronic respiratory tract infections, salmonellosis, pasteurellosis and psittacosis.

Bacterial diseases in the rearing and keeping of stock and ornamental fishes can also be treated, the antibacterial spectrum extending beyond the abovementioned pathogens to further pathogens, such as, for example, *Pasteurella*, *Brucella*, *Campylobacter*, *Listeria*, *Erysipelothrix*, *Corynebacteria*, *Borrelia*, *Treponema*, *Nocardia*, *Rickettsia* and *Yersinia*.

The present invention includes pharmaceutical formulations which contain, in addition to non-toxic, inert pharmaceutically suitable excipients, one or more compounds according to the invention or consist of one or more active compounds according to the invention, and processes for the preparation of these formulations.

The present invention also includes pharmaceutical formulations in dosage units. This means that the formulations are present in the form of individual parts, for example tablets, coated tablets, capsules, pills, suppositories and ampoules, the active compound content of which corresponds to a fraction or a multiple of an individual dose. The dosage units can contain, for example, 1, 2, 3 or 4 individual doses or $\frac{1}{2}$, $\frac{1}{3}$ or $\frac{1}{4}$ of an individual dose. An individual dose preferably contains the amount of active compound which is administered in one application and which usually corresponds to a whole, one half, one third or a quarter of a daily dose.

Non-toxic inert pharmaceutically suitable excipients are to be understood as solid, semi-solid or liquid diluents, fillers and formulation auxiliaries of all types.

Preferred pharmaceutical formulations which may be mentioned are tablets, coated tablets, capsules, pills, granules, suppositories, solutions, suspensions and emulsions, pastes, ointments, gels, creams, lotions, dusting powders and sprays.

Tablets, coated tablets, capsules, pills and granules can contain the active compound or compounds in addition to the customary excipients, such as (a) fillers and extenders, for example starches, lactose, sucrose, glucose, mannitol and silicic acid, (b) binders, for example carboxymethylcellulose, alginates, gelatine and polyvinylpyrrolidone, (c) humectants, for example glycerol, (d) disintegrating agents, for example agar-agar, calcium carbonate and sodium carbonate, (e) solution retarders, for example paraffin, and (f) absorption accelerators, for example quaternary ammonium com-

pounds, (g) wetting agents, for example cetyl alcohol and glycerol monostearate, (h) adsorbents, for example kaolin and bentonite, and (i) lubricants, for example talc, calcium stearate, magnesium stearate and solid polyethylene glycols, or mixtures of the substances listed under (a) to (i).

The tablets, coated tablets, capsules, pills and granules can be provided with the customary coatings and shells, optionally containing opacifying agents, and can also be of a composition such that they release the active compound or compounds only or preferentially in a certain part of the intestinal tract, if appropriate in a delayed manner, examples of embedding compositions which can be used being polymeric substances and waxes.

If appropriate, the active compound or compounds can also be present in microencapsulated form with one or more of the abovementioned excipients.

Suppositories can contain, in addition to the active compound or compounds, the customary water-soluble or water-insoluble excipients, for example polyethylene glycols, fats, for example cacao fat, and higher esters (for example C_{14} -alcohol with C_{16} -fatty acid) or mixtures of these substances.

Ointments, pastes, creams and gels can contain, in addition to the active compound or compounds, the customary excipients, for example animal and vegetable fats, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures of these substances.

Dusting powders and sprays can contain, in addition to the active compound or compounds, the customary excipients, for example lactose, talc, silicic acid, aluminum hydroxide, calcium silicate and polyamide powder, or mixtures of these substances. Sprays can additionally contain the customary propellants, for example chlorofluorohydrocarbons.

Solutions and emulsions can contain, in addition to the active compound or compounds, the customary excipients, such as solvents, solubilizing agents and emulsifiers, for example water, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils, in particular cottonseed oil, groundnut oil, corn germ oil, olive oil, castor oil and sesame oil, glycerol, glycerol formal, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, or mixtures of these substances.

For parenteral administration, the solutions and emulsions can also be in a sterile form which is isotonic with blood.

Suspensions can contain, in addition to the active compound or compounds, the customary excipients, such as liquid diluents, for example water, ethyl alcohol and propylene glycol, and suspending agents, for example ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, or mixtures of these substances.

The formulation forms mentioned can also contain colouring agents, preservatives and additives which improve the smell and taste, for example peppermint oil and eucalyptus oil, and sweeteners, for example saccharin.

The therapeutically active compounds should preferably be present in the abovementioned pharmaceutical formulations in a concentration of about 0.1 to 99.5,

220 15X

preferably about 0.5 to 95% by weight of the total mixture.

The abovementioned pharmaceutical formulations can also contain other pharmaceutical active compounds in addition to the compounds according to the invention.

The abovementioned pharmaceutical formulations are prepared in the customary manner by known methods, for example by mixing the active compound or compounds with the excipient or excipients.

The formulations mentioned can be used on humans and animals either orally, rectally, parenterally (intravenously, intramuscularly or subcutaneously), intracisterially, intravaginally, intraperitoneally or locally (dusting powder, ointment, drops) and for the therapy of infections in hollow spaces and body cavities. Possible suitable formulations are injection solutions, solutions and suspensions for oral therapy and gels, infusion formulations, emulsions, ointments or drops. Ophthalmological and dermatological formulations, silver salts and other salts, eardrops, eye ointments, dusting powders or solutions can be used for local therapy. In the case of animals, intake can also be in suitable formulations via the feed or drinking water. Gels, powders, dusting powders, tablets, delayed release tablets, premixes, concentrates, granules, pellets, boli, capsules, aerosols, sprays and inhalants can furthermore be used on humans and animals. The compounds according to the invention can moreover be incorporated into other carrier materials, such as, for example, plastics (chains of plastic for local therapy), collagen or bone cement.

In general, it has proved advantageous both in human and in veterinary medicine to administer the active compound or compounds according to the invention in total amounts of about 0.5 to about 500, preferably 5 to 100 mg/kg of body weight every 24 hours, if appropriate in the form of several individual doses, to achieve the desired results. An individual dose preferably contains the active compound or compounds according to the invention in amounts of about 1 to about 80, in

particular 3 to 30 mg/kg of body weight. However, it may be necessary to deviate from the dosages mentioned, and in particular to do so as a function of the nature and body weight of the object to be treated, the nature and severity of the disease, the nature of the formulation and of the administration of the medication and the period or interval within which administration takes place.

Thus in some cases it can suffice to manage with less than the abovementioned amount of active compound, while in other cases the abovementioned amount of active compound must be exceeded. The particular optimum dosage and mode of administration required for the active compounds can easily be determined by any expert on the basis of his expert knowledge.

The new compounds can be administered in the customary concentrations and formulations together with the feed or with feed formulations or with the drinking water. Infection by Gram-negative or Gram-positive bacteria can in this way be prevented, alleviated and/or cured and promotion of growth and an improvement in feed utilization can in this way be achieved.

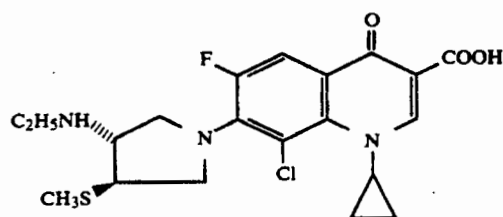
The minimum inhibitory concentrations (MIC) were determined by the series dilution method on Iso-Sensitest agar (Oxoid). For each test substance, a series of agar plates which contained concentrations of the active compound which decreased by a dilution factor of two each time was prepared. The agar plates were inoculated with a multipoint inoculator (Denley). Overnight cultures of the pathogens which had first been diluted so that each inoculation point contained about 10^4 colony-forming particles were used for the inoculation. The inoculated agar plates were incubated at 37° C. and the germ growth was read off after about 20 hours. The MIC value ($\mu\text{g/ml}$) indicates the lowest active compound concentration at which no germ growth was to be detected with the naked eye.

The MIC values of some of the compounds according to the invention are shown in comparison with ciprofloxacin in the following table.

MIC values (mg/l) determined by the agar dilution test (Denley multipoint inoculator: Iso-sensitest agar)								
Test strain	Example							
	1	2	3	4	5	8	9	10
<i>Escherichia coli</i> Neumann	≤ 0.015	≤ 0.015	≤ 0.015	≤ 0.015	≤ 0.015	≤ 0.015	0.25	0.125
<i>Proteus mirabilis</i> 8223	1	4	1	0.5	2	2	8	16
<i>Proteus vulgaris</i> 1017	≤ 0.015	0.125	≤ 0.015	≤ 0.015	0.03	0.06	0.5	1
<i>Morganella morganii</i> 932	≤ 0.015	0.03	0.03	≤ 0.015	≤ 0.015	0.06	0.5	0.5
<i>Providencia stuarti</i> 12052	1	4	2	0.5	4	4	32	64
<i>Staphylococcus aureus</i> FK								
422	0.06	0.125	0.06	≤ 0.015	0.125	0.03	0.06	0.125
1756	0.06	0.125	0.06	≤ 0.015	0.125	0.03	0.06	0.125
133	0.06	0.125	0.03	≤ 0.015	0.125	0.03	0.06	0.125
<i>Enterococcus faecalis</i>								
27101	0.125	—	0.125	0.06	0.25	0.125	0.25	2
9790	0.125	0.5	0.25	0.06	0.25	0.125	0.25	2
Test strain	Example						Ciprofloxacin	
	13	14	15	16	17	18		
<i>Escherichia coli</i> Neumann	0.06	0.06	≤ 0.015	0.06	0.125	0.03	≤ 0.015	
<i>Proteus mira-</i>	1	4	0.5	4	8	1	1	

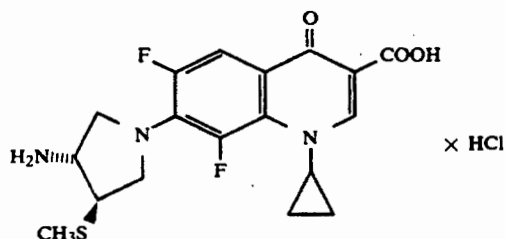
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EXAMPLE 55



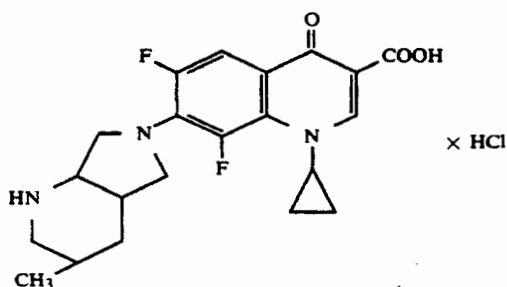
The reaction is carried out analogously to Example 13 with trans-3-ethylamino-4-methylthio-pyrrolidine and 8-chloro-1-cyclopropyl-6,7-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid to give 8-chloro-1-cyclopropyl-3-ethylamino-4-methylthio-1-pyrrolidinyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid, melting point: 217°-218° C. (with decomposition).

EXAMPLE 56



7-(trans-3-amino-4-methylthio-1-pyrrolidinyl)-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid, melting point: 208°-211° C. (with decomposition) and 7-(trans-3-amino-4-methylthio-1-pyrrolidinyl)-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid hydrochloride, melting point: 255°-257° C. (with decomposition), are obtained with trans-3-amino-4-methylthio-pyrrolidine analogously to Examples 13 and 15.

EXAMPLE 57



1-Cyclopropyl-6,8-difluoro-1,4-dihydro-7-(4-methyl-2,8-diazabicyclo[4.3.0]non-8-yl)-4-oxo-3-quinolinecarboxylic acid, melting point 213°-215° C. (with decomposition) (recrystallized from glycol monomethyl ether), 60 and 1-cyclopropyl-6,8-difluoro-1,4-dihydro-7-(4-methyl-2,8-diazabicyclo[4.3.0]non-8-yl)-4-oxo-3-quinolinecarboxylic acid hydrochloride, melting point 204°-212° C. (with decomposition) are obtained with 4-methyl-2,8-diazabicyclo[4.3.0]nonane analogously to Examples 13 and 15.

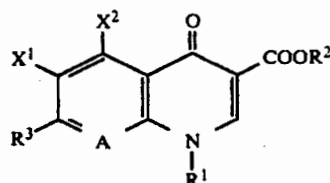
The product consists of a mixture of two stereoisomers.

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It is understood that the specification and examples are illustrative but not limitative of the present invention and that other embodiments within the spirit and scope of the invention will suggest themselves to those skilled in the art.

What is claimed is:

1. A 7-(pyrrolidinyl)-3-quinolone- or -naphthyridonecarboxylic acid derivative of the formula



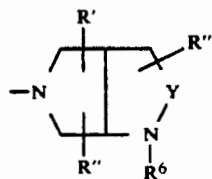
in which

X¹ represents halogen,

X² represents hydrogen, amino, alkylamino having 1 to 4 carbon atoms, dialkylamino having 1 to 3 carbon atoms per alkyl group, hydroxyl, alkoxy having 1 to 4 carbon atoms, mercapto, alkylthio having 1 to 4 carbon atoms, arylthio or halogen,

R¹ represents alkyl having 1 to 4 carbon atoms, alk- enyl having 2 to 4 carbon atoms, cycloalkyl having 3 to 6 carbon atoms, 2-hydroxyethyl, 2-fluoroethyl, methoxy amino, methylamino, ethylamino, dimethylamino or phenyl which is optionally substituted by 1 or 2 fluorine atoms,

R² represents hydrogen, alkyl having 1 to 4 carbon atoms or (5-methyl-2-oxo-1,3-dioxol-4-yl)-methyl, R³ represents a radical of the structure



wherein

R⁶ represents H, optionally hydroxyl-substituted C₁-C₄-alkyl, as well as phenyl, benzyl, C₁-C₄-alkoxycarbonyl, C₁-C₄-acyl, (5-methyl-2-oxo-1,3-dioxol-4-yl)-methyl, or C₃-C₈-cycloalkyl,

R' represents H, CH₃ or phenyl,

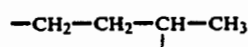
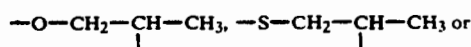
R'' represents H, CH₃ or phenyl,

R''' represents H or CH₃,

Y represents O, CH₂, CH₂CH₂ or CH₂-O, it being possible for the CH₂-O group to be linked to the nitrogen either via O or via CH₂, and

A represents N or C-R⁸, wherein

R⁸ represents H, halogen, methyl, cyano, nitro, hydroxyl or methoxy or, together with R¹, forms a bridge having the structure



or an addition product thereof with water, an acid or an alkali.

2. A compound or addition product thereof according to claim 1, in which

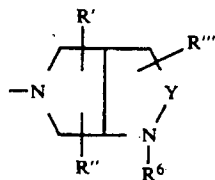
X¹ represents fluorine or chlorine,

X² represents hydrogen, amino, alkylamino having 1 or 2 carbon atoms, dimethylamino, hydroxyl, methoxy, mercapto, methylthio, phenylthio, fluorine or chlorine,

R¹ represents alkyl having 1 to 3 carbon atoms, alkenyl having 2 or 3 carbon atoms, cycloalkyl having 3 to 5 carbon atoms, 2-hydroxyethyl, 2-fluoroethyl, methoxy, amino, methylamino, ethylamino, dimethylamino or phenyl which is optionally substituted by 1 or 2 fluorine atoms,

R² represents hydrogen, alkyl having 1 to 3 carbon atoms or (5-methyl-2-oxo-1,3-dioxol-4-yl)-methyl,

R³ represents a radical having the structure



wherein

R⁶ represents H, optionally hydroxyl-substituted C₁-C₃-alkyl, as well as phenyl, benzyl, C₁-C₄-alkoxycarbonyl, C₁-C₂-acyl, (5-methyl-2-oxo-1,3-dioxol-4-yl)-methyl, or C₃-C₅-cycloalkyl,

R' represents H or CH₃,

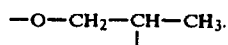
R'' represents H or CH₃,

R''' represents H or CH₃,

Y represents O, CH₂, CH₂CH₂ or CH₂-O, it being possible for the CH₂-O group to be linked to the nitrogen either via O or via CH₂, and

A represents N or C-R⁸, wherein

R⁸ represents H, fluorine, chlorine, bromine, methyl, nitro, hydroxyl or methoxy or together with R¹ forms a bridge having the structure



3. A compound or addition product thereof according to claim 1, in which

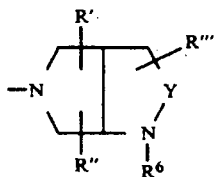
X¹ represents fluorine,

X² represents hydrogen, amino, methylamino or fluorine,

R¹ represents alkyl having 1 or 2 carbon atoms, vinyl, cyclopropyl, 2-hydroxyethyl, 2-fluoroethyl, methoxy, methylamino, 4-fluorophenyl or 2,4-difluorophenyl,

R² represents hydrogen or alkyl having 1 or 2 carbon atoms,

R³ represents a radical having the structure



wherein

R⁶ represents H, CH₃, C₂H₅, HOCH₂CH₂, benzyl, C₁-C₄-alkoxycarbonyl or C₁-C₂-acyl,

R' represents H or CH₃,

R'' represents H or CH₃,

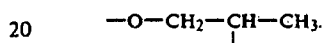
R''' represents H or CH₃,

Y represents O, CH₂, CH₂CH₂ or CH₂-O, it being possible for the CH₂-O group to be linked to the nitrogen either via O or via CH₂, and

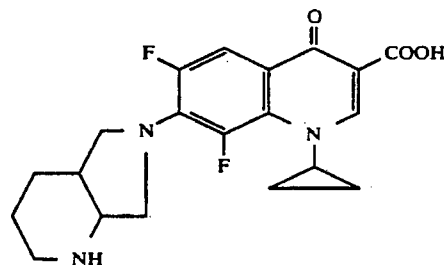
Z represents O or S, and

A represents N or C-Rhu 8, wherein

R: represents H, fluorine or chlorine, or together with R¹ also can form a bridge having the structure

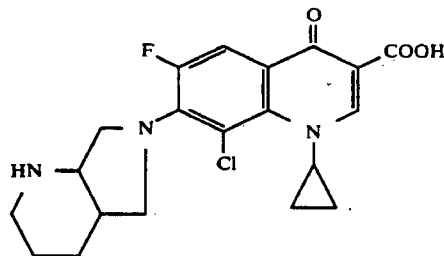


4. A compound according to claim 1, wherein such compound is 1-cyclopropyl-7-(2,8-diazabicyclo[4.3.0]non-8-yl)-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid of the formula



or an addition product thereof with water, an acid or an alkali.

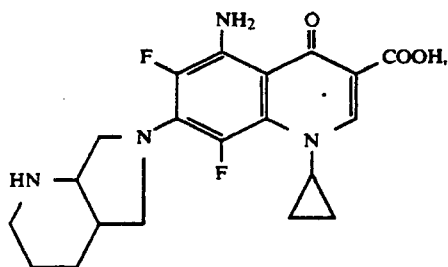
5. A compound according to claim 1, wherein such compound is 8-chloro-1-cyclopropyl-7-(2,8-diazabicyclo[4.3.0]non-8-yl)-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid of the formula



or an addition product thereof with water, an acid or an alkali.

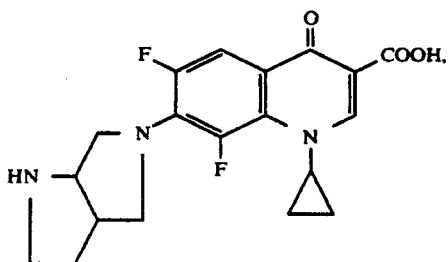
6. A compound according to claim 1, wherein such compound is 5-amino-1-cyclopropyl-7-(2,8-diazabicyclo[4.3.0]non-8-yl)-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid of the formula

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or an addition product thereof with water, an acid or an alkali.

7. A compound according to claim 1, wherein such compound is 1-cyclopropyl-7-(2,7-diazabicyclo[3.3.0]oct-7-yl)-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid of the formula



or an addition product thereof with water, an acid or an alkali.

8. An antibacterial composition comprising an antibacterially effective amount of a compound or addition product thereof according to claim 1 and a diluent.

9. A composition according to claim 8 in the form of a tablet, capsule or ampule.

10. A composition according to claim 8, wherein the diluent comprises an animal feed stock.

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11. A method of combating bacteria in a patient in need thereof which comprises administering to such patient an antibacterially effective amount of a compound or addition product thereof according to claim 1.

12. A method of promoting the growth of an animal which comprises administering to said animal a growth promoting effective amount of a compound or addition product thereof according to claim 1.

13. The method according to claim 11, wherein such compound is

1-cyclopropyl-7-(2,8-diazabicyclo[4.3.0]non-8-yl)-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid,

8-chloro-1-cyclopropyl-3-(2,8-diazabicyclo[4.3.0]non-8-yl)-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid,

5-amino-1-cyclopropyl-7-(2,8-diazabicyclo[4.3.0]non-8-yl)-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid, or

1-cyclopropyl-7-(2,7-diazabicyclo[3.3.0]oct-7-yl)-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid

or an addition product thereof with water, an acid or an alkali.

14. The method according to claim 12, wherein such compound is

1-cyclopropyl-7-(2,8-diazabicyclo[4.3.0]non-8-yl)-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid,

8-chloro-1-cyclopropyl-3-(2,8-diazabicyclo[4.3.0]non-8-yl)-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid,

5-amino-1-cyclopropyl-7-(2,8-diazabicyclo[4.3.0]non-8-yl)-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid or

1-cyclopropyl-7-(2,7-diazabicyclo[3.3.0]oct-7-yl)-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid

or an addition product thereof with water, an acid or an alkali.

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[54] **7-(1-PYRROLIDINYL)-3-QUINOLONE- AND -NAPHTHYRIDONE-CARBOXYLIC ACID DERIVATIVES AS ANTIBACTERIAL AGENTS AND FEED ADDITIVES**

John M. Domagala, Quinolone activity and side-effect relationships, *Journal of Antimicrobial Chemotherapy* (1994) 33, 685-706.

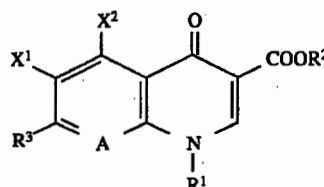
(List continued on next page.)

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Primary Examiner—Richard L. Raymond
Attorney, Agent, or Firm—Sprung Horn Kramer & Woods

[57] **ABSTRACT**

7-(1-Pyrrolidiny)-3-quinolone- and -naphthyridone-carboxylic acid derivatives as antibacterial agents and feed additives, of the formula



in which

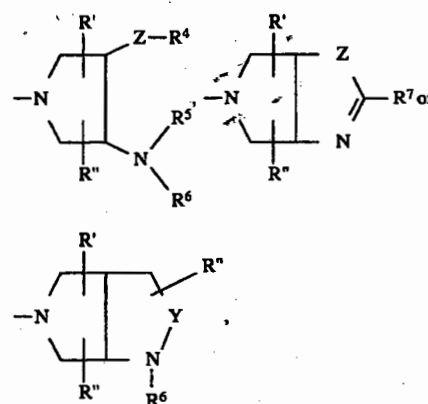
X¹ is halogen,

X² is hydrogen, halogen, amino or other radical,

R¹ is alkyl, cycloalkyl, optionally substituted phenyl or other radical,

R² is hydrogen, alkyl or a dioxolymethyl radical,

R³ is



and

A is N, CH, C-halogen, or the like, or forms a bridge with R¹, and addition products thereof.

8 Claims, No Drawings

[73] **Assignee:** Bayer Aktiengesellschaft, Leverkusen, Germany

[21] **Appl. No.:** 406,448

[22] **Filed:** Mar. 20, 1995

Related U.S. Application Data

[62] Division of Ser. No. 737,631, Jul. 30, 1991, Pat. No. 5,416,096, which is a division of Ser. No. 580,906, Sep. 10, 1990, Pat. No. 5,059,597, which is a division of Ser. No. 375,434, Jun. 30, 1989, Pat. No. 4,990,517.

[30] **Foreign Application Priority Data**

Jul. 15, 1988 [DE] Germany 38 24 072.6
 Mar. 1, 1989 [DE] Germany 39 06 365.8

[51] **Int. Cl.⁶** A61K 31/47; C07D 471/04
 [52] **U.S. Cl.** 546/200; 546/113
 [58] **Field of Search** 546/113; 514/300

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 Sparfloxacin Monograph Adis, 35-39 (1994).
 James H. Paton et al, Clinical Features and Management of Adverse Effects of Quinolone Antibacterials, *Drug Safety*, 6 1991, pp. 9-27.

Preferred pharmaceutical formulations which may be mentioned are tablets, coated tablets, capsules, pills, granules, suppositories, solutions, suspensions and emulsions, pastes, ointments, gels, creams, lotions, dusting powders and sprays.

Tablets, coated tablets, capsules, pills and granules can contain the active compound or compounds in addition to the customary excipients, such as (a) fillers and extenders, for example starches, lactose, sucrose, glucose, mannitol and silicic acid, (b) binders, for example carboxymethylcellulose, alginates, gelatine and polyvinylpyrrolidone, (c) humectants, for example glycerol, (d) disintegrating agents, for example agar-agar, calcium carbonate and sodium carbonate, (e) solution retarders, for example paraffin, and (f) absorption accelerators, for example quaternary ammonium compounds, (g) wetting agents, for example cetyl alcohol and glycerol monostearate, (h) adsorbents, for example kaolin and bentonite, and (i) lubricants, for example talc, calcium stearate, magnesium stearate and solid polyethylene glycols, or mixtures of the substances listed under (a) to (i),

The tablets, coated tablets, capsules, pills and granules can be provided with the customary coatings and shells, optionally containing opacifying agents, and can also be of a composition such that they release the active compound or compounds only or preferentially in a certain part of the intestinal tract, if appropriate in a delayed manner, examples of embedding compositions which can be used being polymeric substances and waxes.

If appropriate, the active compound or compounds can also be present in microencapsulated form with one or more of the abovementioned excipients.

Suppositories can contain, in addition to the active compound or compounds, the customary water-soluble or water-insoluble excipients, for example polyethylene glycols, fats, for example cacao fat, and higher esters (for example C₁₄-alcohol with C₁₆-fatty acid) or mixtures of these substances.

Ointments, pastes, creams and gels can contain, in addition to the active compound or compounds, the customary excipients, for example animal and vegetable fats, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures of these substances.

Dusting powders and sprays can contain, in addition to the active compound or compounds, the customary excipients, for example lactose, talc, silicic acid, aluminum hydroxide, calcium silicate and polyamide powder, or mixtures of these substances. Sprays can additionally contain the customary propellants, for example chlorofluorohydrocarbons.

Solutions and emulsions can contain, in addition to the active compound or compounds, the customary excipients, such as solvents, solubilizing agents and emulsifiers, for example water, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils, in particular cottonseed oil, groundnut oil, corn germ oil, olive oil, castor oil and sesame oil, glycerol, glycerol formal, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, or mixtures of these substances.

For parenteral administration, the solutions and emulsions can also be in a sterile form which is isotonic with blood.

Suspensions can contain, in addition to the active compound or compounds, the customary excipients, such as liquid diluents, for example water, ethyl alcohol and propylene glycol, and suspending agents, for example ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide,

bentonite, agar-agar and tragacanth, or mixtures of these substances.

The formulation forms mentioned can also contain colouring agents, preservatives and additives which improve the smell and taste, for example peppermint oil and eucalyptus oil, and sweeteners, for example saccharin.

The therapeutically active compounds should preferably be present in the abovementioned pharmaceutical formulations in a concentration of about 0.1 to 99.5, preferably about 0.5 to 95% by weight of the total mixture.

The abovementioned pharmaceutical formulations can also contain other pharmaceutical active compounds in addition to the compounds according to the invention.

The abovementioned pharmaceutical formulations are prepared in the customary manner by known methods, for example by mixing the active compound or compounds with the excipient or excipients.

The formulations mentioned can be used on humans and animals either orally, rectally, parenterally (intravenously, intramuscularly or subcutaneously), intracisternally, intravaginally, intraperitoneally or locally (dusting powder, ointment, drops) and for the therapy of infections in hollow spaces and body cavities. Possible suitable formulations are injection solutions, solutions and suspensions for oral therapy and gels, infusion formulations, emulsions, ointments or drops. Ophthalmological and dermatological formulations, silver salts and other salts, eardrops, eye ointments, dusting powders or solutions can be used for local therapy. In the case of animals, intake can also be in suitable formulations via the feed or drinking water. Gels, powders, dusting powders, tablets, delayed release tablets, premixes, concentrates, granules, pellets, boli, capsules, aerosols, sprays and inhalants can furthermore be used on humans and animals. The compounds according to the invention can moreover be incorporated into other carrier materials, such as, for example, plastics (chains of plastic for local therapy), collagen or bone cement.

In general, it has proved advantageous both in human and in veterinary medicine to administer the active compound or compounds according to the invention in total amounts of about 0.5 to about 500, preferably 5 to 100 mg/kg of body weight every 24 hours, if appropriate in the form of several individual doses, to achieve the desired results. An individual dose preferably contains the active compound or compounds according to the invention in amounts of about 1 to about 80, in particular 3 to 30 mg/kg of body weight. However, it may be necessary to deviate from the dosages mentioned, and in particular to do so as a function of the nature and body weight of the object to be treated, the nature and severity of the disease, the nature of the formulation and of the administration of the medicament and the period or interval within which administration takes place.

Thus in some cases it can suffice to manage with less than the abovementioned amount of active compound, while in other cases the abovementioned amount of active compound must be exceeded. The particular optimum dosage and mode of administration required for the active compounds can easily be determined by any expert on the basis of his expert knowledge.

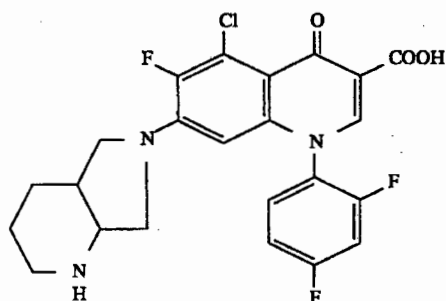
The new compounds can be administered in the customary concentrations and formulations together with the feed or with feed formulations or with the drinking water. Infection by Gram-negative or Gram-positive bacteria can in this way be prevented, alleviated and/or cured and promotion of growth and an improvement in feed utilization can in this way be achieved.

226
163

Solutions
pre
injection

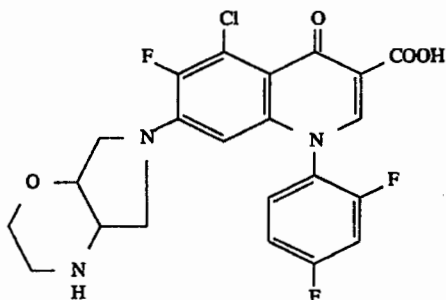
1-80
mg/kg

97
EXAMPLE 53



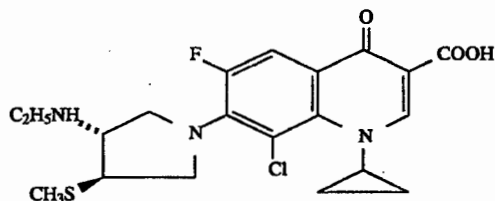
Analogously to Example 15 A, 5-chloro-7-(2,8-diazabicyclo[4.3.0]non-8-yl)-6-fluoro-1-(2,4-difluorophenyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid is obtained with 5,7-dichloro-6-fluoro-1-(2,4-difluorophenyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid (reflux for 5 hours).

EXAMPLE 54



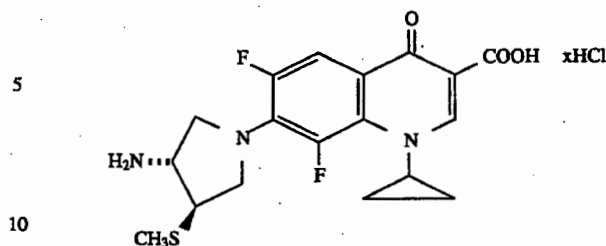
Analogously to Example 8, 5-chloro-6-fluoro-1-(2,4-difluorophenyl)-1,4-dihydro-7-(2-oxa-5,8-diazabicyclo[4.3.0]non-8-yl)-4-oxo-3-quinolinecarboxylic acid is obtained with 5,7-dichloro-6-fluoro-1-(2,4-difluorophenyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid (reflux for 5 hours).

EXAMPLE 55



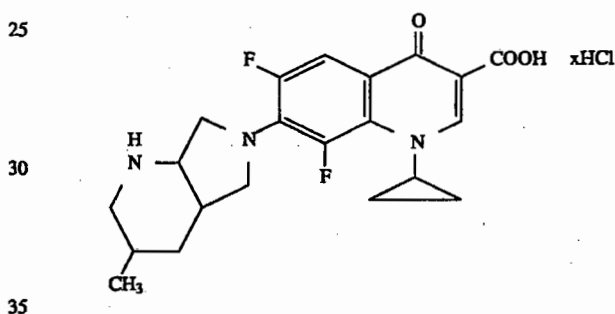
The reaction is carried out analogously to Example 13 with trans-3-ethylamino-4-methylthio-pyrrolidine and 8-chloro-1-cyclopropyl-6,7-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid to give 8-chloro-1-cyclopropyl-7-(trans-3-ethylamino-4-methylthio-1-pyrrolidinyl)-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid, melting points 217°-218° C. (with decomposition).

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EXAMPLE 56



7-(trans-3-Amino-4-methylthio-1-pyrrolidinyl)-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid, melting point: 208°-211° C. (with decomposition) and 7-(trans-3-amino-4-methylthio-1-pyrrolidinyl)-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid hydrochloride, melting point: 255°-257° C. (with decomposition), are obtained with trans-3-amino-4-methylthio-pyrrolidine analogously to Examples 13 and 15.

EXAMPLE 57

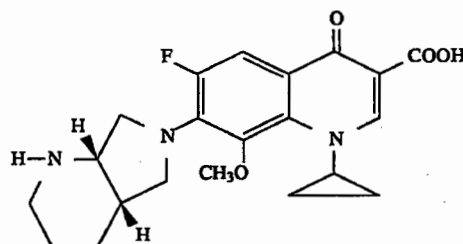


1-Cyclopropyl-6,8-difluoro-1,4-dihydro-7-(4-methyl-2,8-diazabicyclo[4.3.0]non-8-yl)-4-oxo-3-quinolinecarboxylic acid, melting point: 213°-215° C. (with decomposition) (recrystallized from glycol monomethyl ether), and 1-cyclopropyl-6,8-difluoro-1,4-dihydro-7-(4-methyl-2,8-diazabicyclo[4.3.0]non-8-yl)-4-oxo-3-quinolinecarboxylic acid hydrochloride, melting point: 204°-212° C. (with decomposition) are obtained with 4-methyl-2,8-diazabicyclo[4.3.0]nonane analogously to Examples 13 and 15. The product consists of a mixture of two stereoisomers.

It is understood that the specification and examples are illustrative but not limitative of the present invention and that other embodiments within the spirit and scope of the invention will suggest themselves to those skilled in the art.

We claim:

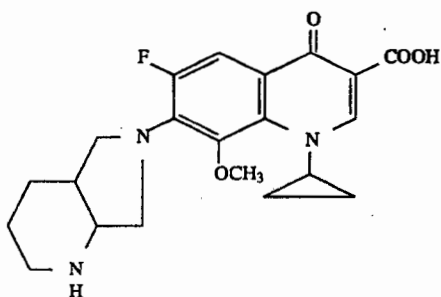
1. The compound 1-cyclopropyl-7-[(S,S)-2,8-diazabicyclo[4.3.0]non-8-yl)-6-fluoro-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid having the formula:



or an alkali metal, alkaline earth metal, silver or guanidinium salt thereof or a pharmaceutically utilizable hydrate

or acid addition salt thereof, said compound substantially free of other enantiomers and stereoisomers.

2. The compound (1-cyclopropyl-7-(2,8-diazabicyclo[4.3.0]non-8-yl)-6-fluoro-8-methoxy-1,4-dihydro-4-oxo-3-quinolonecarboxylic acid) of the formula



or an addition product thereof with water, an acid or an alkali.

3. An antibacterial composition comprising an antibacterially effective amount of a compound or addition product thereof according to claim 1 and a diluent.

4. An antibacterial composition comprising an antibacterially effective amount of a compound or addition product thereof according to claim 2 and a diluent.

5. A method of combating bacteria in a patient in need thereof which comprises administering to such patient an antibacterially effective amount of a compound or addition product thereof according to claim 1.

6. A method of promoting the growth of an animal which comprises administering to said animal a growth promoting effective amount of a compound or addition product thereof according to claim 1.

7. A method of combating bacteria in a patient in need thereof which comprises administering to such patient an antibacterially effective amount of a compound or addition product thereof according to claim 2.

8. A method of promoting the growth of an animal which comprises administering to said animal a growth promoting effective amount of a compound or addition product thereof according to claim 2.

* * * * *

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D3

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CAPÍTULO 36

Tonicidad, osmotividad, osmolalidad y osmolaridad

Irwin Reich

Roger Schnaare

Edwin T. Sugita

Definiciones básicas

Si se coloca una solución en contacto con una membrana que es permeable a las moléculas del solvente, pero no a las moléculas del soluto, el movimiento del solvente a través de la membrana se llama ósmosis. A menudo se denomina a esta membrana semipermeable. Como los distintos tipos de membranas del organismo varían en su permeabilidad, está bien destacar que son *selectivamente* permeables. Casi todas las membranas de las células vivas normales mantienen distintos gradientes de concentración de soluto. Una membrana selectivamente permeable puede definirse como la que no permite la difusión libre y sin obstáculos de todos los solutos presentes o la que mantiene como mínimo el gradiente de concentración de un soluto a través de ella. Entonces, la ósmosis, es la difusión del agua a través de una membrana que mantiene por lo menos un gradiente de concentración de un soluto a través de sí misma.

Asumamos que la Solución A se encuentra a un lado de la membrana y la Solución B del mismo soluto, pero de una concentración mayor, está del otro lado; el solvente tenderá a pasar hacia la solución más concentrada hasta establecer el equilibrio. La presión necesaria para impedir este movimiento es la presión osmótica, que se define como el exceso de presión o una presión mayor que la que hay por encima del solvente puro, que debe ser aplicada a la Solución B para evitar el pasaje del solvente a través de una membrana semipermeable perfecta desde A hasta B. La concentración de una solución con respecto al efecto sobre la presión osmótica se relaciona con el número de partículas (moléculas no ionizadas, iones, macromoléculas, agregados) de soluto(s) en solución y, por lo tanto, es afectada por el grado de ionización o agregación del soluto. Véase el capítulo 16 para la revisión de las propiedades coligativas de las soluciones.

Los líquidos corporales, que incluyen la sangre y el líquido lagrimal, normalmente poseen una presión osmótica que se describe como correspondiente a la de una solución de cloruro de sodio al 0,9%. El organismo también intenta mantener la presión osmótica

del contenido del tracto gastrointestinal aproximadamente en este nivel, pero allí el intervalo normal es mucho más amplio que el de la mayoría de los líquidos corporales. Se dice que la solución de cloruro de sodio al 0,9% es *isoosmótica* con los líquidos fisiológicos. El término *isotónico*, que significa igual tonicidad, es empleado a menudo en medicina en forma intercambiable con *isoosmótico*. Sin embargo, términos como *isotónico* o *tonicidad* sólo deben emplearse con referencia a un líquido fisiológico. En realidad, *isoosmótico* es un término físico que compara la presión osmótica (u otra propiedad coligativa, como disminución del punto de congelamiento) de dos líquidos, ninguno de los cuales puede ser un líquido fisiológico, o que puede ser un líquido fisiológico sólo bajo ciertas circunstancias. Por ejemplo, una solución de ácido bórico que es *isoosmótica* con la sangre y el líquido lagrimal, es *isotónica* sólo con el líquido lagrimal. Esta solución produce hemólisis de los glóbulos rojos porque las moléculas de ácido bórico pasan libremente a través de la membrana eritrocítica cualquiera que sea la concentración. Por lo tanto, la *isotonicidad* infiere un sentido de compatibilidad fisiológica mientras que la *isoosmotividad* no lo necesita. Como otro ejemplo, una "dieta elemental químicamente definida" o líquido nutricional enteral puede ser *isoosmótica* con el contenido del tracto gastrointestinal, pero no sería considerada un líquido fisiológico ni apropiada para uso parenteral.

Una solución es *isotónica* con una célula viva si no hay ganancia ni pérdida neta de agua por la célula ni ningún otro cambio en ella cuando está en contacto con esa solución. Las soluciones fisiológicas con una presión osmótica menor que la de los líquidos corporales o que la de una solución de cloruro de sodio al 0,9%, se denominan habitualmente *hipotónicas*. Las soluciones fisiológicas con una presión osmótica mayor se llaman *hipertónicas*.

Estos términos cualitativos tienen un valor limitado y se ha vuelto necesario establecer propiedades osmóticas en términos cuantitativos. Para hacerlo, debe emplearse un término que represente todas las partículas que pueden estar presentes en un sistema dado.

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Remington Farmacia
GENNARO, Alfonso R.
19 av. ed. Editorial Médica Panamericana.

El término usado es *osmol*. Un osmol se define como el peso, en gramos, de un soluto, que existe en una solución como moléculas (y/o iones, macromoléculas, agregados, etc.), que es osmóticamente equivalente a un mol de un no electrólito de comportamiento ideal. Por lo tanto, el peso en osmoles de un no electrólito, en una solución diluida, por lo general es igual a su peso molecular en gramos. Un miliosmol, abreviado mOsm, es el peso establecido en miligramos.

Si se extrapola este concepto de relacionar un osmol y un mol de un no electrólito como equivalentes, también podemos definir un osmol de las siguientes formas: es la cantidad de soluto que aporta un número de Avogadro ($6,02 \times 10^{23}$) de partículas en solución y es la cantidad de soluto que, al disolverlo en 1 kg de agua, produce un aumento de la presión osmótica de 17.000 mmHg a 0° o 19.300 mmHg a 37°. Un mOsmol es la milésima parte de un osmol. Por ejemplo, 1 mol de dextrosa anhidra es igual a 180 g. Un osmol de este no electrólito es también 180 g. Un mOsmol sería 180 mg. Así, 180 mg de este soluto disueltos en 1 kg de agua producen un aumento en la presión osmótica de 19.3 mmHg a temperatura corporal.

Para una solución de un electrólito como cloruro de sodio, una molécula de cloruro de sodio representa un ion sodio y un ion cloruro. Por ende, un mol representa teóricamente 2 osmoles de cloruro de sodio. Por lo tanto, 1 osmol de NaCl = 58,5 g/2 o 29,25 g. Esta cantidad representa la suma total de $6,02 \times 10^{23}$ iones como el número total de partículas. Las soluciones ideales corresponden a soluciones muy diluidas o dilución infinita. Sin embargo, a medida que la concentración aumenta, entran otros factores. Con electrólitos fuertes, la atracción interiónica reduce su efecto sobre las propiedades coligativas. Además, para todos los solutos, incluyendo los no electrólitos, intervienen otros factores como la solvatación y posiblemente otros factores que operan para intensificar su efecto coligativo. Por lo tanto, es muy difícil y a menudo imposible predecir con precisión la osmotividad de una solución. Puede ser posible hacerlo para una solución diluida de un soluto único, puro y bien caracterizado, pero no para la mayoría de los líquidos parenterales y enterales medicinales o nutricionales, o ambos; es probable que se requiera una determinación experimental.

Consideraciones terapéuticas

Por lo general, se acepta que los efectos osmóticos ocupan un lugar importante en el mantenimiento de la homeostasis (el estado de equilibrio del organismo vivo en relación con las distintas funciones y con la composición química de los líquidos y tejidos, p. ej., temperatura, frecuencia cardíaca, presión arterial, contenido de agua o glucemia). En gran medida, estos efectos ocurren dentro o entre las células y tejidos donde no se pueden medir. Uno de los problemas más

difíciles en clínica médica es el mantenimiento adecuado de los líquidos corporales y de un equilibrio apropiado entre los volúmenes de los líquidos intracelulares y extracelulares en los pacientes gravemente enfermos. No obstante, debe tenerse en cuenta que las anomalías hidroelectrolíticas no constituyen enfermedades, sino que son manifestaciones de ellas.

Los mecanismos fisiológicos que controlan el ingreso y egreso de agua parecen responder principalmente a la osmotividad sérica. La regulación renal del egreso está influida por la variación en la velocidad de liberación de la hormona antidiurética hipofisaria (ADH) y de otros factores como respuesta a cambios en la osmotividad sérica. Los cambios osmóticos también sirven como estímulo para la sed moderada. Este mecanismo es suficientemente sensible como para limitar las variaciones en osmotividad hasta menos del 1% en el individuo normal. El líquido corporal oscila continuamente dentro de este intervalo estrecho. Un aumento del 1% en la osmotividad plasmática estimula la liberación de ADH, produce reducción del flujo urinario y, al mismo tiempo, estimula la sed que produce un ingreso elevado de agua. Tanto la reabsorción renal elevada de agua (sin soluto) estimulada por la ADH circulante como el ingreso elevado de agua tienden a reducir la osmotividad sérica.

La transferencia de agua a través de la membrana celular ocurre tan rápidamente que cualquier desequilibrio osmótico entre los dos compartimientos de líquido en cualquier tejido dado suele corregirse en algunos segundos y, a lo sumo, en un minuto más o menos. Sin embargo, esta rápida transferencia de agua no significa que ocurra un equilibrio completo entre los compartimientos extracelular e intracelular en todo el organismo en tan poco tiempo. La razón es que habitualmente el líquido ingresa al organismo a través del intestino y entonces debe ser transportado por el sistema circulatorio a todos los tejidos antes de que pueda ocurrir un equilibrio completo. En la persona normal puede llevar 30 a 60 minutos lograr un equilibrio razonablemente bueno en todo el organismo después de beber agua. La osmotividad es la propiedad que determina en gran parte la aceptabilidad fisiológica de distintas soluciones usadas con fines terapéuticos y nutricionales.

La consideración farmacéutica y terapéutica de los efectos osmóticos se ha dirigido, en gran medida, a los efectos colaterales de los medicamentos para uso oftálmico y parenterales debido a la osmotividad anormal y a cambiar la fórmula para evitar los efectos colaterales o encontrar métodos de administración para minimizarlos. Más recientemente, esta consideración se ha extendido a la nutrición parenteral total (central), a la hiperalimentación enteral (alimentación con sonda) y a fórmulas de líquidos concentrados para lactantes.¹ Además, en años recientes, se ha reconocido la importancia de la osmometría del suero y la orina en el diagnóstico de muchos trastornos patológicos.

Debe mantenerse equilibrio osmótico o preparar! s
oftal y parenteral.

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

DIVISION DE NUEVAS CREACIONES

2020
Bogotá, D.C., Noviembre 22 de 2005

Doctor
EMILIO FERRERO

ASUNTO	Radicación No.	00 058 178
	Trámite	002
	Evento	001
	Actuación	430 11265
	Oficio No.	
	Folios	0

Como resultado del examen de patentabilidad de la solicitud de patente de invención, realizado según lo establece el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se notifica el siguiente concepto técnico:

1. Documentos estudiados

Para el presente estudio se tuvieron en cuenta el capítulo descriptivo comprendido en los folios 2 – 28, el nuevo capítulo reivindicatorio de los folios 29 – 31, los argumentos de la Oposición, de los folios 108 – 114, 166 – 173 y 204 – 209 y la respuesta del Solicitante a la Oposición, de los folios 177 - 1888 de la solicitud en estudio.

2. Objeto de la Invención

El objeto de la presente solicitud de patente de invención consiste en:

Las reivindicaciones 1 – 5 y 10 se refieren a una formulación acuosa que contiene clorhidrato de moxifloxacina y cloruro de sodio.

Las reivindicaciones 6 y 7 se refieren a un procedimiento para preparar una formulación acuosa que contiene clorhidrato de moxifloxacina y cloruro de sodio caracterizado porque se prepara una solución acuosa de clorhidrato de moxifloxacina y luego se agrega cloruro de sodio, ó se mezclan una solución acuosa de clorhidrato de moxifloxacina y una de cloruro de sodio.

La reivindicación 9 se refiere a un preparado de combinación que comprende una solución acuosa de contiene clorhidrato de moxifloxacina y una solución acuosa de cloruro de sodio, separadas una de la otra.

Las reivindicaciones 8 y 11 se refieren al uso de una formulación acuosa que contiene clorhidrato de moxifloxacina y cloruro de sodio, para preparar un medicamento.

El problema planteado en esta solicitud es la necesidad de proporcionar una composición para tratamiento de infecciones bacterianas.

Para resolver este problema técnico la solicitud en estudio proporciona una formulación acuosa que contiene clorhidrato de moxifloxacina y cloruro de sodio.

El objeto de la invención definido anteriormente se clasificó de acuerdo con la IPC: A 61 K 31/47 // 31/185 // 47/02.

También se reivindica prioridad de la Solicitud de Patente de Alemania DE 199 37 116.4 de agosto 6 de 1999, con respecto a la cual la fecha de presentación de la actual solicitud cumple el plazo máximo permitido.

3. Usos

El artículo 21 de la Decisión 486 de la Comisión de la Comunidad Andina establece que: *"Los productos o procedimientos ya patentados, comprendidos en el estado de la técnica, de conformidad con el artículo 16 de la presente Decisión, no serán objeto de nueva patente, por el simple hecho de atribuirse un uso distinto al originalmente comprendido por la patente inicial"*.

Se aclara que los usos de las reivindicaciones 8 y 11 no pueden ser objeto de nueva patente, aunque el solicitante los considere distintos a los originalmente comprendidos por la patente inicial, porque estos se conocían originalmente en la Pat US 5 607 942 (ver columnas 56 y 99), donde se enseñan soluciones para inyección y soluciones para administración oral que contienen moxifloxacina y un diluyente, indicadas como antibacteriales.

4. Claridad de la Solicitud

La descripción divulga la invención de manera suficientemente clara y completa para su comprensión, tal como lo establece el Art 28 de la decisión 486 de la Comisión Andina. Menciona el sector tecnológico al que pertenece, los antecedentes de la técnica, la divulgación del problema técnico, la solución propuesta y la ventaja frente a la tecnología anterior.

Pero en cuanto a la reivindicación 10 se observa que menciona "una formulación acuosa" pero no menciona en forma clara y ordenada los componentes que la conforman y la caracterizan. Debe hacerse claridad al respecto.

5. Determinación del Estado de la Técnica

El artículo 16 de la decisión 486 de la comisión de la Comunidad Andina que establece que *"El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida"*.

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

Considerando que la fecha de presentación de la primera solicitud de patente de la cual se reivindica prioridad es agosto 6 de 1999, se consultaron las bases de datos y los archivos con que cuenta la entidad con fecha de publicación anterior y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

No.	Documento	Título	Fecha de Publicación
D1	US 4 990 517	Derivados de 7-(1-pirrolidinil)-3-quinolon y ácido - naftiridoncarboxílico como agentes antibacteriales y aditivos de piensos	Feb 5, 1991
D2	US 5 607 942	Derivados de 7-(1-pirrolidinil)-3-quinolon y ácido - naftiridoncarboxílico como agentes antibacteriales y aditivos de piensos	Mar 4, 1997
D3	Libro (*)	Remington Farmacia	1995
D4	Oposición	Lafrancol S. A.	-

cd 58, 59, 105

cd 56, 98, 99

(*) GENNARO, Alfonso R. "Remington Farmacia". 19 ava. ed. Editorial Médica Panamericana.

6. Evaluación de los requisitos de Patentabilidad

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

En cumplimiento del artículo 14 de la Decisión 486, se procedió a evaluar el cumplimiento de los requisitos de novedad, nivel inventivo y aplicación industrial, con el fin de establecer la patentabilidad de la invención reivindicada en la solicitud en estudio.

Evaluación de la Novedad

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

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

Las reivindicaciones 1 – 5 y 10 se refieren a una formulación acuosa que contiene clorhidrato de moxifloxacin y cloruro de sodio.

Las reivindicaciones 6 y 7 se refieren a un procedimiento para preparar una formulación acuosa que contiene clorhidrato de moxifloxacin y cloruro de sodio caracterizado porque se prepara una solución acuosa de clorhidrato de moxifloxacin y luego se agrega cloruro de sodio, ó se mezclan una solución acuosa de clorhidrato de moxifloxacin y una de cloruro de sodio.

La reivindicación 9 se refiere a un preparado de combinación que comprende una solución acuosa de contiene clorhidrato de moxifloxacin y una solución acuosa de cloruro de sodio, separadas una de la otra.

D1 enseña soluciones para inyección y soluciones para administración oral que contienen moxifloxacin y un diluyente, indicadas como antibacteriales.

D2 enseña soluciones para inyección y soluciones para administración oral que contienen moxifloxacin y un diluyente, indicadas como antibacteriales.

D3 enseña la forma común como se preparan las soluciones de inyectables.

Se observa que los elementos constitutivos de las soluciones para inyección y soluciones para administración oral que contienen moxifloxacin y un diluyente, indicadas como antibacteriales, ya estaban contenidos en las anterioridades, por lo cual no puede considerarse nuevo el objeto de las reivindicaciones 1 – 5, 10, 6 – 7, y 9.

Evaluación del Nivel Inventivo

El artículo 18 de la Decisión 486 de la Comisión de la Comunidad Andina establece que *Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica.*

Se observa que los elementos constitutivos de las soluciones para inyección y soluciones para administración oral que contienen moxifloxacin y un diluyente, indicadas como antibacteriales de las reivindicaciones 1 - 5, ya estaban contenidos en las anterioridades. Se observa además, con base en lo enseñado en D3, que para cualquier persona normalmente conocedora de la materia era obvio el elaborar las soluciones parenterales (inyectables) de modo que sean isotónicas; y esto se logra siempre con la concentración salina (es decir la proporción de cloruro de sodio) apropiada; de manera que combinando esto con las soluciones de moxifloxacin mencionadas en D1 ó D2, se sugieren las soluciones para inyección y soluciones para administración oral que contienen moxifloxacin y un diluyente, indicadas como antibacteriales que son objeto de esta solicitud, por lo cual no hay nivel inventivo.

Entonces debido a que: (a) los compuestos que caracterizan a las composiciones de esta solicitud (moxifloxacin, diluyente, cloruro de sodio) eran conocidos en las anterioridades, para una persona conocedora de la materia era evidente el elaborar las composiciones de manera similar, teniendo en cuenta estos compuestos; (b) las reivindicaciones de esta solicitud no mencionan una característica que conceda un efecto diferente o especial a las composiciones, que pueda considerarse como un aporte a la técnica, así que son obvias para una persona versada en la materia y (c) el problema planteado en esta solicitud que era la necesidad de una composición para tratamiento de infecciones bacterianas se resuelve proporcionando una formulación acuosa que contiene clorhidrato de moxifloxacin y cloruro de sodio, es decir de manera similar a como se resolvía en las anterioridades; las reivindicaciones son obvias y evidentes para una persona versada en la materia. De manera que no tienen nivel inventivo.

7. Argumentos de la Oposición

a. Dice el Opositor en el folio 111 que la moxifloxacin está en el Estado de

la Técnica, en las Patentes US 4 990 517 y 5 607 942.

- b. Dice el Opositor en el folio 111 que la publicación WO 00 18386 menciona una composición que contiene moxifloxacina y NaCl, por lo cual afecta la novedad de esta solicitud.
- c. Dice el Opositor en el folio 112 que la Farmacia de Remington enseña que las soluciones de cloruro de sodio (NaCl) son muy conocidas como diluyentes de formulaciones para inyección.
- d. Dice el Opositor en el folio 113 que existen muchas soluciones salinas que contienen principios activos antimicrobianos.
- e. Dice el Opositor en el folio 169 que de acuerdo con la publicación *Farm Hosp.* 1997; 21(1):52-56, es recomendable diluir los inyectables con solución salina fisiológica (concentración NaCl = 0.9 %) antes de su administración.

8. Respuesta del Solicitante a la Oposición

- a. Dice el Solicitante en el folio 183 que el documento WO 00 18386 no afecta la patentabilidad de esta solicitud porque su fecha de publicación es posterior a la fecha de presentación de la primera solicitud de patente de la cual la solicitud en estudio reivindica prioridad (agosto 6 de 1999).
- b. Dice el Solicitante en el folio 185 que los clorhidratos de ácidos quinolon-carboxílicos no son muy solubles en presencia de NaCl, por lo cual considera que el mencionar ahora que una solución de 0.04 – 0.40 % de moxifloxacina en una solución fisiológica de NaCl tiene nivel inventivo.
- c. Dice el Solicitante que una solución de Ciprofloxacina en presencia de HCl y NaCl solo es capaz de contener una baja concentración de Ciprofloxacina, porque es poco soluble.
- d. Dice el Solicitante que moxifloxacina es presencia de NaCl no es sensible a iones-Hierro y además es poco soluble. Y que en esta solicitud se encontró una concentración de moxifloxacina en la que sí es soluble. Por lo cual considera que esta solicitud tiene nivel inventivo.

9. Respuesta a la Oposición y al Solicitante

En atención a los argumentos se hacen las siguientes aclaraciones:

- a. Es cierto que la moxifloxacina está en el Estado de la Técnica, en las Patentes US 4 990 517 y 5 607 942.
- b. La publicación WO 00 18386 menciona una composición que contiene moxifloxacina y NaCl, pero no afecta la novedad de esta solicitud, porque su fecha de publicación es posterior a la fecha de presentación de la primera solicitud de patente de la cual la solicitud en estudio reivindica prioridad (agosto 6 de 1999).
- c. Es cierto que la Farmacia de Remington enseña que las soluciones de cloruro de sodio (NaCl) son muy conocidas como diluyentes de formulaciones para inyección y el NaCl se utiliza con el fin de hacer que las soluciones sean isotónicas. Es decir que tengan una concentración salina tal, que posean la misma presión osmótica que tienen naturalmente los fluidos corporales, para que al contacto con estos, no produzcan ganancia ni pérdida neta de agua a través de la membrana celular. Y esta concentración, en el caso del NaCl, es de 0.9 %. (ver Remington Farmacia, páginas 896 – 897).
- d. Es cierto que existen muchas soluciones salinas que contienen principios activos antimicrobianos, y esto eventualmente, haría obvia la composición de esta solicitud, que es una solución salina que contiene un principio activo antimicrobiano, para una persona normalmente

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- conocedora de la materia.
- e. Es cierto que la publicación *Farm Hosp.* 1997; 21(1):52-56, la cual aclara que es recomendable diluir los inyectables con solución salina fisiológica (concentración NaCl = 0.9 %) antes de su administración, puede eventualmente afectar al nivel inventivo de esta solicitud porque sugiere la posibilidad de diluir el principio activo del inyectable en la solución salina.
 - f. Justamente porque los clorhidratos de ácidos quinolon-carboxílicos no son muy solubles en presencia de NaCl, una solución de 0.04 – 0.40 % de moxifloxacina en una solución fisiológica de NaCl no tiene nivel inventivo. Porque esta es la concentración máxima que puede alcanzar la moxifloxacina en la solución fisiológica de NaCl y por lo tanto en los fluidos fisiológicos y porque era conocida la moxifloxacina, era conocida la solución fisiológica de NaCl y eran conocidos los inyectables de antimicrobianos en solución fisiológica de NaCl.

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10. Conclusión

En conclusión, los requisitos de patentabilidad de la presente solicitud están afectados así:

Item	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	US 4 990 517	1 – 5, 10, 6 – 7, y 9	Novedad y Nivel inventivo
D2	US 5 607 942	1 – 5, 10, 6 – 7, y 9	Novedad y Nivel inventivo
D3	Libro (*)	1 – 5, 10, 6 – 7, y 9	Novedad y Nivel inventivo

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta días contados a partir de la fecha de la notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Unica No. 10 de 2001.


ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones.

El anterior requerimiento fue notificado por fijación en lista, de fecha

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