(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 342 675**
A2

(12) **EUROPEAN PATENT APPLICATION**

(21) Application number: 89108963.3

(51) Int. Cl.4: **C07D 401/04 , A61K 31/47**

(22) Date of filing: **18.05.89**

(30) Priority: **19.05.88 JP 122722/88**
08.12.88 JP 310418/88

(43) Date of publication of application:
23.11.89 Bulletin 89/47

(84) Designated Contracting States:
AT BE CH DE ES FR GB IT LI NL SE

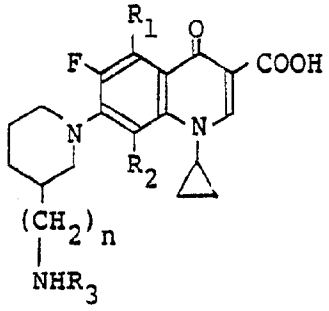
(71) Applicant: **Chugai Seiyaku Kabushiki Kaisha**
5-1, 5-chome, Ukima Kita-ku
Tokyo(JP)

(72) Inventor: **Nagano, Hiroyuki**
2-9-17, Ohta
Iwatsuki-shi Saitama-ken(JP)
Inventor: **Yokota, Takeshi**
3-7-1, Narashinodai
Funabashi-shi Chiba-ken(JP)
Inventor: **Katoh, Yasuyuki**
750-10, Tokura
Mishima-shi Shizuoka-ken(JP)

(74) Representative: **Vossius & Partner**
Siebertstrasse 4 P.O. Box 86 07 67
D-8000 München 86(DE)

(54) Novel quinolonecarboxylic acid derivatives.

(57) Novel compounds of the present invention are represented by the general formula (I)



(1)

wherein R_1 is hydrogen atom or amino, R_2 is fluorine atom or methoxy, R_3 is hydrogen atom or a lower alkyl having 1 to 3 carbon atoms, and n is 0 or 1. The compounds of the general formula (1) exhibit higher antibacterial activity with fewer side-effects than known quinolone antibiotics such as ofloxacin and norfloxacin. Further, the compounds having the general formula (1) have reduced phototoxicity which normally accompanies 6,8-difluoroquinoline antibiotics.

EP 0 342 675 A2

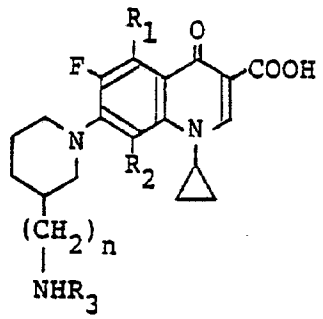
NOVEL QUINOLONECARBOXYLIC ACID DERIVATIVES

The present invention relates to novel quinolonecarboxylic acid derivatives that exhibit strong antibacterial activity and are useful as medicines.

A number of quinolone antibiotics are known, including commercially available ones, but they involve certain problems such as the fact that these compounds must be used with utmost caution because many of them show side-effects in the central nervous system. Recently, much attention has been paid to the antibacterial activity of quinoline derivatives that have a fluorine substituent at both 6- and 8-position, or a fluorine substituent at 6-position and a lower alkoxy substituent at 8-position (US-A-4.556.658, EP-A-106,489, EP-A-230,295, EP-A-241,206).

However, they are not always satisfactory antibiotics, since many of them have phototoxicity along with the side-effects mentioned above.

The present inventors zealously investigated ways of eliminating the drawbacks of quinolone antibiotics and found that compounds of the general formula (1) shown below which have at 7-position a piperidin-1-yl group whose 3-position is substituted by an amino, lower alkyl or aminomethyl group, for example, 3-aminopiperidin-1-yl group, exhibit higher antibacterial activity with fewer side-effects than known quinolone antibiotics such as ofloxacin and norfloxacin. Further, the compounds of the present invention having the general formula (1) have reduced phototoxicity which normally accompanies 6,8-difluoroquinoline antibiotics.



(1)

(wherein R_1 is hydrogen atom or amino, R_2 is fluorine atom or methoxy, R_3 is hydrogen atom or a lower alkyl having 1 to 3 carbon atoms, and n is 0 or 1).

The quinolone derivatives of this invention having the general formula (1) are novel compounds. Those which have a fluorine atom at 8-position can be provided by the reaction of 3-acetamidopiperidines with known starting materials, for example, 1-cyclopropyl-6,7,8-trifluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid, 5-amino-1-cyclopropyl-6,7,8-trifluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid or a lower alkyl ester thereof followed by hydrolysis. Compounds of the invention having the general formula (1) where a methoxy group exists at 8-position may be provided by the reaction of the compound obtained from the foregoing step with sodium methoxide. While there exist two optical isomers of each compound of the invention having the general formula (1), both of them can be utilized as compounds of the invention. In the case of synthesis of an optical active compound, for instance, starting with 3-aminopiperidine that has been prepared from optical active ornithine, the synthesis may be performed in a manner similar to that described above.

Preferable examples of the compound of the invention having the general formula (1) include the following: 7-(3-aminopiperidin-1-yl)-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid, (S)-7-(3-amino-1-piperidin-1-yl)-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid, (R)-7-(3-aminopiperidin-1-yl)-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid, 7-(3-aminopiperidin-1-yl)-1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid, 5-amino-7-(3-aminopiperidin-1-yl)-1-cyclopropy-6,8-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid, 7-(3-aminomethylpiperidin-1-yl)-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid, 1-cyclopropyl6-fluoro-1,4-dihydro-8-methoxy-7-(3-methylaminopiperidin-1-yl)-4-oxoquinoline-3-carboxylic acid, 5-amino-1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methylaminopiperidin- 1-yl)-4-oxoquinoline-3-carboxylic acid, and 7-(3-aminomethylpiperidin-1-yl)-1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid.

The compounds of the invention form salts with acids. Examples of pharmaceutically acceptable acids

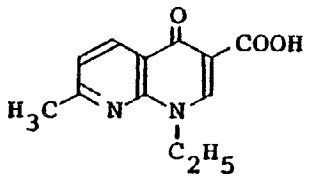
include inorganic acids such as hydrochloric acid, sulfuric acid and nitric acid and organic acids such as oxalic acid, fumaric acid, and p-toluenesulfonic acid. The antibacterial activity of a typical compound of the invention (the compound which will be described in Example 1) was compared with that of known quinolone antibiotics such as ofloxacin and norfloxacin by measuring MIC values. The results are shown in Table 1. The MIC values were measured by means of a conventional method.

Table 1

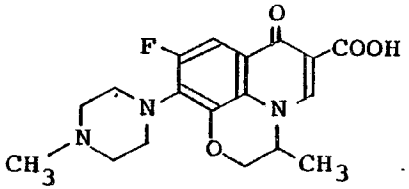
(μg/ml)

Organisms \ Sample Compound	Compound Ex. 1	nalidixic acid*1	ofloxacin*2	norfloxacin*3
Staphylococcus aureus FDA 209P JC-1	0.012	12.5	0.10	0.05
Escherichia coli NIHJ JC-2	0.024	6.25	0.05	0.05
Klebsiella pneumoniae No. 42	0.024	1.56	0.05	0.05
Proteus mirabilis JY10	0.012	0.78	0.012	0.012
Serrata marcescens No. 16-2	0.20	0.78	0.78	0.39
Pseudomonas aeruginosa AK 109	0.39	100	0.39	0.20
Pseudomonas cepacia 23	12.5	50	12.5	25

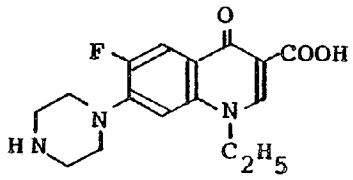
*1



*2



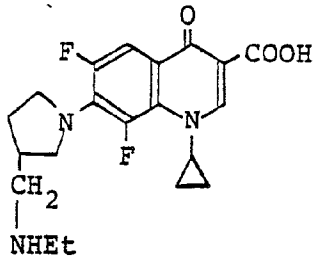
*3



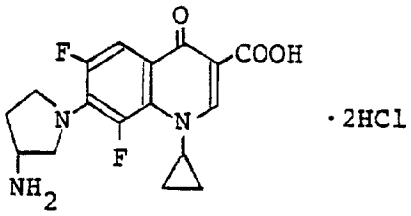
As indicated in Table 1, the compound of this invention possesses higher antibacterial activity than the known quinolone antibiotics. The characteristic feature of the compounds of the invention is that the antibacterial activity thereof is particularly high against Gram-positive bacteria.

The phototoxicity of a typical compound of the invention was compared with that of the known 6,8-difluoroquinoline antibiotics shown below as reference compounds and the results are summarized in Table 2. The compound which will be described in Example 1 was used as being typical of this invention.

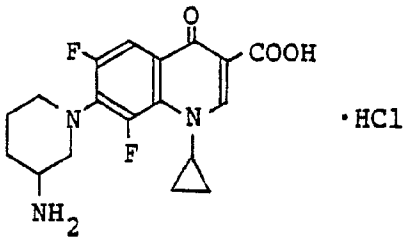
reference compound A:



reference compound B:



a compound of this invention:



DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.