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⑦3 Īpašnieks(i):
KRKA, TOVARNA ZDRAVIL, P.O.;
Cesta herojev 45, 68000 Novo Mesto, SI

⑦2 Izgudrotājs(i):
Nataša ZUPANČIČ (SI),
Martin BARBO (SI),
Boris ŠKET (SI),
Pavel ZUPET (SI)

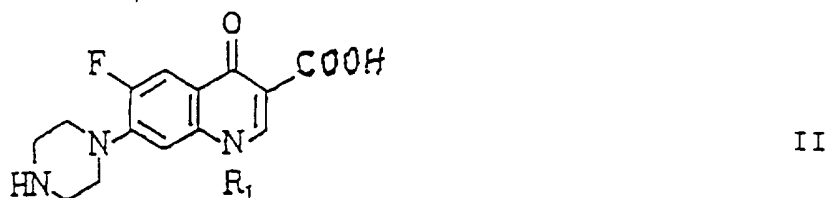
⑦4 Pilnvarotais vai pārstāvis:
Gunārs ROTBERGS,
Aģentūra "FORAL",
Raiņa bulv.19, Rīga LV-1159, LV

⑤4 Virsraksts: 1-Aizvietotās-6-fluor-4-oksi-7-(1-piperazinil)-1,4-dihidrohinolīn-3-karbonskābes
izgatavošanas paņēmieni, jauns starpprodukts, kas noderīgs minētajā paņēmienā un
minētā starpprodukta izgatavošanas paņēmieni

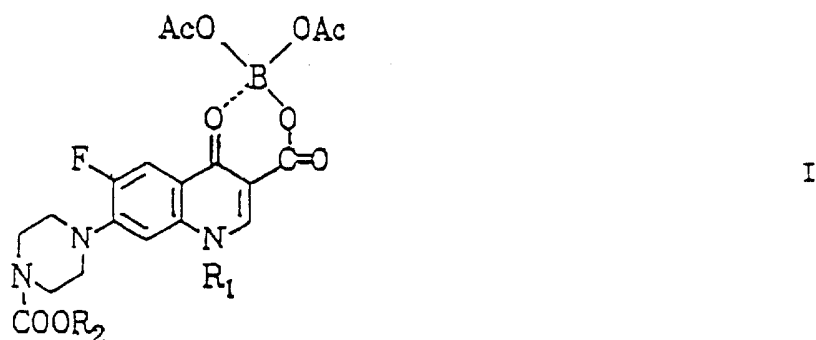
⑤7 Kopsavilkums:
Izgudrojumā aprakstīts 1-aizvietotu-6-fluor-4-oksi-7-(1-piperazinil)-1,4-dihidrohinolīn-3-karbonskābes, kas ir
izmantojama medicīnā, iegūšanas paņēmieni hidrolizējot sārmainā vidē attiecīgu 1-aizvietotu-6-fluor-4-oksi-7-(4-
aizvietotu-1-piperazinil)-1,4-dihidrohinolīn-3-karboksilāta bora diacetātu. Pēdējais nosauktais savienojums ir jauns,
aprakstīts tā iegūšanas paņēmieni.

IZGUDROJUMA FORMULA

1. Paņēmiens 1-aizvietotās-6-fluor-4-oksi-7-(1-piperazinil)-1,4-dihidrohinoīn-3-karbonskābes, kuras vispārējā formula ir (II), izgatavošanai

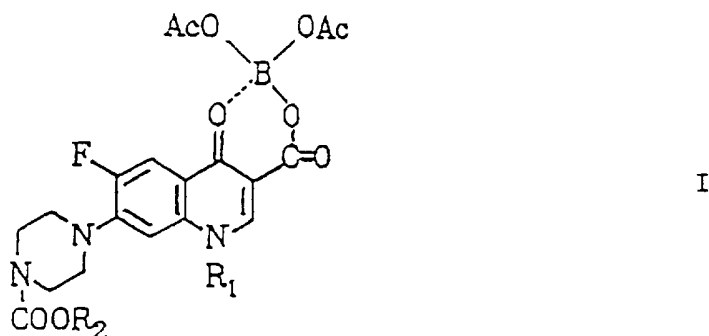


kur R_1 ir zemākā alkil-, zemākā cikloalkil- vai 2,4-difluorfenilgrupa vai farmokoloģiski saderīga pievienotās skābes sāls, tāda kā hidrohlorīds vai laktāts un to hidrāti, raksturīgs ar to, ka savienojums ar vispārējo formulu (I)



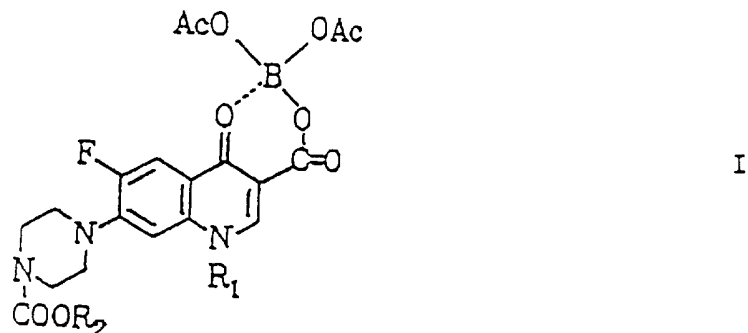
kur R ir augšminētais un R_2 ir zemākā alkilgrupa vai pēc izvēles aizvietota fenilgrupa, tiek pakļauts sārmainai hidrolīzei un, pēc izvēles, iegūto savienojumu ar vispārējo formulu (II) pārveido farmakoloģiski saderīga pievienotās skābes sāli, tādā kā hidrohlorīds vai laktāts un to hidrāti.

2. 1-aizvietotais-6-fluor-4-oksi-7-(4-aizvietotais-1-piperazinil)-1,4-dihidrohinoīn-3-karboksilāta bora diacetāts ar vispārējo formulu (I)

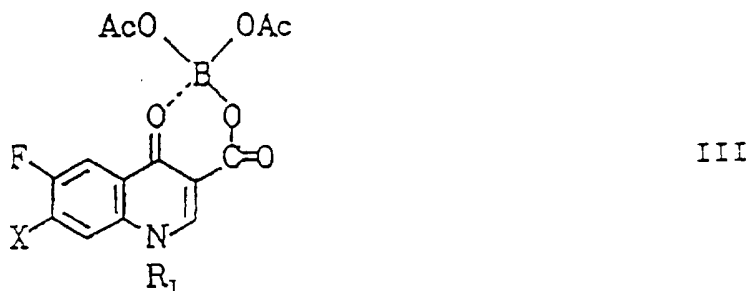


kur R_1 ir zemākā alkil-, zemākā cikloalkil- vai 2,4-difluorfenilgrupa un R_2 ir zemākā alkil- vai pēc izvēles aizvietota fenilgrupa.

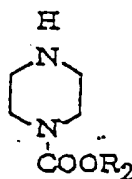
3. Paņēmiens 1-aizvietota-6-fluor-4-oksi-7-(4-aizvietotā-1-piperazinil)-1,4-dihidrohinoīn-3-karboksilāta bora diacetāta, kura vispārējā formula ir (I), iegūšanai



kur R_1 ir zemākā alikil-, zemākā cikloalkil- vai 2,4-difluorfenilgrupa un R_2 ir zemākā alkilgrupa vai pēc izvēles aizvietota fenilgrupa, raksturīgs ar to, ka 1-aizvietotā-6-fluor-7-halogēn-4-oksi-1,4-dihidrohinoīn-3-karboksilāta bora diacetātā, kura vispārējā formula ir (III)



kur X ir F vai Cl, bet R_1 ir augšminētais, veic halogēna atoma nukleofilo aizvietošanu 7-stāvoklī ar 1-aizvietoto piperazīnu, kura formula ir



un kur R_2 ir augšminētais.

4. Paņēmiens saskaņā ar 1.punktu, raksturīgs ar to, ka to veic ūdens vai spirta/ūdens vidē.

5. Paņēmiens saskaņā ar 1.punktu, raksturīgs ar to, ka to veic temperatūrā no 50°C līdz reakcijas maisījuma flegmas temperatūrai.

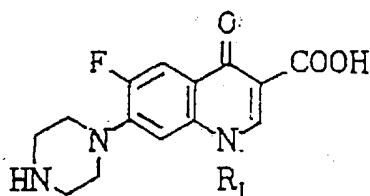
6. Paņēmiens saskaņā ar 3.punktu, raksturīgs ar to, ka to veic organiskā šķīdinātājā, tādā kā piridīns, dimetisufoksīds, dimetilformamīds, 1-metil-2-pirolidons, ieteicamāk 1-metil-2-pirolidonā.

7. Paņēmiens saskaņā ar 3.punktu, raksturīgs ar to, ka to veic temperatūrā no 0° līdz 40°C, ieteicamāk no 20°C līdz 30°C.

Process for preparing 1-substituted-6-fluoro-4-oxo-7-(1-piperazinyl)-1,4-dihydroquinoline-3-carboxylic acid, a novel intermediate useful in said process, and a process for preparing said intermediate

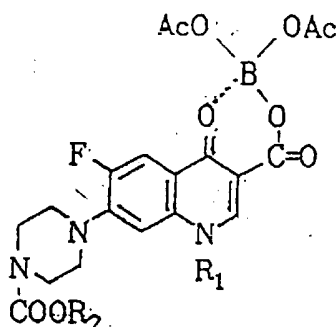
Technical Field

The present invention belongs to the field of organic chemistry and relates to a process for preparing a bioactive compound 1-substituted-6-fluoro-4-oxo-7-(1-piperazinyl)-1,4-dihydroquinoline-3-carboxylic acid of the general formula II



II

wherein R_1 represents lower alkyl, lower cycloalkyl or 2,4-difluorophenyl, to a novel intermediate 1-substituted-6-fluoro-4-oxo-7-(4-substituted-1-piperazinyl)-1,4-dihydroquinoline-3-carboxylate boron diacetate of the general formula I



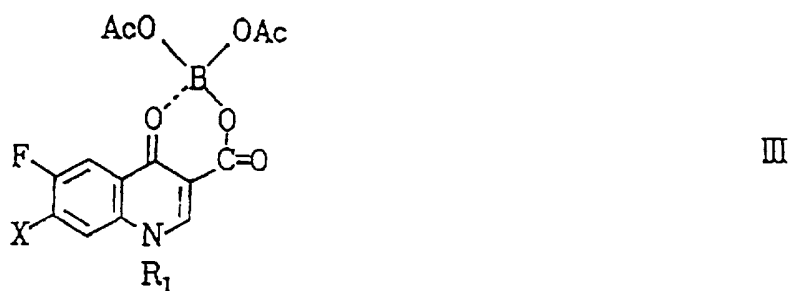
I

wherein R_1 has the above meaning and R_2 represents a lower alkyl or an optionally substituted phenyl, and to a process for the preparation thereof.

The compounds of the formula II are used in medicine for treatment of inflammatory diseases. The activity spectrum thereof is broad since they are active against gram-positive as well as against gram-negative bacteria.

Technical Problem

There was a need to provide a novel process for preparing bioactive compounds of the general formula II, wherein a nucleophilic substitution of halo atom in 7-position in the starting compound 1-substituted-6-fluoro-7-halo-4-oxo-1,4-dihydroquinoline-3-carboxylate boron diacetate of the general formula III



wherein X represents F or Cl, whereas R_1 has the above meaning, with a secondary amine could be carried out under milder reaction conditions in order to reduce the proportion of the obtained substitution product in 6-position.

Prior Art

The synthesis of the compounds of the general formula II is described in several patent documents, e.g. as a substitution of chloro in 7-position of 1-alkyl-6-fluoro-7-halo-4-oxo-1,4-dihydroquinoline-3-carboxylic acid with piperazine in JP 66686/1979 and JP 33453/1980, in DE 2840910 and DE 3308909 and as a hydrolysis reaction of an alkyl ester in 3-position of 1-alkyl-6-fluoro-7-(1-piperazinyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid in BE 890223.

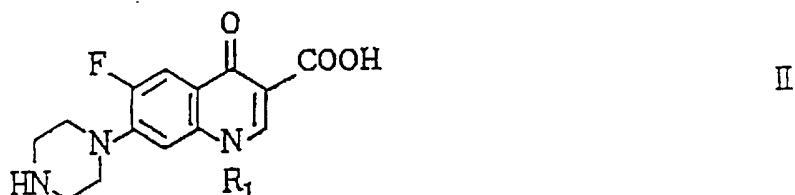
It is characteristic for all these processes that the substitution reaction takes place effectively only at temperatures above 100 °C which gives rise to a large percentage of the competitive reaction in 6-position.

In ES 9001782 there is disclosed a nucleophilic substitution in boron, aluminum and silicon chelates, however the substitution product obtained was not isolated and the hydrolysis to the bioactive compound was immediately carried out. In HU 1505/87 there is also disclosed a nucleophilic substitution of the halo atom in 7-position in a

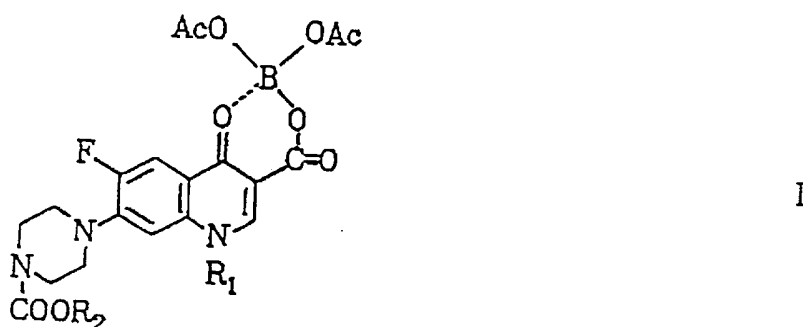
boron chelate complex, which substitution takes place at temperatures above 100 °C. Also in this case the substitution product obtained was not isolated and the hydrolysis was carried out immediately.

The Description of the Inventive Solution

The first object of the invention is a process for preparing 1-substituted-6-fluoro-4-oxo-7-(1-piperazinyl)-1,4-dihydroquinoline-3-carboxylic acid of the general formula II



wherein R_1 represents lower alkyl, lower cycloalkyl or 2,4-difluorophenyl, or a pharmaceutically acceptable acid addition salt thereof such as hydrochloride or lactate and hydrates thereof, characterized in that a compound of the general formula I



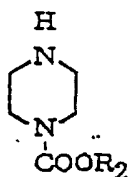
wherein R_1 has the above meaning and R_2 represents a lower alkyl or an optionally substituted phenyl, is subjected to an alkaline hydrolysis and, if desired, the obtained compounds of the general formula I is converted into a pharmaceutically acceptable acid addition salt thereof such as hydrochloride or lactate and hydrates thereof.

The alkaline hydrolysis is carried out in an aqueous or aqueous-ethanolic medium e.g. with an alkali hydroxide solution such as 10% KOH or 10% NaOH, at a temperature from 50 °C to the reflux temperature, preferably at the reflux temperature of the reaction mixture.

After the neutralisation with an acid, preferably acetic acid, there is obtained a product containing (without additional purification) under 0.5% of total impurities.

Another object of the invention is a novel intermediate, i.e. 1-substituted-6-fluoro-4-oxo-7-(4-substituted-1-piperazinyl)-1,4-dihydroquinoline-3-carboxylate boron diacetate of the general formula I, useful as a starting material in the above process for preparing the bioactive compound of the general formula II.

Still another object of the invention is a process for preparing the novel intermediate of the general formula I, wherein in 1-substituted 6-fluoro-7-halo-4-oxo-1,4-dihydroquinoline-3-carboxylate boron diacetate of the general formula III a nucleophilic substitution of the halo atom in 7-position is carried out with 1-substituted piperazine of the formula



wherein R_2 has the above meaning.

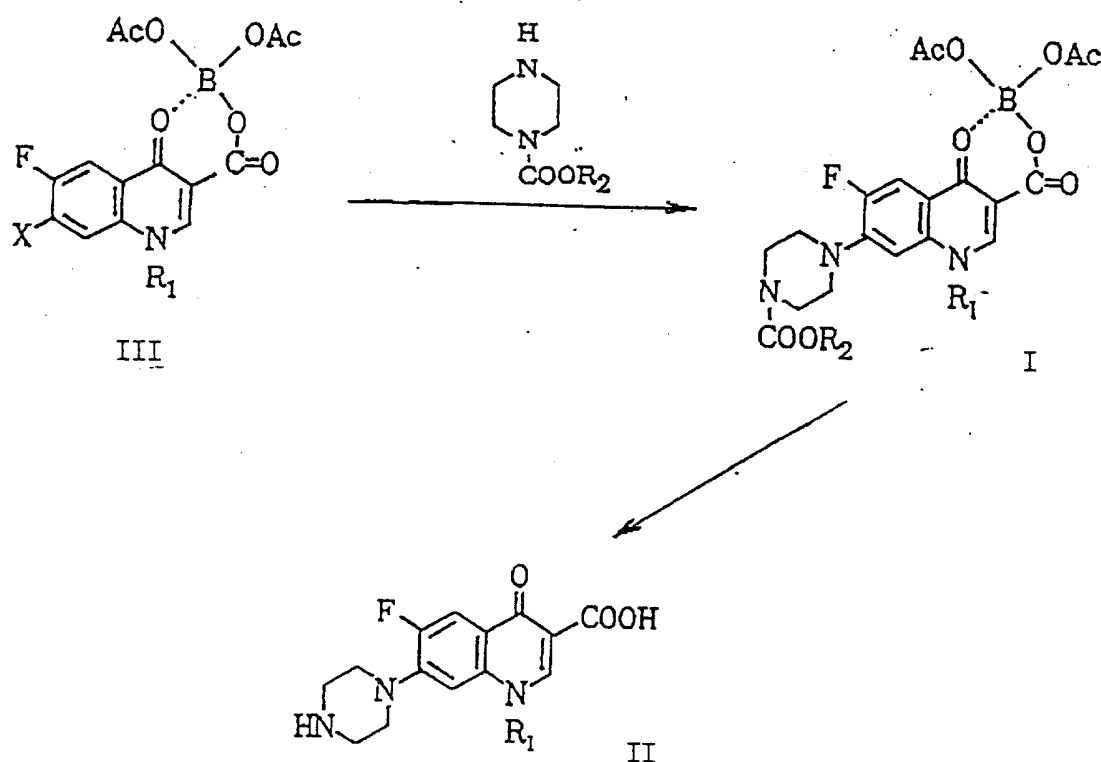
The reaction is carried out in an organic solvent such as pyridine, dimethylsulfoxide, dimethylformamide, 1-methyl-2-pyrrolidone, preferably in 1-methyl-2-pyrrolidone, at temperatures from 0 °C to 40 °C, preferably from 25 °C to 30 °C. At these temperatures the reaction is completed in 1-methyl-2-pyrrolidone as a solvent in 10 to 15 hours, no by-products are formed and also the hydrolysis of the boron salt does not occur. At the reaction temperatures above 40 °C the decomposition of the boron salt is noticeable and increases very rapidly with the elevated temperature. The 3-carboxylic acid formed as a result of this decomposition is much less reactive since the nucleophilic substitution occurs at temperatures above 100 °C.

The isolation of the obtained compound of the formula I is very simple, since at precipitating with alcohol it is obtained in a pure form and no additional purification is necessary.

The compound of the general formula I is used as a starting material for preparing the compound of the general formula II in an isolated form or *in situ*.

All reactants are either commercially available or may be obtained as described herein.

Both inventive processes are illustrated by the following reaction scheme, wherein X, R₁ and R₂ have the above meanings.



The invention is disclosed more in detail in the following Examples but it is in no way limited thereto.

Example 1

1-cyclopropyl-6-fluoro-4-oxo-7-(4-carboethoxy-1-piperazinyl)-1,4-dihydroquinoline-3-carboxylate boron diacetate

1-cyclopropyl-6-fluoro-4-oxo-7-chloro-1,4-dihydroquinoline-3-carboxylate boron diacetate (10 g; 0.0244 moles) and 1-carboethoxypiperazine (15.44 g; 0.0977 moles) was suspended in 1-methyl-2-pyrrolidone (40 ml) and stirred at the temperature of 30 °C for 12 hours. After the reaction was completed, absolute ethanol (60 ml) was added to the reaction mixture and it was stirred at room temperature for 2 hours. The precipitate obtained was suction-filtered, washed with ethanol and dried *in vacuo* at 80 °C. The filtrate was cooled to 0 - 5 °C and the obtained precipitate was suction-filtered, suspended into a 1-methyl-2-pyrrolidone/ethanol mixture (2:1) and macerated for 2 hours, suction-filtered and dried. The products were combined. Thus a chromatographically pure 1-cyclopropyl-6-fluoro-4-oxo-7-(4-carboethoxy-1-piperazinyl)-1,4-dihydroquinoline-3-carboxylate boron diacetate (10.75 g; 83%), m.p. 235 to 240 °C, was obtained.

Spectroscopic data:

¹H NMR spectrum (CF₃COOH, TMS) (recorded on a 300 MHz instrument):

$\delta_{\text{CH}_2(\text{cyclopropyl})} = 1.29$ (m, J=8Hz, 2H), $\delta_{\text{CH}_3} = 1.30$ (t, J=8Hz, 3H), $\delta_{\text{CH}_2(\text{cyclopropyl})} = 1.52$ (m, J=8Hz, 2H), $\delta_{\text{CH}_3} = 2.03$ (s, 6H), $\delta_{\text{CH}_2(\text{piperazinyl})} = 3.42$ (m, 4H), $\delta_{\text{CH}_2(\text{piperazinyl})} = 3.74$ (m, 4H), $\delta_{\text{CH}(\text{cyclopropyl})} = 3.73$ (m, J=8Hz, 1H), $\delta_{\text{OCH}_2} = 4.2$ (q, J=8Hz, 2H), $\delta_{\text{H}_8} = 7.48$ ppm (d, J=8Hz, 1H), $\delta_{\text{H}_5} = 8.08$ (d, J=14.3Hz, 1H), $\delta_{\text{H}_2} = 9.0$ ppm (s, 1H).

IR spectrum:

1700, 1630, 1480, 1370, 1275, 1240, 1060, 960 cm⁻¹.

Example 2

1-ethyl-6-fluoro-4-oxo-7-(4-carboethoxy-1-piperazinyl)-1,4-dihydroquinoline-3-carboxylate boron diacetate

1-ethyl-6-fluoro-4-oxo-7-chloro-1,4-dihydroquinoline-3-carboxylate boron diacetate (2.37 g, 0.006 moles) and 1-carboethoxypiperazine (3.78 g; 0.024 moles) were suspended in 1-methyl-2-pyrrolidone (9.5 ml) and stirred at 30 °C for 9 hours. After the reaction was completed, absolute ethanol (19 ml) was added to the reaction mixture and it was stirred at room temperature for 2 hours. The obtained product was suction-filtered, washed with ethanol and dried *in vacuo* at 80 °C. Thus 1-ethyl-6-fluoro-4-oxo-7-(4-carboethoxy-1-piperazinyl)-1,4-dihydroquinoline-3-carboxylate boron diacetate (2.7 g; 87%), m.p. 235 to 238 °C, was obtained.

Spectroscopic data:

¹H NMR spectrum (CF₃COOH, TMS) (recorded on a 60 MHz instrument):

$\delta_{\text{CH}_3} = 1.53$ (t, J=7Hz, 3H), $\delta_{\text{CH}_3} = 1.97$ (t, J=7Hz, 3H), $\delta_{\text{CH}_3} = 2.4$ (s, 6H), $\delta_{\text{CH}_2(\text{piperazinyl})} = 4.0$ (m, 8H), $\delta_{\text{NCH}_2} = 4.53$ (q, J=7Hz, 2H), $\delta_{\text{OCH}_2} = 5.03$ (q, J=7Hz, 2H), $\delta_{\text{H}_8} = 7.7$ (d, J=6Hz, 1H), $\delta_{\text{H}_5} = 8.4$ (d, J=12Hz, 1H), $\delta_{\text{H}_2} = 9.6$ ppm (s, 1H).

¹⁹F NMR spectrum (CF₃COOH, CFCl₃) (recorded on a 60 MHz instrument):

$\delta_{\text{F}} = -114.0$ ppm (dd, J=12Hz; 6Hz).

IR spectrum:

1700, 1635, 1490, 1375, 1285, 1240, 1060, 970 cm⁻¹.

Example 3

1-cyclopropyl-6-fluoro-4-oxo-7-(1-piperazinyl)-1,4-dihydroquinoline-3-carboxylic acid

1-cyclopropyl-6-fluoro-4-oxo-7-(4-carboethoxy-1-piperazinyl)-1,4-dihydroquinoline-3-carboxylate boron diacetate (10 g; 0.0188 mole) was suspended in 10% KOH (187 ml) and heated at reflux temperature for 1.5 hours. Then the reaction mixture was cooled to room temperature and the pH was adjusted to 7.2-7.4 with acetic acid. The reaction mixture was stirred for another 30 minutes, the precipitate was suction-

filtered, washed with water and dried. Thus 1-cyclopropyl-6-fluoro-4-oxo-7-(1-piperazinyl)-1,4-dihydroquinoline-3-carboxylic acid (5.95 g; 96%), m.p. 258 to 263 °C, was obtained.

Example 4

1-cyclopropyl-6-fluoro-4-oxo-7-(1-piperazinyl)-1,4-dihydroquinoline-3-carboxylic acid hydrochloride monohydrate

1-cyclopropyl-6-fluoro-4-oxo-7-(4-carboethoxy-1-piperazinyl)-1,4-dihydroquinoline-3-carboxylate boron diacetate (3 g; 0.0056 moles) was suspended in 10% KOH (56 ml) and heated at reflux temperature for 1.5 hours. After the reaction was completed, concentrated HCl (8 ml) was added and it was heated at the temperature of 80 °C for 30 minutes. Then the reaction mixture was cooled to room temperature, ethanol (14 ml) was added, it was stirred for another 30 minutes, the obtained precipitate was suction-filtered, washed with water and dried to the constant weight. Thus 1-cyclopropyl-6-fluoro-4-oxo-7-(1-piperazinyl)-1,4-dihydroquinoline-3-carboxylic acid hydrochloride monohydrate (1.98 g; 92%), m.p. 282 to 288 °C, was obtained.

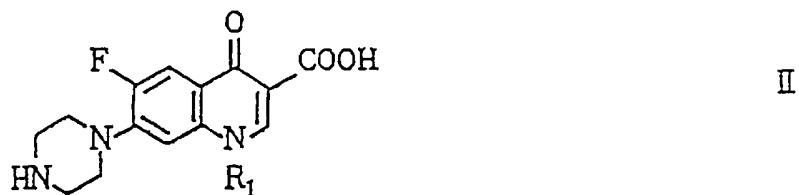
Example 5

1-ethyl-6-fluoro-4-oxo-7-(1-piperazinyl)-1,4-dihydroquinoline-3-carboxylic acid

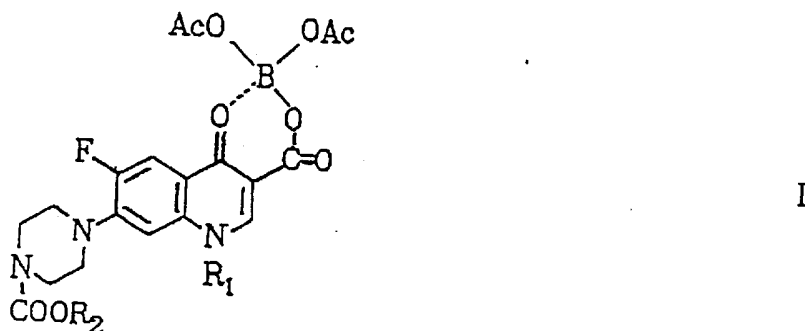
1-ethyl-6-fluoro-4-oxo-7-(4-carboethoxy-1-piperazinyl)-1,4-dihydroquinoline-3-carboxylate boron diacetate (1.04 g; 0.002 mole) was suspended in 10% KOH (16 ml) and ethanol (12 ml) and heated at the reflux temperature of the mixture for 11 hours. Then the mixture was cooled to 15 °C, the pH was adjusted to 7.2-7.4 with 15% HCl and it was stirred at this temperature for further 30 minutes. The precipitate obtained was suction-filtered, washed with water and dried to a constant weight in a vacuum drier at 100 °C. Thus 1-ethyl-6-fluoro-4-oxo-7-(1-piperazinyl)-1,4-dihydroquinoline-3-carboxylic acid (0.6 g; 93%), m.p. 218 to 221 °C, was obtained.

CLAIMS

1. Process for preparing 1-substituted-6-fluoro-4-oxo-7-(1-piperazinyl)-1,4-dihydroquinoline-3-carboxylic acid of the general formula II

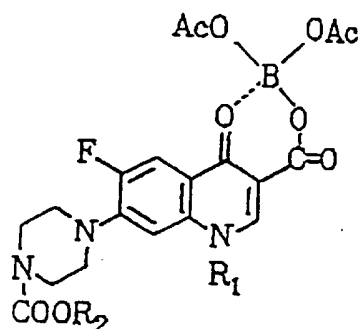


wherein R_1 represents a lower alkyl, a lower cycloalkyl or 2,4-difluorophenyl, or a pharmaceutically acceptable acid addition salt thereof such as hydrochloride or lactate and hydrates thereof, characterized in that a compound of the general formula I



wherein R_1 has the above meaning and R_2 represents a lower alkyl or an optionally substituted phenyl, is subjected to an alkaline hydrolysis and, optionally, the obtained compound of the general formula II is converted into a pharmaceutically acceptable acid addition salt thereof such as hydrochloride or lactate and hydrates thereof.

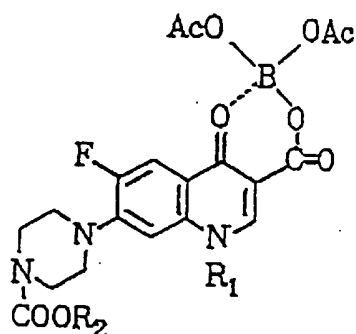
2. 1-substituted-6-fluoro-4-oxo-7-(4-substituted-1-piperazinyl)-1,4-dihydroquinoline-3-carboxylate boron diacetate of the general formula I



I

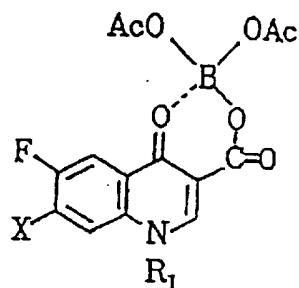
wherein R_1 represents a lower alkyl, a lower cycloalkyl or 2,4-difluorophenyl and R_2 represents a lower alkyl or an optionally substituted phenyl.

3. Process for preparing 1-substituted-6-fluoro-4-oxo-7-(4-substituted-1-piperazinyl)-1,4-dihydroquinoline-3-carboxylate boron diacetate of the general formula I



I

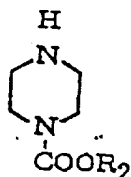
wherein R_1 represents a lower alkyl, a lower cycloalkyl or 2,4-difluorophenyl and R_2 represents a lower alkyl or an optionally substituted phenyl, characterized in that in 1-substituted-6-fluoro-7-halo-4-oxo-1,4-dihydroquinoline-3-carboxylate boron diacetate of the general formula III



III

wherein X represents F or Cl, whereas R_1 has the above meaning,

a nucleophilic substitution of the halo atom in 7-position is carried out with 1-substituted piperazine of the formula

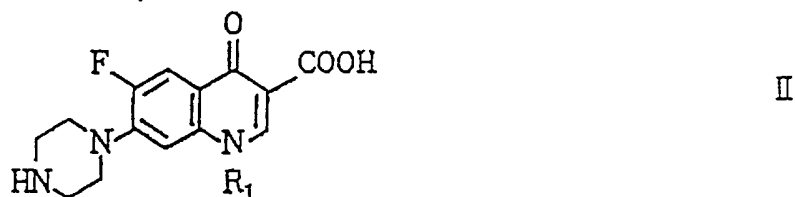


wherein R₂ has the above meaning.

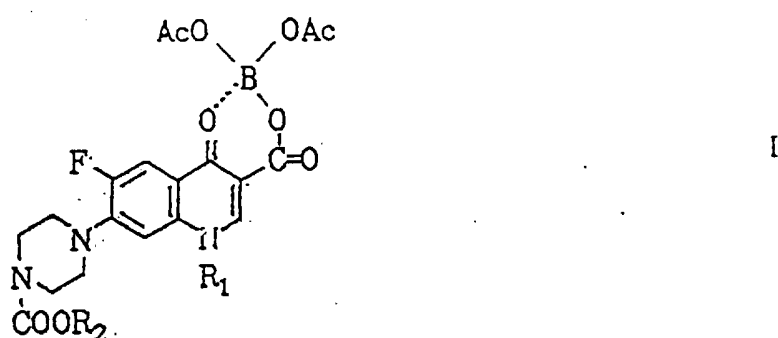
4. Process according to claim 1, characterized in that it is carried out in an aqueous or ethanolic/aqueous medium.
5. Process according to claim 1, characterized in that it is carried out at a temperature from 50 °C to the reflux temperature of the reaction mixture.
6. Process according to claim 3, characterized in that it is carried out in an organic solvent such as pyridine, dimethylsulfoxide, dimethylformamide, 1-methyl-2-pyrrolidone, preferably in 1-methyl-2-pyrrolidone.
7. Process according to claim 3, characterized in that it is carried out at temperatures from 0 °C to 40 °C, preferably from 20 °C to 30 °C.

ABSTRACT

Disclosed is a process for preparing 1-substituted-6-fluoro-4-oxo-7-(1-piperazinyl)-1,4-dihydroquinoline-3-carboxylic acid of the formula II

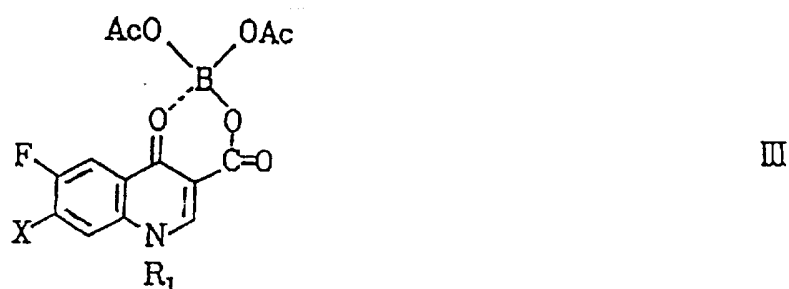


wherein R_1 represents a lower alkyl, a lower cycloalkyl or 2,4-difluorophenyl, wherein 1-substituted-6-fluoro-4-oxo-7-(4-substituted-1-piperazinyl)-1,4-dihydroquinoline-3-carboxylate boron diacetate of the formula I



wherein R_2 represents a lower alkyl or an optionally substituted phenyl, is subjected to an alkaline hydrolysis. Compounds of the formula II are used in medicine for the treatment of inflammatory diseases.

The compound of the formula I is novel. It is obtained by a nucleophilic substitution of the halo atom in 7-position in the compound of the formula III



with 1-substituted piperazine of the formula

