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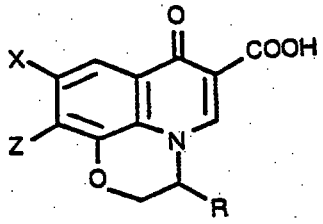
Description

Background of the Invention

US—A—3,883,522 and US—A—3,984,548 describe 9-fluoro-3-methyl-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid, Japanese Patent Application (OPI) No. 138582/1979 describe 1-ethyl-6-fluoro-7-(4-methyl-1-piperazinyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid similar compounds are known from DE—A—2939286, Japanese Patent Application (OPI) No. 76875/1980 describes 8-(4-methyl-1-piperazinyl)-9-fluoro-5-methyl-6,7-dihydro-1-oxo-1H,5H-benz[ij]quinolizine-2-carboxylic acid (the term "OPI" as used herein refers to a "published unexamined patent application"); similar compounds are disclosed in DE—A—2914258. The known compounds are all antibacterially active.

Summary of the Invention

This invention relates to anti-bacterially active to 9-halo-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid derivatives having the formula I



(I)

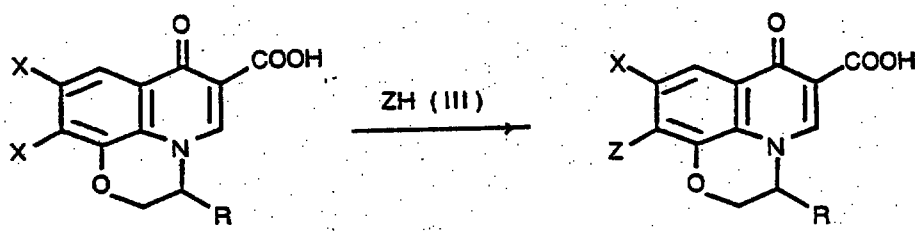
wherein X represents a halogen atom, R represents a hydrogen atom or an alkyl group having from 1 to 6 carbon atoms and Z represents monoethylamino, monomethylamino, diethylamino, dimethylamino, hydrazyl, methylhydrazyl, azetidinyl, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl and homopiperazinyl, in which the alkyl radicals and heterocycles may be further substituted by one or more substituents selected from the group consisting of a hydroxy group, an alkyl group having from 1 to 6 carbon atoms, an amino group, a hydroxyalkyl group having from 1 to 6 carbon atoms, and a monoalkylamino and a dialkylamino group having from 1 to 6 carbon atoms in each alkyl moeity, and the pharmaceutically acceptable salts thereof.

The invention also comprises the compound 9 - fluoro - 3 - methyl - 7 - oxo - 10 - (4 - thiamorpholinyl) - 2,3 - dihydro - 7H - pyrido[1,2,3 - de][1.4]benzoxazine - 6 - carboxylic acid. The substituent Z in formula I means, for example, 4-methyl-1-piperazinyl, 1-piperazinyl, 1-pyrrolidinyl, 3-hydroxy-1-pyrrolidinyl, 1-piperidinyl, 4-hydroxy-1-piperidinyl, 3-hydroxy-1-piperidinyl, 4-morpholinyl, 4-(2-hydroxyethyl)piperazinyl, 3,5-dimethyl-1-piperazinyl, 4-dimethylamino-1-piperidinyl, homopiperazinyl, 1-pyrazolidinyl, 2-methyl-1-pyrazolidinyl, N-(2-hydroxyethyl)amino, N-(2-hydroxyethyl)-N-methylamino, hydrazyl, and methylhydrazyl.

The compounds of this invention can form an acid addition salt with an inorganic or organic acid such as hydrochloric acid, sulfuric acid, methanesulfonic acid and the like and can form the corresponding carboxylate with sodium, potassium and the like. In comparison with the above-described known compounds, the compounds of this invention have more excellent antibacterial activity against gram-negative and gram-positive bacteria, as well as lower toxicity.

Detailed description of the Invention

Compounds according to this invention can be prepared by the reaction illustrated below.



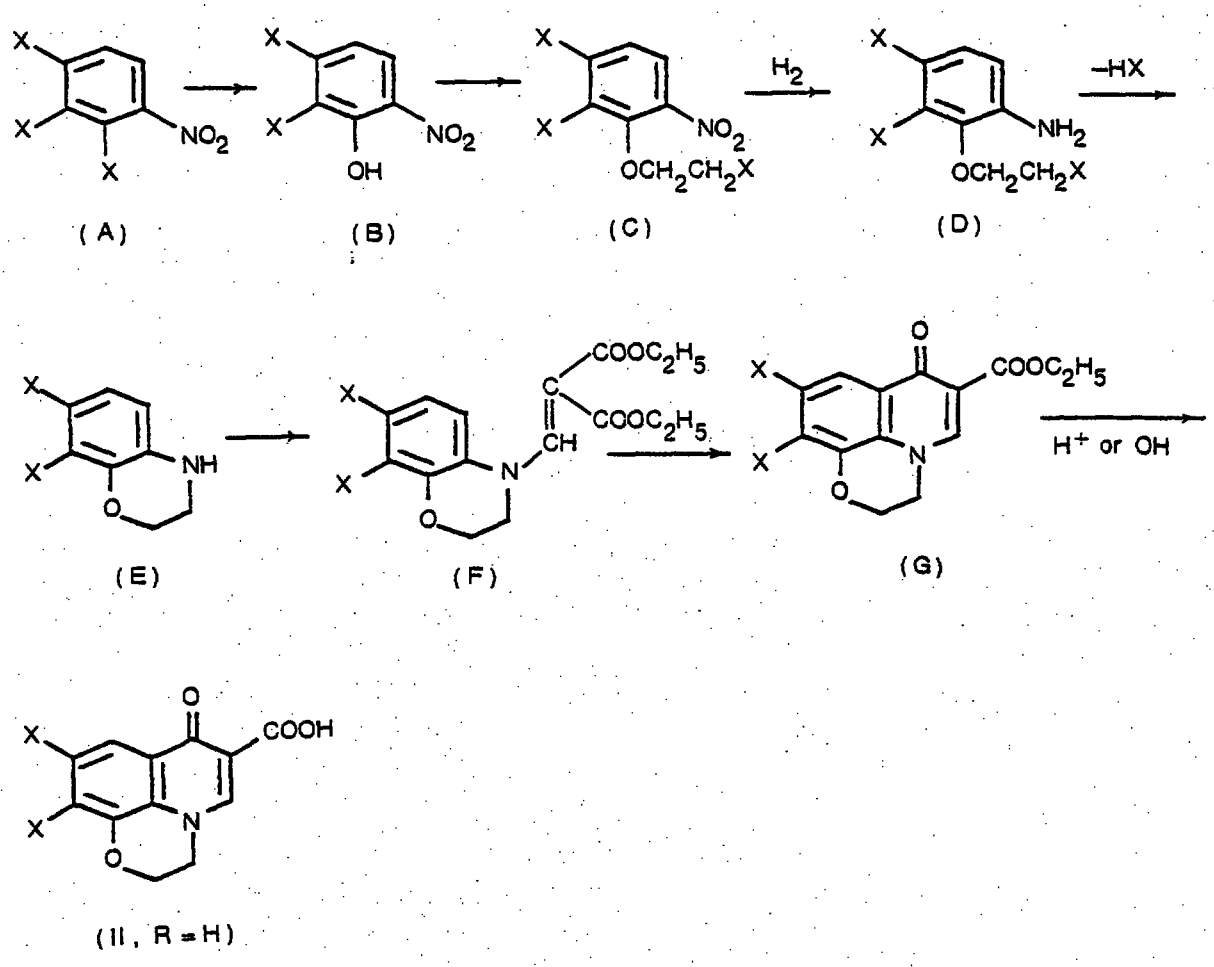
(II) (I)

(10)

wherein X, R and Z are the same as described above. The reaction may be performed by heating a compound of the formula (II) with an amine of the formula (III) at a temperature of from 30°C to 200°C, and preferably from 70°C to 150°C, in the presence of a suitable organic polar solvent such as dimethylsulfoxide, sulfolane, dimethylformamide, dimethylacetamide or water. It is desirable to carry out the reaction in the presence of an acid-acceptor such as triethylamine, dimethylaniline, potassium carbonate at a molar ratio of 1.0 to 1.2 mol of the acid-acceptor per mol of the compound of the formula II. As the raw material of the formula III is an amine itself, it may act also as the acid-acceptor. In such a case, it is desirable to use two or more moles of the amine of the formula III to one mole of the compound of the formula II. When another acid-acceptor like triethylamine is employed, it may be adequate to use the amine of the formula III at a molar ratio of 1.0 to 1.2 mol per mol of the compound of the formula II.

The reaction is normally completed in a period of from 1 to 48 hours and the product can be isolated and purified by conventional techniques such as evaporation, filtration, extraction, chromatography, recrystallization and a combination thereof. For example, when the product is precipitated by cooling the reaction mixture, it is collected by filtration and if precipitation is not found, the reaction mixture is concentrated to dryness under reduced pressure and the residue is shaken with a mixture of chloroform and water, then the product is obtained by concentrating the chloroform layer. In case the product is colored or contains some by-products, further purification can be performed by a silica gel chromatography or recrystallization.

Starting compounds of the formula II for preparing the compounds of this invention are novel compounds and can be prepared from known compound (A) [J. Amer. Chem. Soc., *81*, 94—101 (1959)] by the method outlined below.



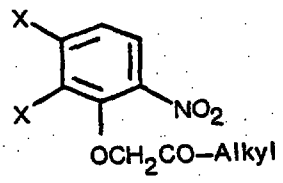
In the formula, X represents a halogen atom.

When 2,3,4-trihalonitrobenzene (A) is hydrolyzed in the presence of potassium hydroxide, triethylamine and the like, 2,3-dihalo-6-nitrophenol (B) is produced. The compound (B) is heated with 1,2-dihalogenoethane at a temperature of from 50°C to 150°C, and preferably at from 80°C to 120°C.

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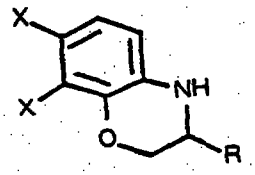
While stirring in an organic polar solvent such as ethanol, dimethylformamide or dimethylsulfoxide in the presence of an acid-acceptor such as an inorganic base, for instance potassium carbonate and sodium carbonate, or an organic base, for instance triethylamine and N,N-dimethylaniline, to produce the compound of the formula (C). The nitro group of the compound (C) is then reduced by a common reduction using sodium dithionite or iron-hydrochloric acid or a catalytical reduction with Raney nickel, and the compound of the formula (D) is produced. When the compound (D) is heated at a temperature of from 50°C to 150°C in the presence of an acid-acceptor which is used in the process (B) to (C), in a polar solvent such as ethanol or dimethylformamide, a benzoxazine derivative (E) is obtained. The benzoxazine derivative (E) is heated with diethyl ethoxymethylenemalonate at from 80°C to 150°C in the presence of a solvent such as ethanol or in the absence of solvent to produce the compound (F). When ring closure reaction is performed by heating the compound (F) at a temperature of from 120°C to 150°C in polyphosphoric acid or an ester thereof, a tricyclic compound (G) is prepared. The ester moiety of the compound (G) is hydrolyzed by a conventional method using an acid or base, the starting compound of the formula II wherein substituent R is a hydrogen is obtained. The compounds (B) to (G) are also novel compounds.

In case the substituent R in formula II is alkyl, the starting material of the formula II can be prepared by a somewhat different process. That is, the compound of the formula (B) described above is heated with a halomethylalkylketone, such as monochloroacetone, at from 50°C to 150°C in the presence of an acid-acceptor such as potassium carbonate or sodium carbonate in a polar solvent such as acetone, alcohols or dimethylformamide, preferably in the presence of a catalytic amount of potassium iodide, to produce the compound of the formula (H).



(H)

When the compound (H) is catalytically treated with Raney nickel or palladium/carbon, reduction of the nitro group, ring closure with dehydration from the resulting amino group and the oxo group and hydrogenation of the resulting double bond proceed simultaneously and a compound of the formula (J) is obtained.



(J)

The compound (J) can be converted into the starting material of the formula II wherin the substituent R is alkyl according to the method as used when R is hydrogen.

The antibacterial activity (in vitro) of compounds of this invention (9 - fluoro - 10 - (4 - methyl - 1 - piperazinyl) - 3 - methyl - 7 - oxo - 2,3 - dihydro - 7H - pyrido[1,2,3 - de][1,4]benzoxazine - 6 - carboxylic acid (Ia), 9 - fluoro - 3 - methyl - 7 - oxo - 10 - (1 - piperazinyl) - 2,3 - dihydro - 7H - pyrido[1,2,3 - de][1,4]benzoxazine - 6 - carboxylic acid (Ib), 9 - fluoro - 10 - (3 - hydroxy - 1 - pyrrolidinyl) - 3 - methyl - 7 - oxo - 2,3 - dihydro - 7H - pyrido[1,2,3 - de][1,4]benzoxazine - 6 - carboxylic acid (Ic), and 9 - chloro - 3 - methyl - 10 - (4 - methyl - 1 - piperazinyl) - 7 - oxo - 2,3 - dihydro - 7H - pyrido[1,2,3 - de][1,4]benzoxazine - 6 - carboxylic acid (Id) is shown in the following Tables 1 and 2 in comparison with pipemidic acid (8-ethyl - 5,8 - dihydro - 5 - oxo - 2 - (1 - piperazinyl) - pyrido[2,3 - d]pyrimidine - 6 - carboxylic acid, a known antibacterial drug) (abbreviated as PPA in Table 1).

(12)

TABLE 1

Minimum Inhibitory Concentration (MIC, μg/ml)*

Test Organisms	PPA	Ia	Ib	Ic
Escherichia coli NIHJ	1.56	≦0.025	≦0.025	0.05
Shigella flexneri 2a, 5503	1.56	0.05	0.05	0.1
Proteus vulgaris, 3167	1.56	0.05	0.05	0.1
Proteus mirabilis, 1287	6.25	0.1	0.1	0.1
Klebsiella pneumoniae, 501	6.25	0.2	0.39	0.78
Enterobacter cloacae, 12001	1.56	0.1	0.2	0.2
Serratia marcescens, 13001	6.25	0.2	0.78	0.78
Pseudomonas aeruginosa, 2063	25	1.56	0.78	1.56
Pseudomonas sepacia, II D 1340	100	Not tested	12.5	Not tested
Staphylococcus aureus, 209 P	12.5	0.39	0.39	0.1
Streptococcus pyogenes, G—36	>100	1.56	3.13	0.78
Bacillus subtilis, ATCC 6633	6.25	0.2	0.39	0.05

* Determined by the standard method of the Japan Society of Chemotherapy: dilution method on plate culture (heart infusion agar culture), 10^6/ml of bacteria were seeded and incubated at 37°C for 18 hours.

(13)

TABLE 2

Minimum Inhibitory Concentration (MIC, μg/ml)*

Test Organisms	Ia	Id
Escherichia coli NIHJ	≦0.05	≦0.05
Shigella flexneri 2a, 5503	≦0.05	≦0.05
Proteus vulgaris, 3167	≦0.05	≦0.05
Proteus mirabilis, 1287	0.1	0.1
Klebsiella pneumoniae, 501	0.39	0.2
Enterobacter cloacae, 12001	0.1	≦0.05
Serratia marcescens, 13001	0.1	0.1
Pseudomonas aeruginosa, 2063	0.78	0.78
Pseudomonas sepacia, II D 5132	12.5	6.25
Staphylococcus aureus, 209 P	0.39	0.2
Streptococcus pyogenes, G—36	1.56	12.5
Bacillus subtilis, ATCC 6633	0.1	0.1

* Determined in Müller-Hinton Bouillon, 10^6/ml of bacteria were seeded and incubated at 37°C for 18 hours.

As can be seen from Tables 1 and 2, the compounds of this invention exert higher antibacterial effects on the test organisms than the known drug. Additionally, the compounds of this invention exhibit very low toxicity. For example, the acute toxicity (LD_{50}) of the compound (Ia) is 380 mg/kg, in mice (i.v.).

On the other hand, known compounds, such as 8-(4-methyl-1-piperazinyl)-9-fluoro-5-methyl-6,7-dihydro-1-oxo-1H,5H-benz[ij]quinolizine-2-carboxylic acid (Japanese Patent Application (OPI) No. 76875/1980) and 1-ethyl-6-fluoro-4-oxo-7-(4-methyl-1-piperazinyl)quinoline-3-carboxylic acid (Japanese Patent Application (OPI) No. 138582/1979) have comparatively high toxicity [135 mg/kg and 225 mg/kg, respectively, in mice (i.v.)]. Although PPA has a low toxicity [LD_{50} = 610 to 649 mg/kg in mice (i.v.)], the antibacterial activity of PPA is much weaker than that of the compounds of this invention as shown in Table above.

The present invention is further illustrated by the following Examples. Unless otherwise indicated, all parts, percents, ratios, and the like are by weight.

Example 1

Product of starting material:

20 g of 2,3,4-trifluoronitrobenzene was dissolved in 150 ml of dimethyl sulfoxide, and to this mixture a solution of 10% potassium hydroxide was added dropwise while keeping the temperature at 18 to 20°C. Then the mixture was stirred for 2 hours at room temperature and one liter of water was added to this reaction mixture and the mixture was shaken with chloroform. The water layer was acidified with hydrochloric acid and was extracted with chloroform. The extract was washed with water and was dried, then the chloroform layer was concentrated. The residue was purified by silica gel column chromatography to provide 5.8 g of 2,3-difluoro-6-nitrophenol as yellow oil.

7.9 g of the 2,3-difluoro-6-nitrophenol, 50.1 g of 1,2-dibromoethane and 18.7 g of potassium carbonate were added to 80 ml of dimethylformamide and the mixture was stirred for 2.5 hours at from about 80 to 100°C (bath temperature). The reaction mixture was concentrated to dryness in vacuo and the residue was distributed between ethyl acetate and water. The organic solvent layer was washed with water and was dried, then the solvent was evaporated. The residue was dissolved in benzene and was purified by silica gel column chromatography to provide 7.7 g of 2-(2-bromoethoxy)-3,4-difluoro-nitrobenzene as light yellow oil.

(14)

NMR ($CDCl_3$): δ (ppm)
3.75 (2H, t, J = 7Hz, —CH_2Br)
4.62 (2H, t, J = 7Hz, —OCH_2—)
6.92—7.04 and 7.65—7.93
(respectively 1H, m, C^5—H and C^6—H)

1.74 g of this product was dissolved in 30 ml of methanol and a solution of 6.44 g of sodium dithionite dissolved in 15 ml of water was added thereto. The mixture was stirred for 1 hour at room temperature. Methanol was evaporated and the residue was extracted with chloroform. After the extract was washed with water and dried, the solvent was evaporated to provide 0.44 g of 2-(2-bromoethoxy)-3,4-difluoroaniline.

NMR ($CDCl_3$): δ (ppm)
3.67 (2H, t, J = 6Hz, —CH_2Br)
3.90 (2H, s, NH_2)
4.42 (2H, t, J = 6Hz, —OCH_2—)
6.30—6.90 (2H, m, C^5—H and C^6—H)

1.82 g of this product and 3.03 g of potassium carbonate were added to 10 ml of dimethylformamide and the mixture was stirred for 1 hour at from about 80 to 100°C (bath temperature). The reaction mixture was added to ice-cold water and was extracted with ethyl acetate. After the extract was washed with water and dried, the solvent was distilled off at room temperature to provide 1.21 g of 7,8-difluoro-2,3-dihydro-4H-[1,4]benzoxazine with m.p. 48—54°C.

NMR ($CDCl_3$): δ (ppm)
3.38 (2H, t, J = 5.5Hz, —NHCH_2—)
3.70 (1H, b.s., N*H*)
4.28 (2H, t, J = 5.5Hz, —OCH_2—)
6.17—6.80 (2H, m, C^5—H, C^6—H)

The mixture of 1.1 g of this product and 1.38 g of diethyl ethoxymethylenemalonate was stirred for 2 hours at from about 130 to 135°C (bath temperature). The ethanol produced was evaporated and 20 g of ethyl polyphosphate was added to the residue. Then the mixture was stirred for 1.5 hours at from about 140 to 145°C (bath temperature). The reaction mixture was added to ice-cold water and was extracted with chloroform. The extract was washed fully with water. After drying, the solvent was evaporated and the residue was recrystallized from ethyl acetate. 1.3 g of ethyl 9,10-difluoro-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylate was obtained as colorless needles with m.p. 265—266°C.

NMR (CF_3COOH): δ (ppm)
1.58 (3H, t, J = 7.5Hz, —CH_2CH_3)
4.76 (2H, q, J = 7.5 Hz, —CH_2CH_3)
4.96 (4H, b.s., —CH_2—CH_2—)
8.17 (1H, q, C^8—H)
9.35 (1H, s, C^5—H)

1.15 g of this product was added to 12 ml of mixture of concentrated hydrochloric acid and acetic acid (1:4 by volume) and the mixture was stirred for 4 hours at 100 to 110°C (bath temperature). After cooling, the precipitated crystals were collected by filtration, washed with water, methanol and chloroform to give 0.78 g of 9,10-difluoro-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid as colorless needles with m.p. above 300°C.

Analysis for $C_{12}H_7FNO_4$

Calculated: C 53.94, H 2.64, N 5.24

Found: C 53.81, H 2.75, N 5.26

NMR (CF_2COOH): δ (ppm)
5.0 (4H, b.s., —CH_2CH_2—)
8.17 (1H, q, C^8—H)
9.45 (1H, s, C^5—H)

Example 2

Production of starting material:

5.8 g of 2,3-difluoro-6-nitrophenol, 5.0 g of monochloroacetone, 8.0 g of potassium carbonate and 0.8 g of potassium iodide were added to 100 ml of acetone and the mixture was refluxed for 4 hours. After the removal of insoluble material by filtration, the solvent was evaporated and the residue

(15)

was distributed between chloroform and water. The chloroform layer was washed with water and was dried, then the solvent was evaporated. The residue was treated with n-hexane to provide 5.0 g of 2-acetonyloxy-3,4-difluoronitrobenzene as light yellow crystals with m.p. 61°C.

7.1 g of this product was dissolved in 200 ml of ethanol and 14 ml of Raney-nickel was added to this mixture. The mixture was catalytically reduced under normal atmospheric pressure. After the removal of catalyst by filtration and the evaporation of the solvent, the residue was dissolved in chloroform and decolored by passing through a silica gel column to provide 5.1 g of 7,8-difluoro-2,3-dihydro-3-methyl-4H-benzoxazine in the form of light yellow oil.

The mixture of 4.8 g of this product and 5.3 g of diethyl ethoxymethylenemalonate was heated for 1 hour at from about 140 to 145°C (bath temperature). After reaction, the ethanol produced was removed by evaporation to provide an oily product. 35 g of ethyl polyphosphate was added thereto and the mixture was stirred for 1 hour at from about 140 to 145°C (bath temperature). After cooling, the reaction mixture was added to ice-cold water. Precipitate was extracted with 200 ml of chloroform, this procedure was carried out three times, and the extracts were combined and was washed with a 5% potassium hydroxide solution and water. The chloroform layer was dried with sodium sulfate to provide 5.1 g of ethyl 9,10-difluoro-3-methyl-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylate as white powder with m.p. 261°C.

4.0 g of this product was dissolved in 50 ml of a mixture of concentrated hydrochloric acid and acetic acid (1:4 by volume) and this mixture was refluxed for 3 hours on an oil bath. After cooling the precipitated crystal was collected by filtration, washed thoroughly with water. The crystal was washed with a mixture of ethanol and ether (1/4 volume ratio) and was dried in vacuo to provide 3.7 g of 9,10-difluoro-3-methyl-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid as transparent plates with m.p. above 300°C.

Example 3

1.0 g of 9,10-difluoro-3-methyl-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid and 2.85 g of N-methylpiperazine were added to 15 ml of dimethylsulfoxide. The mixture was stirred at a temperature of from about 100 to 110°C (bath temperature) for 12 hours and the reaction mixture was concentrated to dryness in vacuo and 40 ml of water was added to the residue. Then the product was extracted with chloroform. The extract was dried and concentrated to dryness in vacuo. The residue was recrystallized from ethanol to provide 550 mg of 9-fluoro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid as colorless needles with m.p. 250—257°C (with decomposition).

Analysis for $C_{18}H_{20}FN_3O_4$

Calculated: C 59.82, H 5.58, N 11.63

Found: C 59.62, H 5.59, N 11.65

Example 4

140 mg of 9,10-difluoro-3-methyl-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid and 404 mg of 4-hydroxypiperidine were added to 2 ml of dimethylsulfoxide. The mixture was stirred at a temperature of from about 100 to 110°C (bath temperature) for 5.5 hours and the reaction mixture was concentrated to dryness in vacuo. Water was added to the residue and the mixture was neutralized with diluted hydrochloric acid to yield precipitate. The precipitate was collected by filtration, washed with water, and then recrystallized from ethanol to provide 66 mg of 9-fluoro-10-(4-hydroxy-1-piperidinyl)-3-methyl-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid with m.p. 220—240°C (with decomposition).

Analysis for $C_{18}H_{19}FN_2O_5$

Calculated: C 59.66, H 5.29, N 7.73

Found: C 59.24, H 5.26, N 7.65

Example 5

843 mg of 9,10-difluoro-3-methyl-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid and 646 mg of 3-hydroxypyrrolidine were added to 10 ml of dimethylsulfoxide. The mixture was stirred at a temperature of from about 100 to 110°C (bath temperature) for 1 hour and the reaction mixture was concentrated to dryness in vacuo. Water was added to the residue and the insoluble substance was collected by filtration. The substance was recrystallized from a mixture of chloroform and ethanol to provide 450 mg of 9-fluoro-10-(3-hydroxy-1-pyrrolidinyl)-3-methyl-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid with m.p. 278—280°C (with decomposition).

16

Analysis for $C_{17}H_{17}FN_2O_5$

Calculated: C 58.61, H 4.92, N 8.04

Found: C 58.45, H 5.10, N 7.94

Example 6

In the same manner as in Example 3, 9-fluoro-10-(1-homopiperazinyl)-3-methyl-7-oxo-2,3 dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid with m.p. 230—234°C (with decomposition) was produced. This product was dissolved in diluted hydrochloric acid and the solution was concentrated in vacuo. To the residue, ethanol was added. Crystals precipitated were collected by filtration and washed with ethanol to provide 9-fluoro-10-(1-homopiperazinyl)-3-methyl-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid hydrochloride with m.p. 285—290°C (with decomposition).

Analysis for $C_{18}H_{20}FN_3O_4 \cdot HCl \cdot H_2O$

Calculated: C 51.99, H 5.57, N 10.10

Found: C 51.61, H 5.25, N 10.10

Example 7

133 mg of 9,10-difluoro-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid and 0.2 ml of methylhydrazine were added to 3 ml of dimethylformamide. The mixture was stirred at a temperature of from about 100 to 110°C (bath temperature) for 7 hours. The reaction mixture was concentrated to dryness in vacuo and the residue was treated with water. The insoluble substance was collected by filtration and recrystallized from ethanol to provide 30 mg of 9-fluoro-10-(1-methylhydrazyl)-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid as yellow prisms with m.p. 239—242°C.

Analysis for $C_{13}H_{12}FN_3O_4$

Calculated: C 53.24, H 4.13, N 14.33

Found: C 53.89, H 4.22, N 14.22

Example 8

Production of starting material:

10.5 g (0.05 mol) of 2,4-dichloro-3-fluoronitrobenzene was dissolved in 30 ml of dimethyl sulfoxide, and 8 ml of a 10% aqueous solution of sodium hydroxide was added to the mixture, followed by stirring the mixture at a temperature of 60° to 70°C for 20 hours. After completion of the reaction, 200 ml of water was added thereto and the unreacted starting material was removed by extraction with diethyl ether. The aqueous layer was made acidic with acetic acid and extracted with diethyl ether. The ether extract was dried over sodium sulfate and the ether was distilled off. The resulting residue was purified by silica gel (100 g) column chromatography using chloroform as an eluant to provide 3,4 g (35.5% yield) of 3-chloro-2-fluoro-6-nitrophenol with m.p. 73°C.

A mixture of 3 g (15.7 mmols) of 3-chloro-2-fluoro-6-nitrophenol, 3 ml of chloroacetone and 300 mg of potassium iodide in 50 ml of acetone was refluxed for 6 hours while vigorously stirring. After cooling, any insoluble substance was removed by filtration, and the filtrate was concentrated and purified by silica gel (20 g) column chromatography using chloroform as an eluant to provide 2.5 g (54.5% yield) of 2-acetonyloxy-4-chloro-3-fluoronitrobenzene as an oil.

2.3 g (7.9 mmols) of 2-acetonyloxy-4-chloro-3-fluoronitrobenzene was dissolved in 30 ml of ethanol and catalytically reduced in the presence of 2 g of Raney nickel. After completion of the reduction, the catalyst was removed by filtration, and the filtrate was concentrated. The resulting residue was purified by silica gel (20 g) column chromatography using chloroform as an eluant to provide 1.2 g (75.5% yield) of 7-chloro-8-fluoro-3-methyl-2,3-dihydro-4H-1,4-benzoxazine as an oil.

A mixture of 1.11 g (5.5 mmols) of 7-chloro-8-fluoro-3-methyl-2,3-dihydro-4H-1,4-benzoxazine and 1.4 g (6.2 mmols) of diethyl ethoxymethylenemalonate was stirred for 2 hours while heating at 130—140°C (bath temperature). After confirming disappearance of the starting benzoxazine compound by thin-layer chromatography, 5 g of ethyl polyphosphate was added to the reaction mixture and the mixture was again allowed to react for 1 hour at 140°C (bath temperature). After cooling, 20 ml of water was added to the mixture and the precipitate formed was extracted with 150 ml of chloroform. The chloroform extract was dried with sodium sulfate and chloroform was then distilled off. The resulting residue was purified by silica gel (20 g) column chromatography using methanol-chloroform (5:95 by volume) as an eluant to provide 1.2 g (67.0% yield) of ethyl 9-chloro-10-fluoro-3-

methyl-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylate with m.p. 263—264°C.

(7)

Analysis for $C_{15}H_{13}ClFNO_4$

Calculated: C 55.31, H 4.02, N 4.30

Found: C 55.19, H 3.97, N 4.41

600 mg (1.8 mmol) of the benzoxazine compound obtained above was dissolved in 5 ml of concentrated hydrochloric acid-acetic acid (1:4 by volume) and the solution was heated at 120°C (bath temperature) for 6 hours. After cooling, 20 ml of water was added to the reaction solution and the precipitated crystals were collected by filtration, washed thoroughly with water, ethanol-diethyl ether (4:1 by volume) and then diethyl ether, and dried to provide 459 mg (92.4% yield) of 9-chloro-10-fluoro-3-methyl-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid with m.p. >300°C as transparent plates.

Analysis for $C_{13}H_9ClFNO_4$

Calculated: C 52.45, H 3.05, N 4.71

Found: C 52.20, H 3.13, N 4.74

Example 9

150 mg (0.5 mmol) of 9-chloro-10-fluoro-3-methyl-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid was suspended in 3 ml of dimethyl sulfoxide and 150 mg of N-methylpiperazine was added to the suspension. The mixture was then allowed to react at 120—130°C (bath temperature) for 6 hours. After cooling, the solvent was distilled off under reduced pressure and the residue was washed with diethyl ether to remove any insoluble substance. The resulting residue was purified by silica gel (7 g) column chromatography using methanol-chloroform (5:95 by volume) and then methanol-chloroform (10:90 by volume) as eluants, and the resulting product was recrystallized from ethanol to provide 65 mg (34.4% yield) of 9-chloro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid as pale yellow fine needles with m.p. 275—276°C (with decomposition).

Analysis for $C_{18}H_{20}ClN_3O_4$

Calculated: C 57.22, H 5.34, N 11.12

Found: C 57.20, H 5.11, N 11.23

Examples 10—32

Using the procedures analogous to that described in Example 3 or 4 above, the following products were obtained, which were crystallized from ethanol unless otherwise described:

10. 9-fluoro-10-(4-methyl-1-piperazinyl)-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid as light yellow needles with m.p. 260—270°C (dec.)

11. 9-fluoro-10-(N-2-hydroxyethyl-N-methylamino)-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid as light yellow needles with m.p. 262—265°C

12. 9-fluoro-10-(3-hydroxy-1-piperazinyl)-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid (crystallized from methanol) as yellow needles with m.p. 270—277°C (dec.)

13. 9-fluoro-10-(3-hydroxy-1-piperidinyl)-3-methyl-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid as light yellow needles with m.p. 267—273°C (dec.)

14. 9-fluoro-7-oxo-10-(1-piperazinyl)-2,3-dihydro-7H-pyrido-[1,2,3-de][1,4]benzoxazine-6-carboxylic acid as light yellow needles with m.p. 258—268°C (dec.) (crystallized from water).

15. 9-fluoro-3-methyl-10-(4-morpholinyl)-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid as colorless needles with m.p. >300.

16. 9-fluoro-3-methyl-7-oxo-10-(1-piperazinyl)-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid as light yellowish white crystals with m.p. 260°C (dec.).

17. 9-fluoro-10-(4-(2-hydroxyethyl)piperazinyl)-3-methyl-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]-benzoxazine-6-carboxylic acid with m.p. 282—285°C (dec.).

18. 9-fluoro-3-methyl-10-(1-piperidinyl)-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid with m.p. 268—275°C (dec.).

19. 10-(4-ethyl-1-piperazinyl)-9-fluoro-3-methyl-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid with m.p. 263.5—264.5°C.

20. 9-fluoro-3-methyl-7-oxo-19-(1-pyrrolidinyl)-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid with m.p. 268—269°C.

21. 10-(4-dimethylamino-1-piperidinyl)-9-fluoro-3-methyl-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid with m.p. 245—248°C (dec.).
22. 10-dimethylamino-9-fluoro-3-methyl-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid with m.p. 233—235°C.
23. 9-fluoro-3-methyl-10-(4-methyl-1-homopiperazinyl)-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid with m.p. 234—237°C (dec.).
24. 9-fluoro-3-methyl-10-(2-methyl-1-pyrazolidinyl)-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid with m.p. 233—236°C.
25. 9-fluoro-3-methyl-7-oxo-10-(1-pyrazolidinyl)-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid with m.p. 215—225°C (dec.).
26. 9-fluoro-10-(3-hydroxy-1-azetidinyl)-3-methyl-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid with m.p. 286—286.5°C (crystallized from chloroform-ethanol).
27. 9-fluoro-3-methyl-7-oxo-10-(4-thiamorpholinyl)-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid with m.p. >300°C (crystallized from chloroform-ethanol).
28. 9-fluoro-10-(3-hydroxymethyl-1-pyrrolidinyl)-3-methyl-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid with m.p. 237°C (crystallized from chloroform-ethanol).
29. 9-fluoro-10-(2-hydroxymethyl-1-pyrrolidinyl)-3-methyl-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid with m.p. 265°C (crystallized from chloroform-ethanol).
30. 9-fluoro-10-(4-hydroxymethyl-1-piperidinyl)-3-methyl-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid with m.p. 266°C
31. 9-fluoro-10-(3-hydroxymethyl-1-piperidinyl)-3-methyl-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid with m.p. 222°C.
32. 10-(4-amino-1-piperidinyl)-9-fluoro-3-methyl-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid (after reacting the compound (II) with 4 tert-butoxycarbonyl amino-piperidine, the protected product was treated with trifluoroacetic acid to remove tert-butoxy carbonyl group. The final product contains crystal water (3/2 H_2O) and melts at 150—151°C with elevating temperature, then is crystallized at 170—180°C, and melts again at 210—212°C).

The compounds of this invention are effective antibacterial agents for treatment of various infectious diseases such as urinary tract infections or infections in respiratory organs in mammals including human. These compounds are used normally by oral administration but they can be administered also by injection or can be used by external application depending upon the type of diseases to be treated.

For the oral administration, the compounds can be used at a dosage between 100 mg to 1000 mg in adult human per day, normally at 100 mg to 600 mg, in the form of various pharmaceutical preparations such as tablets, capsules, powder, granule, syrup and the like which are well known in the art. Other preparations suitable for injection or external application can also be prepared by the technique known in the art. For example, pharmaceutical preparations can be prepared by a method known per se using suitable diluents, bindings, disintegrators, coating agents and the like.

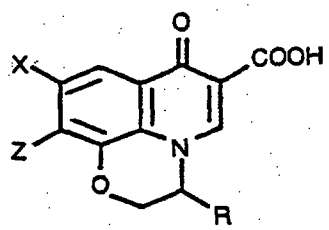
An example of the preparation containing the compound (Ia) suitable for oral administration is described below.

Capsules

Compound (Ia)	100.0 mg
Corn Starch	23.0 mg
CMC Calcium	22.5 mg
Hydroxypropylmethyl Cellulose	3.0 mg
Magnesium Stearate	1.5 mg
Total	150.0 mg per one capsule

Claims for the Contracting States: BE CH LI FR IT NL SE

1. Benzoxazine derivatives of the general formula I



(I)

wherein X is a halogen atom, R is a hydrogen atom or an alkyl group having from 1 to 6 carbon atoms and Z represents monoethylamino, monomethylamino, diethylamino, dimethylamino, hydrazyl, methylhydrazyl, azetidinyl, pyrrolidinyl, piperidinyl, morpholinyl, pyrazolidinyl, piperazinyl and homopiperazinyl, in which the alkyl radicals and heterocycles may be further substituted by one or more substituents selected from the group consisting of a hydroxy group, an alkyl group having from 1 to 6 carbon atoms, an amino group, a hydroxyalkyl group having from 1 to 6 carbon atoms, and a monoalkylamino and a dialkylamino group having from 1 to 6 carbon atoms in each alkyl moiety and the pharmaceutically acceptable salts thereof.

2. A benzoxazine derivative which is 9 - fluoro - 3 - methyl - 7 - oxo - 10 - (4 - thiamorpholinyl) - 2,3 - dihydro - 7H - pyrido[1,2,3 - de][1,4]benzoxazine - 6 - carboxylic acid.

3. A compound according to claim 1, wherein R is methyl and Z is 4-methyl-1-piperazinyl.

4. A compound according to claim 1, wherein R is methyl and Z is 4-hydroxy-1-piperazinyl.

5. A compound according to claim 1, wherein R is methyl and Z is 3-hydroxy-1-pyrrolidinyl.

6. A compound according to claim 1, wherein R is methyl and Z is homopiperazinyl.

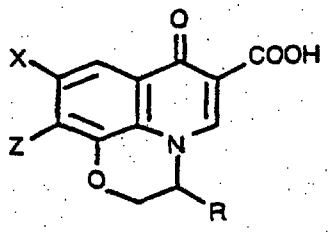
7. Process for preparing the compounds of claim 1 to 6 charracterized in that a 9,10-dihalo-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de] [1,4]benzoxazine-6-carboxylic acid or its 3-alkyl derivative is reacted with an amine corresponding to the substituent Z at a temperature from 30°C to 200°C.

8. Process according to claim 7, characterized in that the reaction is carried out at a temperature of from 70°C to 150°C.

9. Pharmaceutical composition comprising at least one compound of claims 1 to 6.

Claims for the Contracting State: AT

1. A process for preparing benzoxazine derivatives of the general formula I



(I)

wherein X is a halogen atom, R is a hydrogen atom or an alkyl group having from 1 to 6 carbon atoms and Z represents monoethylamino, monomethylamino, diethylamino, dimethylamino, hydrazyl, methylhydrazyl, azetidinyl, pyrrolidinyl, piperidinyl, morpholinyl, pyrazolidinyl, piperazinyl and homopiperazinyl, in which the alkyl radicals and heterocycles may be further substituted by one or more substituents selected from the group consisting of a hydroxy group, an alkyl group having from 1 to 6 carbon atoms, an amino group, a hydroxyalkyl group having from 1 to 6 carbon atoms, and a monoalkylamino and a dialkylamino group having from 1 to 6 carbon atoms in each alkyl moiety and the pharmaceutically acceptable salts thereof, characterized in that a 9,10-dihalo-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de] [1,4]benzoxazine-6-carboxylic acid or its 3-alkyl derivative is reacted with an amine corresponding to the substituent Z at a temperature from 30°C to 200°C.

2. Process according to claim 1, characterized in that the reaction is carried out at a temperature of from 70°C to 150°C.

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3. Process according to claim 1 or 2 for preparing a benzoxazine derivative which is 9-fluoro-3-methyl-7-oxo-10-(4-thiamorpholinyl)-2,3-dihydro-7H-pyrido(1,2,3-de] [1,4]benzoxazine-6-carboxylic acid.

4. Process according to claim 1 or 2 for preparing a benzoxazine derivative of the general formula I, wherein R is methyl and Z is 4-methyl-1-piperazinyl.

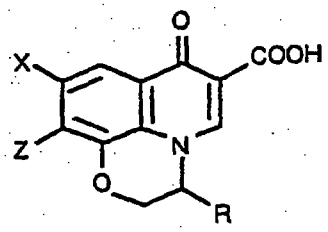
5. Process according to claim 1 or 2 for preparing a benzoxazine derivative of the general formula I, wherein R is methyl and Z is 4-hydroxy-1-piperazinyl.

6. Process according to claim 1 or 2 for preparing a benzoxazine derivative of the general formula I, wherein R is methyl and Z is 3-hydroxy-1-pyrrolidinyl.

7. Process according to claim 1 or 2 for preparing a benzoxazine derivative of the general formula I, wherein R is methyl and Z is homopiperazinyl.

Patentansprüche für die Vertragsstaaten: BE CH LI FR IT NL SE

1. Benzoxazinderivate der allgemeinen Formel I



(I)

worin X ein Halogenatom bedeutet, R ein Wasserstoffatom oder eine Alkylgruppe mit 1 bis 6 Kohlenstoffatomen bedeutet und Z für einen Monoethylamino-, Monomethylamino-, Diethylamino-Dimethylamino-, Hydrazyl-, Methylhydrazyl-, Azetidinyl-, Pyrrolidinyl-, Piperidinyl-, Morpholinyl-, Pyrazolidinyl, Piperazinyl- oder Homopiperazinylrest steht, wobei die Alkylreste und die Heterocyclen durch einen oder mehrere Substituenten weiter substituiert sein können, wobei diese Substituenten ausgewählt sind aus der Gruppe bestehend aus einer Hydroxygruppe, einer Alkylgruppe mit 1—6 Kohlenstoffatomen, einer Aminogruppe, einer Hydroxyalkylgruppe mit 1—6 Kohlenstoffatomen und einer Monoalkylamino- und Dialkylaminogruppe mit 1—6 Kohlenstoffatomen in jeder Alkyleinheit, und die pharmazeutisch verträglichen Salze davon.

2. Benzoxazinderivat, nämlich 9-Fluor-3-methyl-7-oxo-10-(4-thiamorpholinyl)-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazin-6-carbonsäure.

3. Verbindung nach Anspruch 1, worin R für einen Methylrest und Z für einen 4-Methyl-1-piperazinylrest stehen.

4. Verbindung nach Anspruch 1, worin R für einen Methylrest und Z für einen 4-Hydroxy-1-piperazinylrest stehen.

5. Verbindung nach Anspruch 1, worin R für einen Methylrest und Z für einen 3-Hydroxy-1-pyrrolidinylrest stehen.

6. Verbindung nach Anspruch 1, worin R für einen Methylrest und Z für einen Homopiperazinylrest stehen.

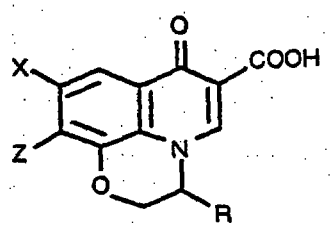
7. Verfahren zur Herstellung der Verbindungen nach Anspruch 1 bis 6, dadurch gekennzeichnet, daß man 9,10-Dihalo-7-oxo-2,3-dihydro-7-H-pyrido[1,2,3-de][1,4]benzoxazin-6-carbonsäure oder deren 3-Alkylderivat mit einem Amin, das dem Substituenten Z entspricht, bei einer Temperatur von 30°C bis 200°C umsetzt.

8. Verfahren nach Anspruch 7, dadurch gekennzeichnet, daß man die Umsetzung bei einer Temperatur von 70°C bis 150°C durchführt.

9. Pharmazeutisches Mittel, enthaltend mindestens eine Verbindung der Ansprüche 1—6.

Patentansprüche für den Vertragsstaat: AT

1. Verfahren zur Herstellung von Benzoxazinderivaten der allgemeinen Formel I



(I)

worin X ein Halogenatom bedeutet, R ein Wasserstoffatom oder eine Alkylgruppe mit 1 bis 6 Kohlenstoffatomen bedeutet und Z für einen Monoethylamino-, Monomethylamino-, Diethylamino-, Dimethylamino-, Hydrazyl-, Methylhydrazyl-, Azetidinyl-, Pyrrolidinyl-, Piperidinyl-, Morpholinyl-, Pyrazolidinyl, Piperazinyl- und Homopiperazinylrest steht, wobei die Alkylreste und die Heterocyclen durch einen oder mehrere Substituenten weiter substituiert sein können, wobei diese Substituenten ausgewählt sind aus der Gruppe bestehend aus einer Hydroxygruppe, einer Alkylgruppe mit 1—6 Kohlenstoffatomen, einer Aminogruppe, einer Hydroxyalkylgruppe mit 1—6 Kohlenstoffatomen und einer Monoalkylamino- und Dialkylaminogruppe mit 1—6 Kohlenstoffatomen in jeder Alkyleinheit, und der pharmazeutisch verträglichen Salze davon, dadurch gekennzeichnet, daß man 9,10-Dihalo-7-oxo-2,3-dihydro-7-H-pyrido[1,2,3-de][1,4]benzoxazin-6-carbonsäure oder deren 3-Alkylderivat mit einem Amin, das dem Substituenten Z entspricht, bei einer Temperatur von 30°C bis 200°C umsetzt.

2. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß man die Umsetzung bei einer Temperatur von 70°C bis 150°C durchführt.

3. Verfahren nach Anspruch 1 oder 2, zur Herstellung eines Benzoxazinderivates, nämlich 9-Fluor-3-methyl-7-oxo-10-(4-thiamorpholinyl)-2,3-dihydro-7H-pyrido[1,2,3-de] [1,4]benzoxazin-6-carbonsäure.

4. Verfahren nach Anspruch 1 oder 2 zur Herstellung eines Benzoxazinderivats der allgemeinen Formel I, worin R für einen Methylrest und Z für einen 4-Methyl-1-piperazinylrest stehen.

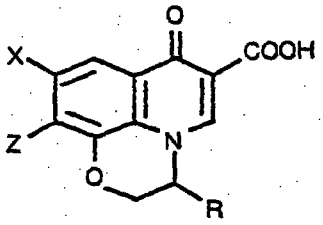
5. Verfahren nach Anspruch 1 oder 2 zur Herstellung eines Benzoxazinderivates der allgemeinen Formel I, worin R für einen Methylrest und Z für einen 4-Hydroxy-1-piperazinylrest stehen.

6. Verfahren nach Anspruch 1 oder 2 zur Herstellung eines Benzoxazinderivates der allgemeinen Formel I, worin R für einen Methylrest und Z für einen 3-Hydroxy-1-pyrrolidinylrest stehen.

7. Verfahren nach Anspruch 1 oder 2 zur Herstellung eines Benzoxazinderivates der allgemeinen Formel I, worin R für einen Methylrest und Z für einen Homopiperazinylrest stehen.

Revendications pour les Etats contractants: BE CH LI FR IT NL SE

1. Dérivés de benzoxazine qui répondent à la formule générale (I)



(I)

dans laquelle X représente un atome d'halogène, R représente un atome d'hydrogène ou un groupe alkyle en C_1—C_6 et Z représente un groupe monoéthylamino, monométhylamino, diéthylamino, diméthylamino, hydrazyle, méthylhydrazyle, azétidinyle, pyrrolidinyle, pipéridinyle, morpholinyle, pyrazolidinyle, pipérazinyle ou homopipérazinyle, les radicaux alkyles et les hétérocycles pouvant en outre porter un ou plusieurs substituants choisis parmi les groupes hydroxy, les groupes alkyles en C_1—C_6, les groupes amino, hydroxyalkyle en C_1—C_6, monoalkylamino et dialkylamino contenant 1 à 6 atomes de carbone dans chaque groupe alkyle, et leurs sels acceptables pour l'usage pharmaceutique.

2. Un dérivé de benzoxazine consistant en l'acide 9-fluoro-3-méthyl-7-oxo-10-(4-thiamorpholinyl)-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylique.

3. Un composé selon la revendication 1, dans lequel R est un groupe méthyle et Z le groupe 4-méthyl-1-pipérazinyle.

4. Un composé selon la revendication 1, dans lequel R est un groupe méthyle et Z un groupe 4-hydroxy-1-pipérazinyle.

5. Un composé selon la revendication 1, dans lequel R est un groupe méthyle et Z un groupe 3-hydroxy-1-pyrrolidinyle.

6. Un composé selon la revendication 1, dans lequel R est un groupe méthyle et Z le groupe homopipérazinyle.

7. Procédé de préparation des composés des revendications 1 à 6, caractérisé en ce que l'on fait réagir un acide, 9,10-dihalogéno-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylique ou un dérivé alkylé en position 3 de cet acide, avec une amine correspondant au substituant Z a une température de 30 à 200°C.

8. Procédé selon la revendication 7, caractérisé en ce que la réaction est effectuée à une température de 70 à 150°C.

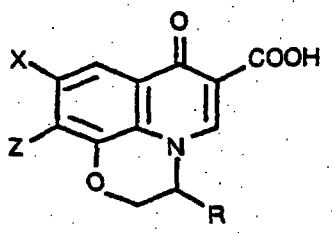
9. Composition pharmaceutique comprenant au moins un composé des revendications 1 à 6.

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22

Revendications pour l'Etat contractant: AT

1. Procédé de préparation des dérivés de benzoxazine qui répondent à la formule générale I



(I)

dans laquelle X représente un atome d'halogène, R représente un atome d'hydrogène ou un groupe alkyle en C_1—C_6 et Z représente un groupe monoéthylamino, monométhylamino, diéthylamino, diméthylamino, hydrazyle, méthylhydrazyle, azétidinyle, pyrrolidinyle, pipéridinyle, morpholinyle, pyrazolidinyle, pipérazinyle ou homopipérazinyle, les radicaux alkyles et les hétérocycles pouvant en outre porter un ou plusieurs substituants choisis parmi les groupes hydroxy, les groupes alkyles en C_1—C_6, les groupes amino, hydroxyalkyle en C_1—C_6, monoalkylamino et dialkylamino contenant 1 à 6 atomes de carbone dans chaque groupe alkyle, et leurs sels acceptables pour l'usage pharmaceutique caractérisé en ce que l'on fait réagir un acide 9,10-dihalogéno-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylique ou un dérivé alkylé en position 3 de cet acide, avec une amine correspondant au substituant Z a une température de 30°C à 200°C.

2. Procédé selon la revendication 1, caractérisé en ce que la réaction est effectuée à une température de 70° à 150°C.

3. Procédé selon la revendication 1 ou 2 pour la préparation d'un dérivé benzoxazine consistent en l'acide 9-fluoro-3-méthyl-7-oxo-10-(4-thiamorpholinyl)-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylique.

4. Procédé selon la revendication 1 ou 2 pour la préparation d'un dérivé benzoxazine qui réponds à la formule générale I, dans lequel R est un groupe méthyle et Z le groupe 4-méthyl-1-pipérazinyle.

5. Procédé selon la revendication 1 ou 2 pour la préparation d'un dérivé benzoxazine qui réponds à la formule générale I, dans lequel R est un groupe méthyle et Z un groupe 4-hydroxy-1-pipérazinyle.

6. Procédé selon la revendication 1 ou 2 pour la préparation d'un dérivé benzoxazine qui réponds à la formule générale I, dans lequel R est un groupe méthyle et Z un groupe 3-hydroxy-1-pyrrolidinyle.

7. Procédé selon la revendication 1 ou 2 pour la préparation d'un dérivé benzoxazine que réponds à la formule générale I, dans lequel R est un groupe méthyle et Z un groupe homopipérazinyle.

* C L M S