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EP 0550903 A1 EP 0167763 A1
UA 000041323 U

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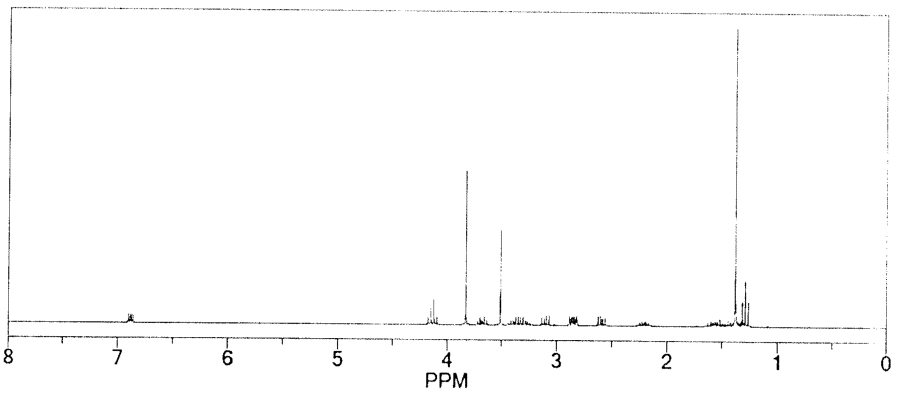
(54) Title of the Invention: **Method for producing (1-cyclopropyl-6-fluoro-1, 4-dihydro-8-methoxy-7-[(4as, 7as)-octahydro-6h-pyrrolo[3, 4-b]pyridin-6-yl]-4-oxo-3-quinoline-carboxylic acid**
Abstract Title: **Method for producing (1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-[(4aS, 7aS)-octahydro-6H-pyrrolo[3, 4-b]pyridin-6-yl]-4-oxo-3-quinoline-carboxylic acid**

(57) The invention relates to methods for producing a chemical compound such as (1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-[(4aS,7aS)-octahydro-6H-pyrrolo[3,4-b]pyridine-6-yl]-4-oxo-3-quinoline-carboxylic acid, the method comprising an addition of heterocyclic amine, which comprises a protective group, to ethyl 3-oxo-3-(2,4,5-trifluoro-3-methoxyphenyl)propanoate, followed by a reaction with triethyl orthoformate and an addition of a cyclic amine, followed by a cyclization thus producing the final product. The claimed production method is technologically simple in comparison with the prior art and does not require special complex technical operations, thus simplifying the method for producing said chemical compound and reducing the cost of the final product, and the industrial manufacture according to the claimed method has a low hazard level.



Фигура 1

At least one drawing originally filed was informal and the print reproduced here is taken from a later filed formal copy.

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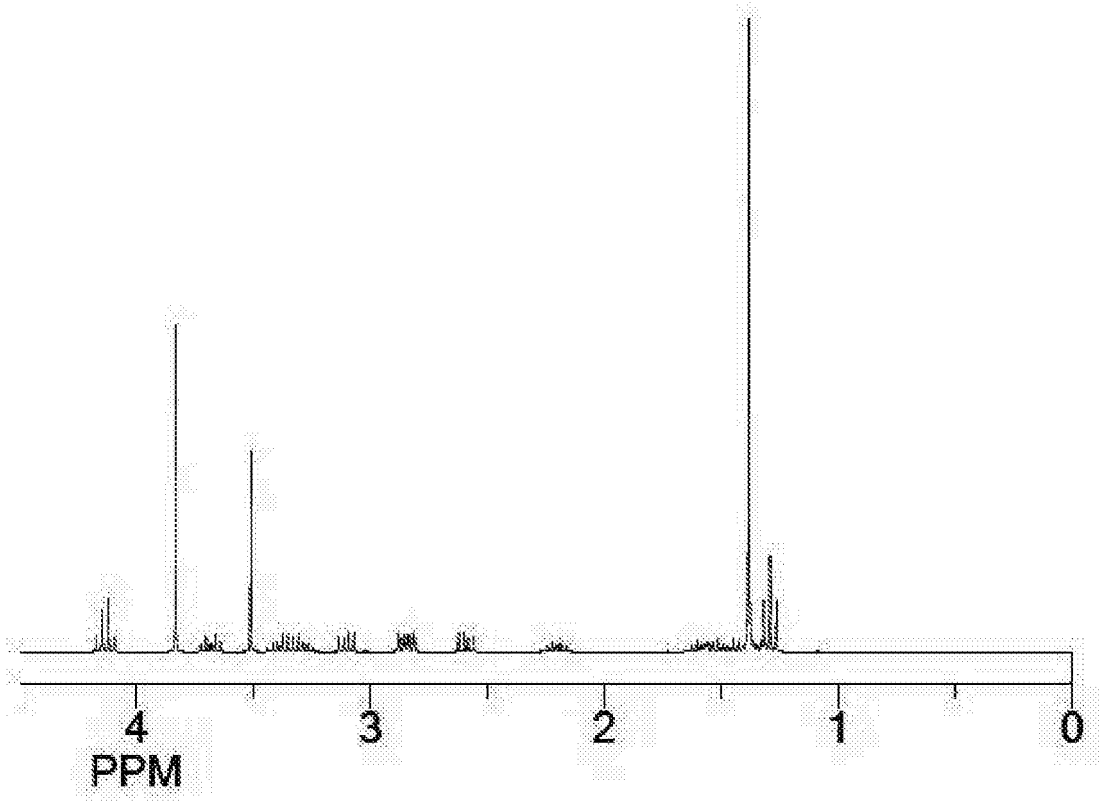


Fig.1

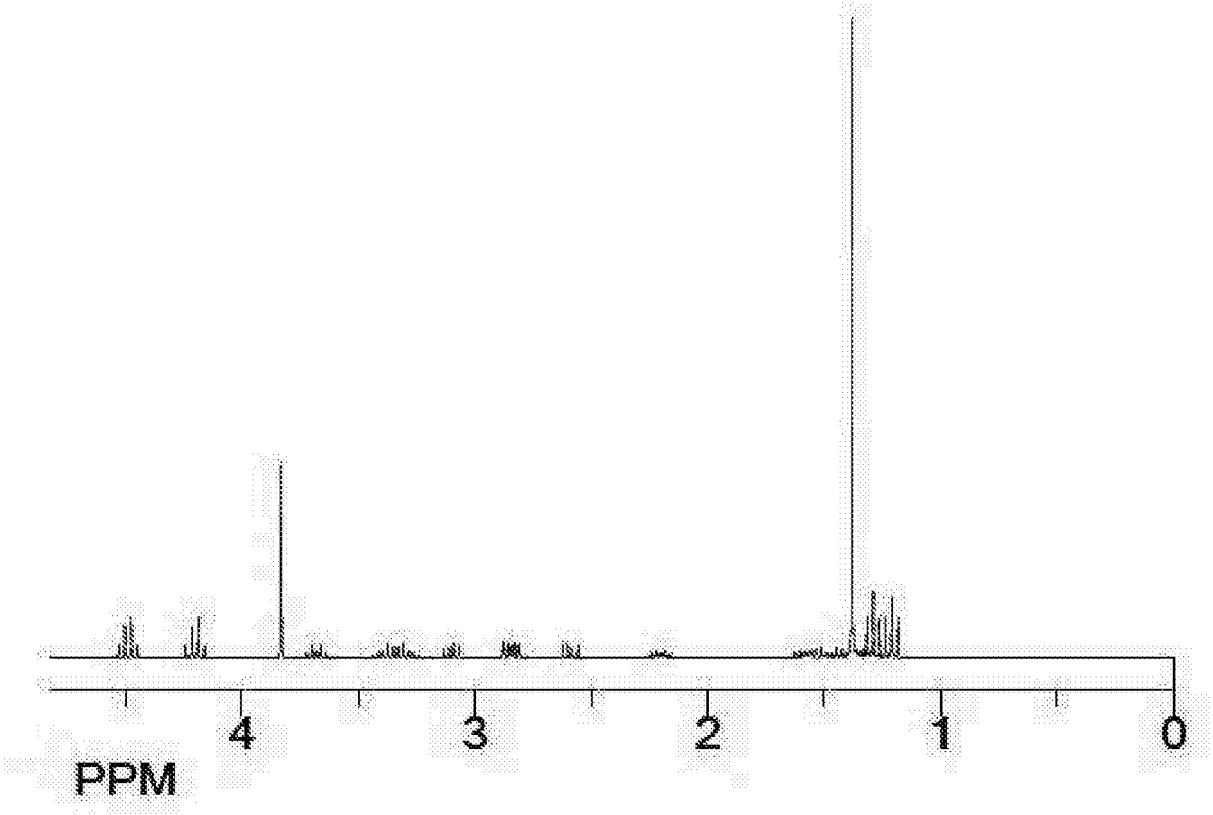


Fig.2

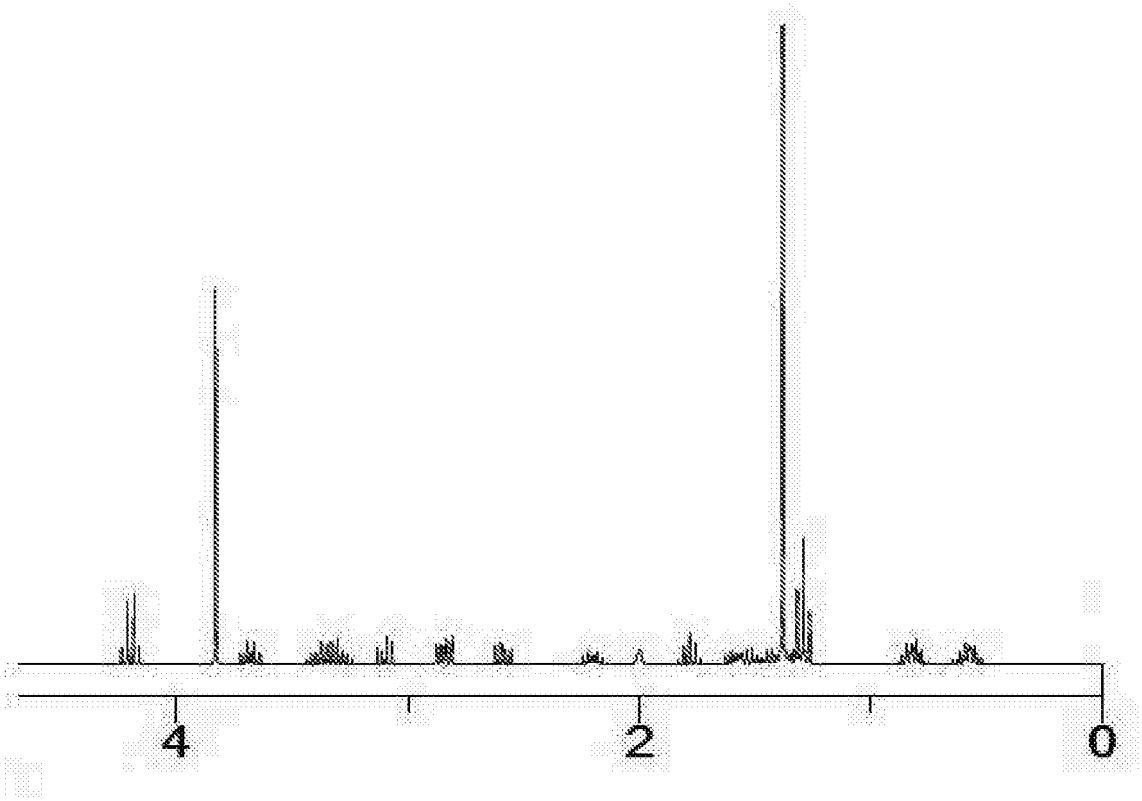


Fig.3

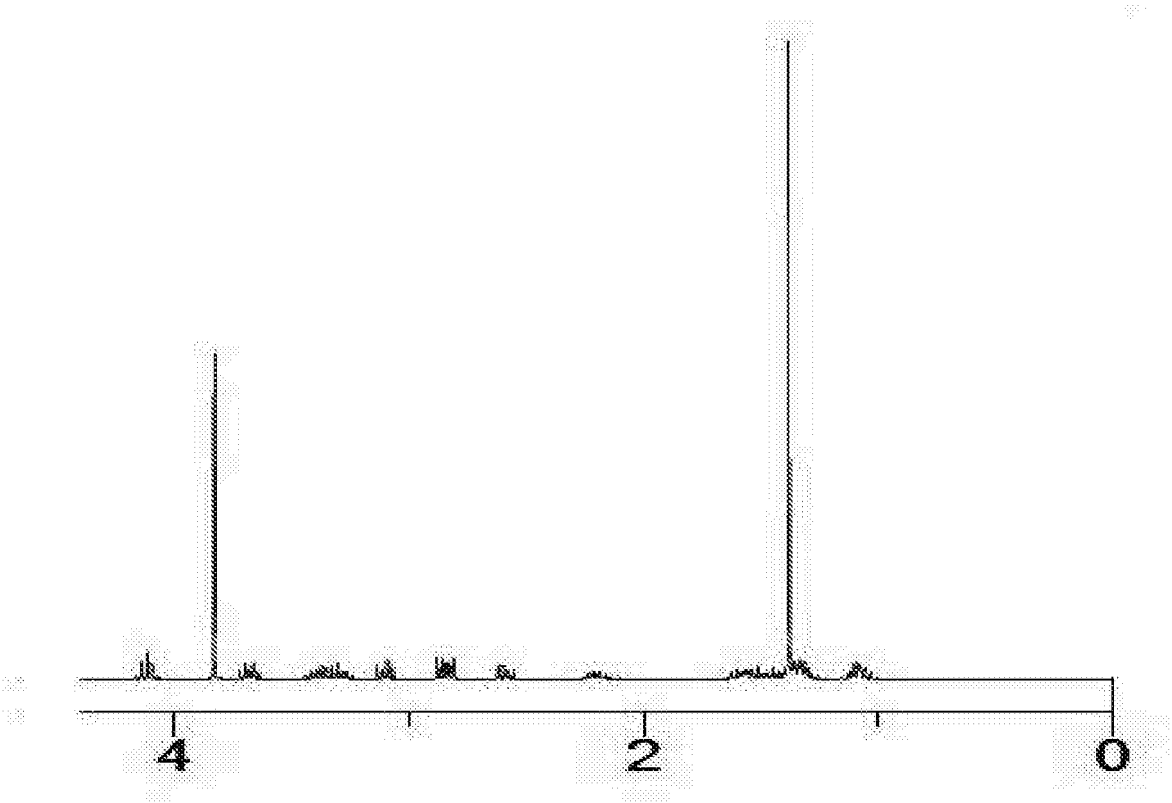


Fig. 4

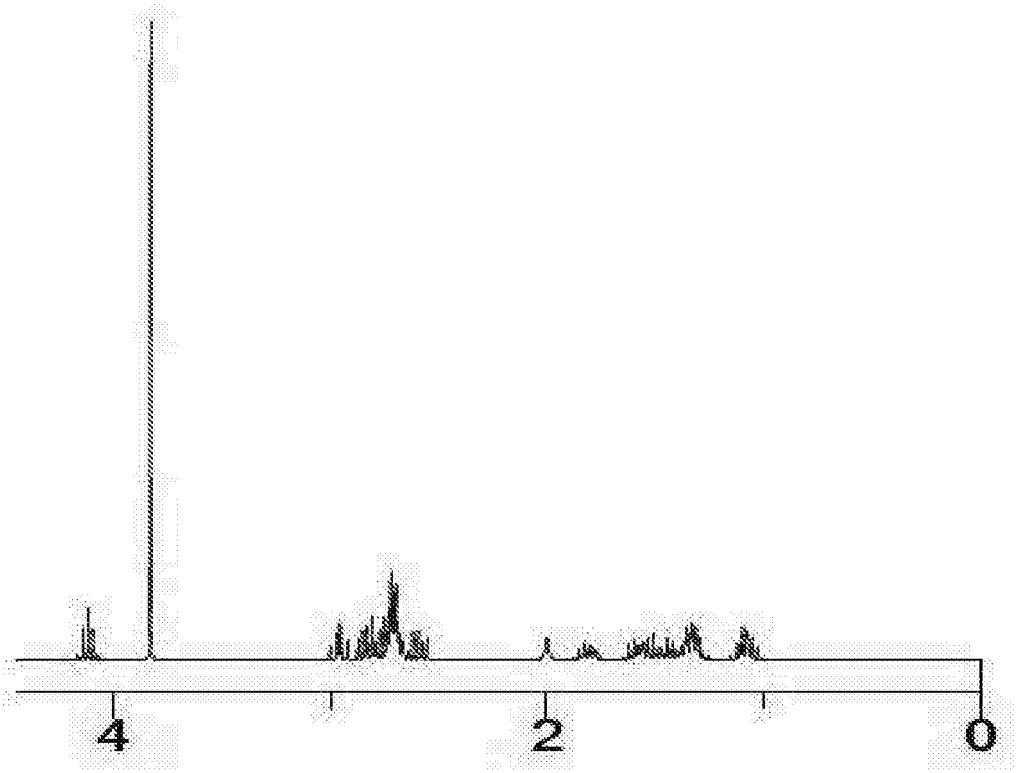


Fig. 5

METHOD FOR PREPARATION OF 1-CYCLOPROPYL-6-FLUORO-1,4-DIHYDRO-8-METHOXY-7-[(4AS,7AS)-OCTAHYDRO-6H-PYRROLO[3,4-B]PYRIDIN-6-YL]-4-OXO-3-QUINOLINECARBOXYLIC ACID

Field of invention

The invention disclosed relates to methods for the preparation of a chemical compound 1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-[(4aS,7aS)-octahydro-6H-pyrrolo[3,4-b]-pyridin-6-yl]-4-oxo-3-quinolinecarboxylic acid.

Prior art

Derivatives of quinolone carboxylic acid are widely used as synthetic antibacterial drugs in medicine. Compounds from the group of fluoroquinolones possess bactericidal action and demonstrate activity against wide spectrum of gram-positive and gram-negative microorganisms, anaerobic, acid-fast and atypical bacteria: Mycoplasma spp., Chlamydia spp., and Legionella spp. Antimicrobial preparations based on 1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-[(4aS,7aS)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]-4-oxo-3-quinolinecarboxylic acid are effective against most of the microorganism strains resistant to beta-lactam antibiotics and macrolides.

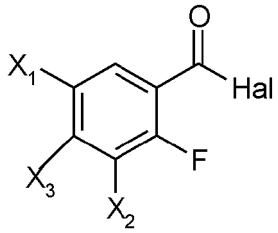
Methods for the preparation of 1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-[(4aS,7aS)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]-4-oxo-3-quinolinecarboxylic acid compound are decribed in application DE 42004144 A1 (published 15.07.1993). The compound is obtained with two methods.

In the first method, 1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-[(4aS,7aS)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]-4-oxo-3-quinolinecarboxylic acid is produced from salts of quinolone- and naphthyridonecarboxylic acid derivatives (acid addition salts, alkali salts, alkaline earth salts, silver and guanidine salts of corresponding acids) comprising cyclic amines, by interaction with halogen containing compounds, in the presence of acid binding agents.

In the second method, the same quinolonecarboxylic acid derivatives are subjected to interaction with Michael's acceptor, such as, acetylenedicarboxylic acid dialkyl ester, propiolic acid allyl ester. In these methods, racemic intermediate compounds interact with enantiomerically pure auxiliary reagent, diastereomers obtained are separated by chromatography, and auxiliary chiral group in diastereomer obtained is removed again. Racemic bicyclic amines can be converted into a mixture of diastereomeric salts via interaction with enantiomeric acids or sulfonic acids, which are then separated by fractional crystallization into

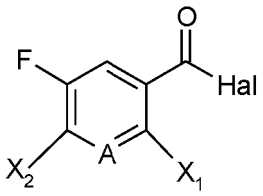
diastereomerically pure salts. The molar ratio of amine and enantiomerically pure acid may vary in a wide range. Treatment of these salts with hydroxides of alkali and alkaline earth metals allows to separate enantiomerically pure amines. Cleavage of racemates of principal intermediate compounds formed during preparation of racemic bicyclic amines with enantiomerically pure acids is performed in a similar manner. Racemic amines and intermediate compounds may be separated chromatographically on chiral carrier, may be converted by chemical binding with chiral acyl residue into a mixture of diastereomers, which are separated by distillation, crystallization or chromatography into diastereomerically pure acyl derivatives, wherefrom enantiomerically pure amines are obtained by saponification. Drawback of these methods is that during the process of their implementation, both racemic mixtures of intermediate compounds and racemic mixtures of final compounds are formed, thus necessitating chromatographic separation, which in its turn requires large expenditure of solvents and time.

There is a known method for preparation of 3-quinolinecarboxylic acid derivatives, wherein compounds of the general formula

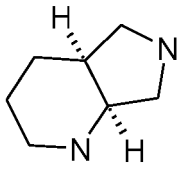


are subjected to interaction with malonic acid diethyl ester in solvent medium in the presence of magnesium methylate with consequent formation of corresponding complex esters, in which corresponding substituents X_1, X_2, X_3, and Hal, representing different substituents, including chloro, fluoro, and methoxy group, may be the same or different, and are then subjected to partial saponification and decarboxylation in an aqueous medium in the presence of catalytic amounts of sulfuric acid or p-toluenesulfonic acid. The compounds obtained are then subjected to interaction with triethyl ester of orthoformic acid in the presence of acetic anhydride. The intermediate compounds formed are further subjected to interaction with cyclopropylamine, followed by the cyclization, after which necessary amine is attached (EP application No. 0167763 A1, published 15.01.1986). The drawback of this method is an unsatisfactory yield of the product. Besides, alkaline saponification may result in side products forming polymers which is undesirable. Also, saponification in acidic conditions results in hydrogen fluoride release, leading to corrosion of production plant and product contamination with metal fluoride complexes. Patent for the invention UA 41323 C2 describes a method for preparation of 3-quinolonecarboxylic acid derivatives including stages of acid halide interaction with carboxylic

acid ester in a solvent in the presence of alkaline agent, interaction with heterocyclic amine, alkaline saponification and product isolation in a free form or in the form of salts. Acid halide of the formula



wherein X_1, X_2, and Hal are chloro or fluoro, and A denotes CH, CF, CCI, are subjected to saponification with aminoacrylic acid, then with cyclopropylamine, and subsequent saponification resulting in cyclization taking place in the presence of potassium carbonate. Each stage is conducted without preliminary isolation and purification of intermediate products. The following compound is used as heterocyclic amine:



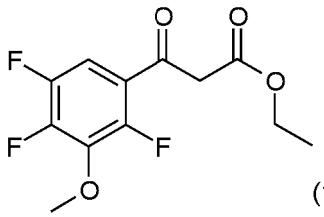
The final product is isolated after alkaline saponification of the reaction mixture is neutralized by acid. The drawback of this method is that interaction with acrylic acid ester results in the formation of side products capable of attaching to an unsaturated bond of the acrylic acid and forming products of polymerization, which are poisonous and explosive. Besides that, carrying out the subsequent stages of the method without isolation and purification of intermediate products results in the formation of a mixture of side products, which itself can actively participate in subsequent stages of the method, resulting in the formation of a small quantity of the final product. The final product contains considerable amounts of impurities and so necessitates substantial expenses in order to isolate it from them. Thus, realization of the method requires considerable expenses for reagents, solvents, and is technologically complex.

Disclosure of the invention

This invention is aimed to improve the method of producing 1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-[(4aS,7aS)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]-4-oxo-3-quinolinecarboxylic acid by changing actions and reagents in the method for preparation of said compound.

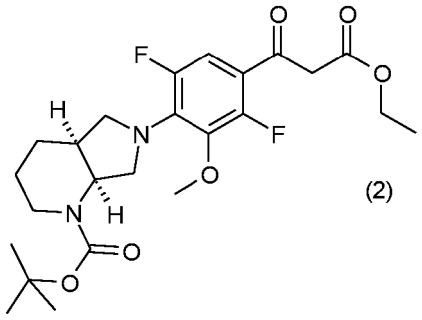
The problem with the preparation of 1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-[(4aS,7aS)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]-4-oxo-3-quinolinecarboxylic acid, is solved by the following stages of its production :

(1) introduction into compound of formula (1)



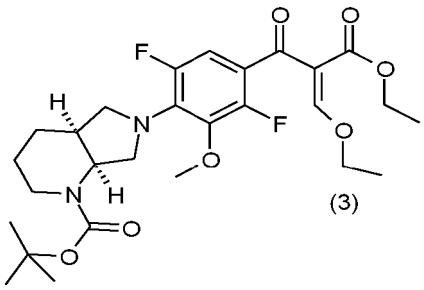
(1)

of tert-butyloctahydro-1H-pyrrolo[3,4b]pyridine-1-carboxylate affording compound of formula (2)



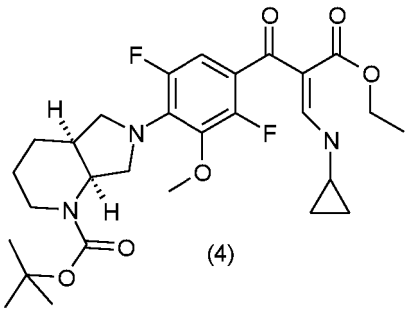
(2)

(2) interaction of compound (2) with triethyl orthoformate in acetic anhydride affording the compound of formula (3)



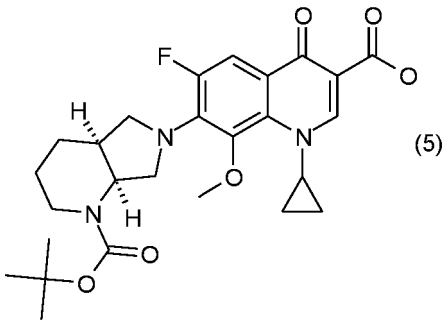
(3)

(3) addition of cyclic amine to the compound of formula (3) affording the compound of formula (4)



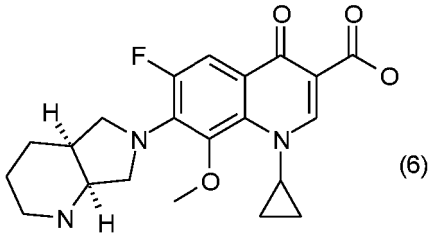
(4)

(4) cyclization of the compound of formula (4) in alkaline conditions affording compound of formula (5)



(5)

(5) cleavage of Boc protecting group from the compound of the formula (5) affording final compound of formula (6)



(6)

Furthermore, in the claimed method step (1) may be conducted in the presence of a base.

Furthermore, in the claimed method step (2) may be conducted in acetic anhydride at 130 °C.

Furthermore, in the claimed method step (3) may be conducted at room temperature.

Furthermore, in the claimed method step (4) may be performed in the presence of 3N potassium hydroxide at 50 °C.

Brief description of drawings

Figure 1 is a spectrum of compound (4aS,7aS)-tert-butyl-6-(4-(3-ethoxypropanol)-3,6-difluoro-2-methoxyphenyl)octahydro-1H-pyrrolo[3,4-b]pyridine-1-carboxylate.

Figure 2 is a spectrum of compound (4aS,7aS)-tert-butyl-6-(4-((Z)3-ethoxy-2-(ethoxycarbonyl)acryloyl)-3,6-difluoro-2-methoxyphenyl)octahydro-1H-pyrrolo[3,4-b]pyridine-1-carboxylate.

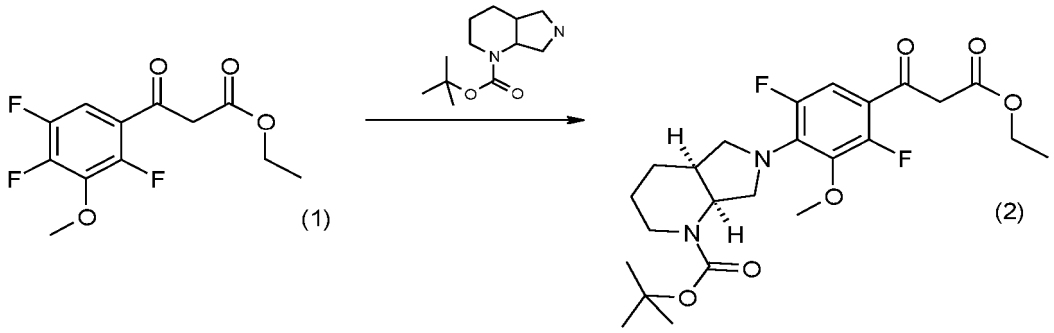
Figure 3 is a spectrum of compound (4aS,7aS)-tert-butyl-6-(4-((Z)3-cyclopropylamino)-2-(ethoxycarbonyl)acryloyl)-3,6-difluoro-2-methoxyphenyl)octahydro-1H-pyrrolo[3,4-b]-pyridine-1-carboxylate.

Figure 4 is a spectrum of compound 7-((4aS,7aS)-1-tert-butoxycarbonyl)hexahydro-1H-pyrrolo[3,4-b]-pyridin-6-(2H)-yl)-1-cyclopropyl-6-fluoro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid.

Figure 5 is a spectrum of compound 1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-[(4aS,7aS)-octahydro-6(H)-pyrrolo[3,4-b]pyridin-6-yl]-4-oxo-3-quinolinecarboxylic acid.

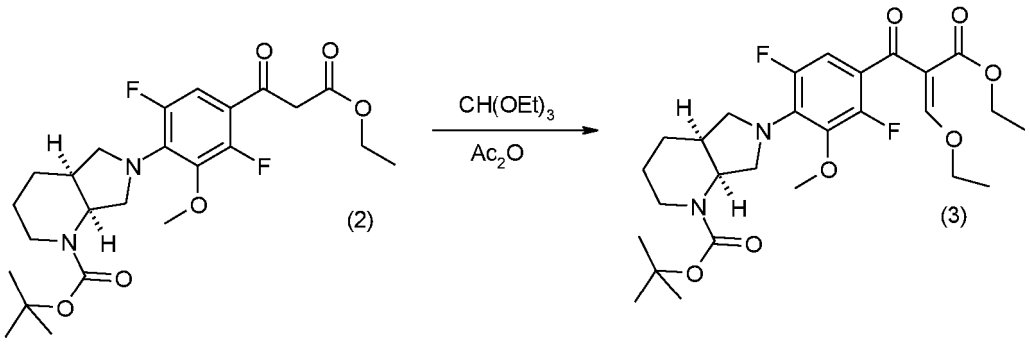
Variations of the invention

Step (1) comprises addition of chiral amine (in this case (4AS,7aS)-tert-butyloctahydro-1H-pyrrolo[3,4-b]pyridine-1-carboxylate) to ethyl-3-oxo-3-(2,4,5-trifluoro-3-methoxyphenyl)propanoate (1) with formation of (4AS,7aS)-tert-butyl-6-(4-(3-ethoxypropanol)-3,6-difluoro-2-methoxyphenyl)octahydro-1H-pyrrolo[3,4-b]pyridine-1-carboxylate (2).



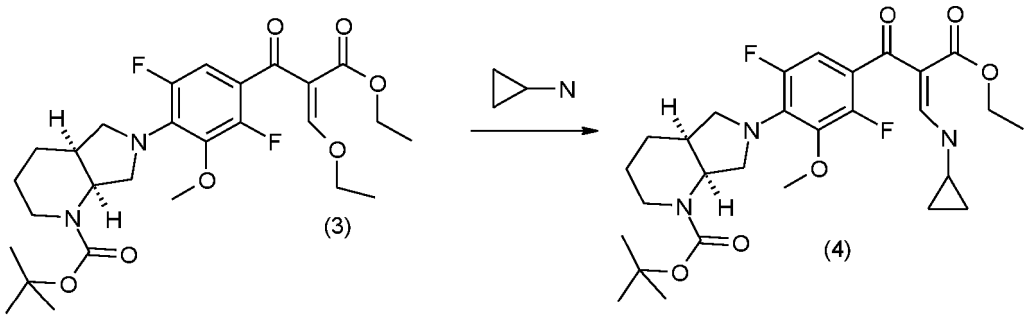
The amine protective group can be selected from the group consisting of alkoxycarbonyl group, arylalkoxycarbonyl group, acyl group, alkoxyalkyl group or substituted silyl group. No special limitations are imposed on the type of the amino-protective group, and some groups may be utilized in reaction until they begin inhibiting interaction between compound (1) and amino compound. It is advantageous to use tert-butoxycarbonyl and 2,2,2-trichloroethoxycarbonyl groups, the tert-butoxycarbonyl group being preferred. One or more amine equivalents are utilized in the reaction. The reaction is carried out in the presence of a base, since HF produced in this step can inhibit reaction with compound (1) by forming amine salt.

Step (2) consists of an interaction of compound (2) with triethyl orthoformate in acetic anhydride resulting in formation of the compound of formula (3).



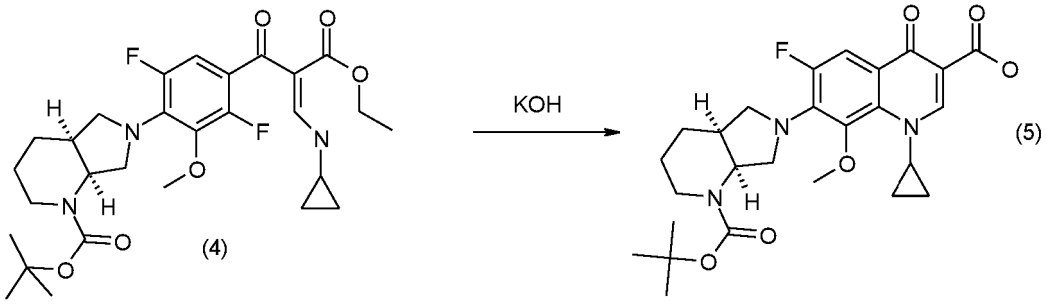
Alkyl orthoformate and acetic anhydride are used in equivalent amounts. Alkyl orthoformate may contain C one to C six alkyl groups. Preferred compounds are ethyl orthoformate and methyl orthoformate. Alkyl orthoformate is used as reagent and solvent simultaneously. Reaction is carried out in the temperature range from room temperature to the boiling point of solvent for one to six hours.

Step (3) consists of interaction of the compound of formula (3) with cyclic amine affording compound of formula (4).



Reaction is carried out in the presence of a base, which may be chosen from the group of organic bases, for example, trimethylamine, triethylamine, and 4-(dimethylamino)pyridine, and inorganic bases, such as ammonium, potassium carbonate, sodium carbonate, sodium hydroxide and potassium hydroxide. Preferred are tertiary amines, in particular, triethylamine. Amine compound may be an acidic salt. The acidic salt may be formed by inorganic acids, such as hydrochloric acid, sulfuric acid, nitric acid, hydrobromic, hydrofluoric, hydroiodic acids, as well as organic acids, such as toluenesulfonic, benzenesulfonic, methanesulfonic (sulfonic acids can contain halogen atom or alkyl group as a substituent), trifluoroacetic acid, maleic and fumaric acids. There is also no limit in choosing solvent, and many solvents are utilized until they begin to inhibit the reaction. It is possible to use toluene, N,N-dimethylacetamide, N,N-dimethylformamide, dimethylsulfoxide, and N-methylpyrrolidone. Toluene is preferred. Reaction is conducted at room temperature for 30 minutes to 6 hours, depending on formation of the final product and consumption of the initial compounds.

Step (4) comprises cyclization of the compound of formula (4) affording compound of formula (5):



Step (4) is carried out in the presence of a base, phase-transfer catalyst may be a combined one, although it is not always necessary to isolate and purify compound (4).

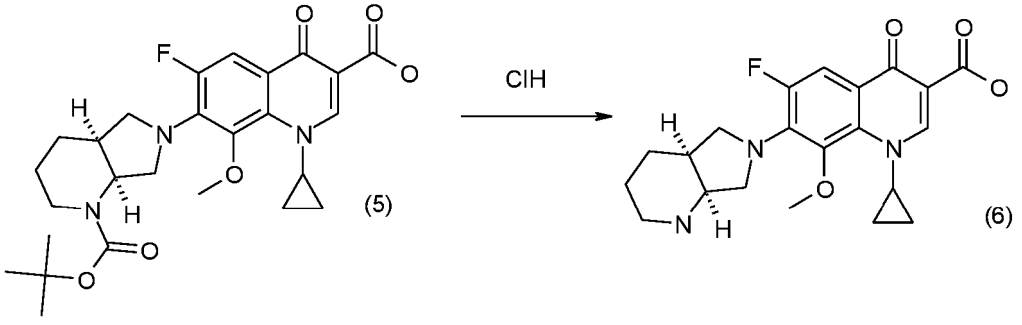
The reaction utilizes both organic bases, such as trimethylamine, triethylamine, and 4-(dimethylamino)pyridine, and inorganic bases, such as ammonium, potassium carbonate, sodium carbonate, sodium hydroxide, and potassium hydroxide. Use of potassium hydroxide is preferred. The base is used in an amount necessary to capture hydrogen fluoride generated at

ring closure, and to hydrolize the complex ester. The base may be added directly into the reaction mixture or it may be added into the reaction mixture as an aqueous solution. Base or solution is not a required form of admixture with the reaction solvent.

Solvents used include toluene, N,N-dimethylacetamide, N,N-dimethylformamide, dimethylsulfoxide, and N-methylpyrrolidone. Use of toluene is preferred. Tetrabutylammonium bromide is used as catalyst. The reaction may be conducted in the temperature range from room temperature to boiling point of the reaction mixture. Time of reaction depends on time of conversion of initial compounds into the final ones and may be from one to 24 hours.

In carrying out the method claimed, compound (5) may be isolated and purified by common techniques. In one method, pH of the reaction mixture is adjusted by the addition of corresponding acid, and the mixture is then agitated while cooled with ice. The precipitating crystals are filtered off. In another method, in order to isolate this particular compound, pH of the reaction mixture is adjusted by addition of corresponding acid and corresponding solvent into the reaction mixture. The extract obtained is concentrated and compound (5) is re-crystallized from corresponding solvent. The compound (5) is obtained in a free form or as a salt by the above mentioned methods. The examples of salts include salts of inorganic acids, such as hydrochloric acid, sulfuric acid, nitric acid, hydrobromic, hydrofluoric, and hydroiodic acids, as well as salts of organic acids, such as toluenesulfonic, benzenesulfonic, methanesulfonic, trifluoroacetic acid, trichloroacetic acid, acetic acid, formic acid, fumaric acid, and salts of alkaline metals and alkaline earth metals, such as sodium, potassium, calcium or lithium. Even if the compound is a mixture of a free form and a salt, it can be isolated as a solvate. Solvate can be formed with water, ethanol, propanol, acetonitrile, acetone, or by water absorption.

Step (5) is carried out by cleavage of tert-butylcarboxylate from the compound of formula (5) affording compound of formula (6):



Step (5) is conducted in solvent on heating with hydrochloric acid.

Below are presented examples demonstrating one of the possible variations of the claimed method for preparation of the compound moxifloxacin (1-cyclopropyl-6-fluoro-1,4-

dihydro-8-methoxy-7-[(4aS,7aS)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]-4-oxo-3-quinoline-carboxylic acid).

Example 1.

Preparation of (4aS,7aS)-tert-butyl-6-(4-(3-ethoxypropanol)-3,6-difluoro-2-methoxyphenyl)octahydro-1H-pyrrolo[3,4-b]pyridine-1-carboxylate.

(4AS,7aS)-tert-butyloctahydro-1H-pyrrolo[3,4 b]pyridine-1-carboxylate (4.10 g, 18.1 mmol) is added to the solution containing ethyl-3-oxo-3-(2,4,5-trifluoro-3-methoxyphenyl)propanoate (5 g, 18.1 mmol), acetonitrile (50 ml), and triethylamine (5.1 ml, 2 eq.), and the mixture is agitated at 25 °C for three days and at 50 °C for 4 hours. After that, the reaction mixture is cooled, and solvent is evaporated at reduced pressure. Toluene (50 ml) is then added to the residue and additionally saturated by saline solution (30 ml). The organic residue is dried over magnesium sulfate, and the solvent is removed at reduced pressure. The compound obtained is a yellow-green substance 7.295 g (84%).

The compound has been identified by physico-chemical methods. NMR spectrum of the compound is presented in Fig.1.

Example 2.

Preparation of (4aS,7aS)-tert-butyl-6-(4-((Z)3-ethoxy-2-(ethoxycarbonyl)-acryloyl)-3,6-difluoro-2-methoxyphenyl)octahydro-1H-pyrrolo[3,4-b]pyridine-1-carboxylate.

(4AS,7aS)-tert-butyl b]pyridine-1-carboxylate (1.033 g, 2.14 mmol) is dissolved in acetic anhydride (1.21 ml, 6 eq.) and triethyl orthoformate (2.13 ml, 6 eq.). The reaction mixture is then agitated for 14 hours at temperature 130 °C. After that, the reaction mixture is cooled, and solvent is removed at low pressure. Toluene (10 ml) is added to the residue, and the reaction mixture is boiled twice. The acetic acid present in the liquid is neutralized by sodium bicarbonate, and inorganic product formed as the result is filtered off. The solvent remained after filtration is removed under reduced pressure leaving a yellow-orange sediment, 933 mg (81%).

The compound has been identified by physico-chemical methods. NMR spectrum of the compound is presented in Fig. 2.

Example 3.

Preparation of (4aS,7aS)-tert-butyl-6-(4-((Z)3-cyclopropylamino)-2-(ethoxycarbonyl)-acryloyl)-3,6-difluoro-2-methoxyphenyl)octahydro-1H-pyrrolo[3,4-b]pyridine-1-carboxylate.

Cyclopropylamine (390 mg, 6.83 mmol) is added to the solution containing (4aS,7aS)-tert-butyl-6-(4-((Z)3-ethoxy-2-(ethoxycarbonyl)acryloyl)-3,6-difluoro-2-methoxyphenyl)-octahydro-1H-pyrrolo[3,4-b]pyridine-1-carboxylate (787 mg, 1.45 mmol), toluene (15.2 ml), and triethylamine (0.22 ml, 1.1 eq.). The reaction mixture is stirred for 10 minutes at

temperature 25°C. The organic residue is washed with water (10 ml × 2) and saline solution (10 ml) and then dried over magnesium sulfate. Solvent is removed at reduced pressure. (4aS,7aS)-tert-butyl-6-(4-((Z)3-cyclopropylamino)-2-(ethoxycarbonyl)acryloyl)-3,6-difluoro-2-methoxyphenyl)octahydro-1H-pyrrolo[3,4-b]pyridine-1-carboxylate, 789 mg (99%), is obtained as a yellow-orange substance.

Example 4.

Preparation of 7-((4aS,7aS)-1-tert-butoxycarbonyl)hexahydro-1H-pyrrolo[3,4-b]-pyridin-6-(2H)-yl)-1-cyclopropyl-6-fluoro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid.

Tetrabutylammonium bromide (TBAB, 8 mg) is added to the solution containing (4aS,7aS)-tert-butyl-6-(4-((Z)3-cyclopropylamino)-2-(ethoxycarbonyl)acryloyl)-3,6-difluoro-2-methoxyphenyl)octahydro-1H-pyrrolo[3,4-b]pyridine-1-carboxylate (736 mg, 1.34 mmol), toluene (14.8 ml), and 3N potassium hydroxide (2.23 ml, 5 eq.). The reaction mixture is then stirred for 4 hours at temperature 50°C. Another portion of 3N potassium hydroxide (2.23 ml, 5 eq.) is added to the reaction mixture, and stirred continuously for 2 hours. Then the reaction mixture is poured on to ice, and acidified slightly with 3N hydrochloric acid solution to form a suspension. Water (15 ml) and saline solution (5 ml) are then added to suspension for separation. Aqueous residue is extracted by using toluene (20 ml × 2) thus restoring organic components and aggregating all organic layers. Aggregated organic components are dried over sodium sulfate and solvent is removed by rotary evaporator under reduced pressure. Residue is crystallized and solvent is removed at reduced pressure. After that, the residue is dissolved in toluene (1.5 ml) and hexane (15 ml). The mixture is then stirred for 3 hours at a temperature 25°C. Precipitates obtained are filtered off and dried. As the result, 558 mg (83%) of the compound is obtained as yellow-orange crystals.

Compound 7-((4aS,7aS)-1-tert-butoxycarbonyl)hexahydro-1H-pyrrolo[3,4-b]-pyridin-6-(2H)-yl)-1-cyclopropyl-6-fluoro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid has been identified by physico-chemical methods. NMR spectrum of the compound presented in Fig.4.

Example 5.

Preparation of 1-cyclopropyl-6-fluoro-7-((4aS,7aS)-hexahydro-1H-pyrrolo[3,4-b]pyridine-6(2H)-yl)-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid.

7-((4aS,7aS)-1-tert-butoxycarbonyl)hexahydro-1H-pyrrolo[3,4-b]-pyridin-6-(2H)-yl)-1-cyclopropyl-6-fluoro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid is suspended in ethanol (727 mg, 1.45 mmol) at 22-30°C, treated with 21.70 mg of hydrochloric acid (37 wt.%) and heated under reflux condenser for 2 hours. After completion of the conversion most of the alcohol is stripped. The formed salt is precipitated, the solution is then heated to 40°C, and

dichloromethane is added. Precipitation of the acid is performed by dissolving hydrochloride salt in the 1:1 mixture of solvents EtOH/water. 30% solution of sodium hydroxide is added in portions at 0-7°C until pH has reaches a value pH >12.5. After 4-48 hours the substance precipitated is filtered off, washed with water and dried under negative pressure. This method produces a powder from white to yellowish colour, 518 mg (89%), with melting point at 324-325 °C.

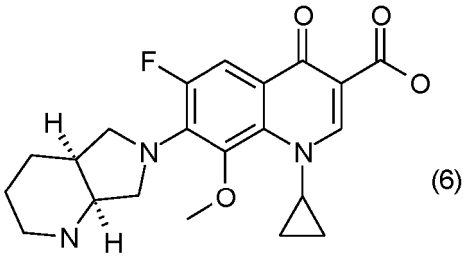
Compound 1-cyclopropyl-6-fluoro-7-((4aS,7aS)-hexahydro-1H-pyrrolo[3,4-b]pyridine-6(2H)-yl)-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid has been identified by physico-chemical methods. NMR spectrum of the compound is presented in Fig. 5.

As it can be seen from the examples presented above, the method claimed of preparation of 1-cyclopropyl-6-fluoro-7-((4aS,7aS)-hexahydro-1H-pyrrolo[3,4-b]pyridine-6(2H)-yl)-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid, more easily accessible reactants are used. And as a result of addition of chiral amine containing protective group, during the first stage, no racemic mixtures are formed, which would require separation and purification on chromatographic column with silica gel. Thus, enantiomerically pure intermediate compounds are formed during implementation of the method claimed, which are easily crystallized and purified, and used in subsequent stages. Because of this, yield of both the intermediate compounds and of the final product is increased. The claimed method makes unnecessary additional expenses for solvents, silica gel, reagents, time, and is economically advantageous. The manufacturing operations themselves are majorly conducted in ordinary conditions (without additional heating or considerable temperature decrease) and without necessity to strictly maintain pH values. In addition, this method is realized without the use of costly solvents. The above mentioned shows that the claimed method is technologically simple in comparison with the prior art and requires no special complex technical operations, which in its turn simplifies the method for preparation of given chemical compound, and reduces cost of the final product, while the industrial manufacture utilizing the method claimed has a low hazard level.

The examples presented of the realization of the method claimed for preparation of 1-cyclopropyl-6-fluoro-7-((4aS,7aS)-hexahydro-1H-pyrrolo[3,4-b]pyridine-6(2H)-yl)-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid are intended only to illustrate the invention but not to limit it.

Claims

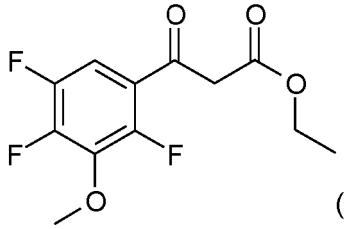
1. Method for preparation of compound of formula (6)



(6)

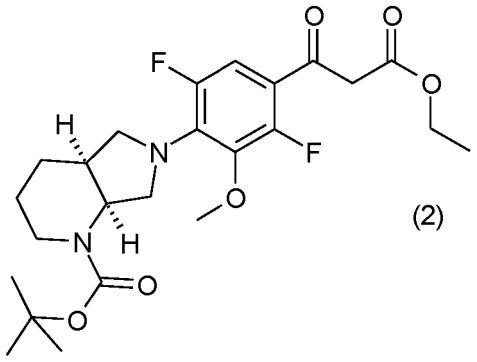
characterized in that the method comprises steps:

(1) introduction into the compound of formula (1)



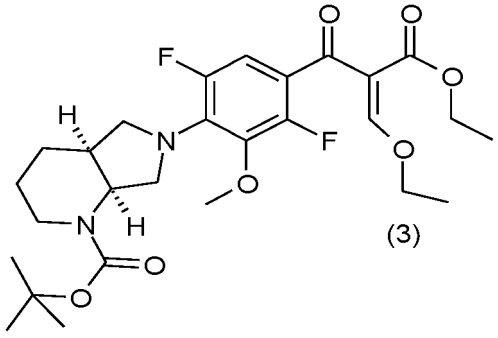
(1)

of tert-butyloctahydro-1H-pyrrolo[3,4b]pyridine-1-carboxylate affording compound of formula (2)



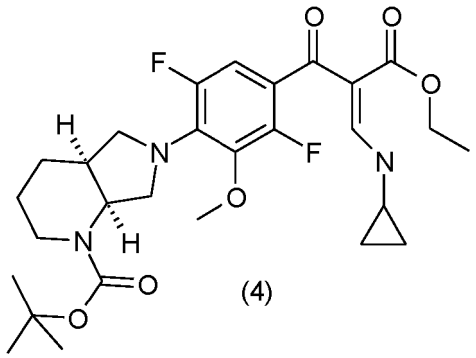
(2)

(2) interaction of the compound (2) with triethyl orthoformate in acetic anhydride affording compound of formula (3)



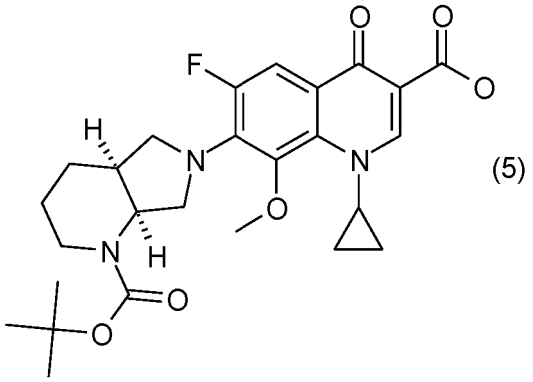
(3)

(3) addition of cyclic amine to the compound of formula (3) affording compound of formula (4)



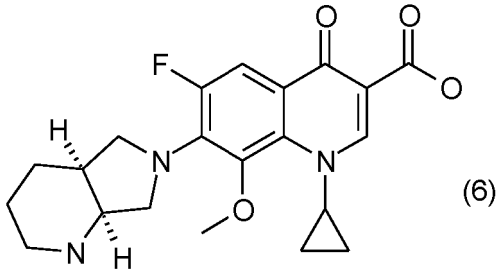
(4)

(4) cyclization of the compound of formula (4) in alkaline conditions affording compound of formula (5)



(5)

(5) cleavage of Boc protective group from the compound of formula (5) affording final compound of formula (6)



(6)

2. The method according to claim 1, characterized in that the step (1) is conducted in the presence of a base.

3. The method according to claim 1, characterized in that the step (2) is conducted in acetic anhydride at 130°C.

4. The method according to claim 1, characterized in that the step (3) is conducted at room temperature.

5. The method according to claim 1, characterized in that the step (4) is conducted in the presence of 3N potassium hydroxide at 50°C.

6. A method for the preparation of compounds substantially as disclosed herein, with reference to any one or more of the figures as shown in the drawing sheets.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/UA 2013/000055

A. CLASSIFICATION OF SUBJECT MATTER
C07D 471/04 (2006.01)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D 471/04

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PatSearch (RUPTO internal), STN on the Web, Espacenet, DWPI

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0167763 A1 (BAYER AG) 15.01.1986, p. 9-10, schema, point 13 of the claims	1-5
A	EP 0550903 A1 (BAYER AG) 14.07.1993, examples 1, 19	1-5
A	UA 41323 S2 (BAIER AG) 17.09.2001, the claims	1-5

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 December 2013 (14.12.2013)	16 January 2014 (16.01.2014)
Name and mailing address of the ISA/ RU Facsimile No.	Authorized officer Telephone No.