PROCESS FOR THE PREPARATION OF GATIFLOXACIN AND REGENERATION OF DEGRADATION PRODUCTS

The subject of the present invention are an improved synthesis process comprising a process for regeneration of a side product of gatifloxacin and an analysis method for process control in the synthesis of gatifloxacin (Formula I).
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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.
The subject of the present invention are an improved synthesis process comprising a process for regeneration of a side product of gatifloxacin and an analysis method for process control in the synthesis of gatifloxacin.
PROCESS FOR THE PREPARATION OF GATIFLOXACIN AND REGENERATION OF DEGRADATION PRODUCTS

Technical Field

The invention relates to the field of organic synthesis, namely to the field of synthesis of active pharmaceutical substances.

Technical Problem

Gatifloxacín is the generic name for the sesquihydrate of the active substance (±)-1-cyclopropyl-6-fluoro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid, which, due to its extremely high activity, is used as an antibiotic for treating infections with Gram-positive and Gram-negative bacteria and, besides, is also used against anaerobic bacteria and Mycoplasmi, which otherwise show a lesser susceptibility to conventional quinolone carboxylic acids. It was discovered independently by the companies Kyorin and Sankyo/Ube, with Kyorin having the earlier priority. It is usually administered once a day, orally or intravenously, and the usual daily dose is 400 mg. The active ingredient is present in medicinal forms as a racemate with the isomers having practically the same bioavailability and activity.

Prior Art

The method of preparing gatifloxacín of the general formula (I) is disclosed in the basic patent EP 0 230 295 B1 to Kyorin.
Therein there are claimed a family of compounds, hydrates and salts of pharmaceutically acceptable acids or bases and a process for the synthesis thereof, of the general formula

The synthesis disclosed in claim 3 is a nucleophilic substitution of fluorine in 7-position in the compound 1-cyclopropyl-6,7-difluoro-1,4-dihydro-8-methoxy-4-oxo-3-quinoline carboxylic acid by 2-methylpiperazine. The purification of the compound as disclosed in this patent is carried out by column chromatography, which is not economical on an industrial scale and is difficult to carry out, the yields are relatively low and this additionally contributes to the synthesis process not being economical.

In EP 0 241 206 to Sankyo and Ube Industries there is disclosed the synthesis of gatifloxacin via boron complexes and subsequent degradations thereof. Regarding the quality and yields of nucleophilic substitution, the synthesis with a transitional boron intermediate is more suitable than the basic synthesis, yet the products formed via this synthesis route on an industrial scale are very irritant. The cost of preparing
boron intermediate is high and additional health and safety regulations have to be observed due to working with HF and tetrafluoroboric acid.

For the above reasons it is believed that there exists a need for an improved process for the preparation of gatifloxacin.

In EP 0 805 156 a process for the preparation of gatifloxacin sesquihydrate is claimed. The process is carried out in such a way that (±)-1-cyclopropyl-6-fluoro-1,4-dihydro-7-(3-methyl-1-piperazinyl)-8-methoxy-4-oxo-3-quinoline carboxylic acid is suspended in water at a neutral pH, heated to 80-90°C and hot filtered.

Detailed Disclosure of the Invention

The present invention solves the problem of chemical yields and of the presence of impurities in gatifloxacin synthesis and includes the HPLC analysis method for monitoring the rate of conversion of the starting compound 1-cyclopropyl-6,7-difluoro-1,4-dihydro-8-methoxy-4-oxo-3-quinoline carboxylic acid to gatifloxacin.

The following scheme shows an improved synthesis process, which includes a process of regeneration of the side product 1-cyclopropyl-6,7-difluoro-1,4-dihydro-8-hydroxy-4-oxo-3-quinoline carboxylic acid.
In the step of nucleophilic substitution in the step of preparing (±)-1-cyclopropyl-6-fluoro-1,4-dihydro-7-(3-methyl-1-piperazinyl)-8-methoxy-4-oxo-quinoline-3-carboxylic acid, a cleavage of ether 8-OMe bond takes place due to the formation of HF. This decomposition takes place according to the basic process disclosed in EP 0 230 295 B1 to Kyorin as well as according to the process with boron complexes disclosed in EP 0 241 206 to Sankyo and Ube Industries. The difference between the
two disclosed synthesis processes in the two patents mentioned lies in the degradation intensity, which is greater in the basic process disclosed in EP 0 230 295 B1 to Kyorin. Because of this degradation the whole yield of the synthesis according to the basic process disclosed in EP 0 230 295 B1 to Kyorin amounts to about 19% calculated upon gatifloxacin sesquihydrate.

The process according to the invention is based on the fact that precipitation should take place at an appropriate pH value of the solution at a determined temperature. At a lower temperature, both at the same and at changed pH values of the solution, besides the main product there are also precipitated side products such as 1-cyclopentyl-6,7-difluoro-1,4-dihydro-8-hydroxy-4-oxo-3-quinoline carboxylic acid, (±)-1-cyclopentyl-6-fluoro-1,4-dihydro-8-hydroxy-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinoline carboxylic acid, (±)-1-cyclopentyl-6-fluoro-1,4-dihydro-7-(3,5-dimethyl-1-piperazinyl)-8-methoxy-4-oxo-3-quinoline carboxylic acid, (±)-1-cyclopentyl-6-fluoro-1,4-dihydro-8-hydroxy-7-(3,5-dimethyl-1-piperazinyl)-4-oxo-3-quinoline carboxylic acid and (±)-1-cyclopentyl-7-fluoro-1,4-dihydro-6-(3-methyl-1-piperazinyl)-4-oxo-8-methoxy-3-quinoline carboxylic acid, which are very difficult to remove, and thus such conditions are not suitable for increasing the yields of the chemical synthesis.

During our research work in the field of gatifloxacin it has been found that the problem of preparing gatifloxacin may be surprisingly improved by the principle of numerical determination of critical parameters and by including regeneration into the process of the preparation of gatifloxacin. At determining the critical parameters it has been surprisingly found that, due to the property of a markedly slow precipitation of the crude product from the reaction solution having a pH value of 9.5-11, preferably between 10.1 and 10.7, at a temperature of from 20°C to 35°C, it is very suitable that this precipitation takes place for more than 5 hours and preferably for 24 hours. In this way a maximum yield of the synthesis with a suitable quality of the product is
achieved. The product so prepared is also essentially better filterable and products of a high purity grade are isolated in a high yield.

The present invention relates to an improved process for the preparation of gatifloxacin sesquihydrate, characterized in that in the isolation step to a suspension or a solution of gatifloxacin in DMSO or in a mixture of DMSO and water an aqueous hydrochloric acid solution is added so that, under stirring, the pH value is maintained in the range of 9.5-11, preferably between 10.1 and 10.7, and in the temperature range between 20°C and 35°C, preferably between 20°C and 30°C, and the product is filtered after a prolonged precipitation time of more than 5 hours, preferably 24 hours.

In addition to the optimization of critical parameters at the precipitation of the product, an essential part of the invention is also the regeneration of degradation products, especially of 1-cyclopropyl-6,7-difluoro-1,4-dihydro-8-hydroxy-4-oxo-3-quinoline carboxylic acid, which is formed in large quantities, and the use of CaCl₂, KCl, CaSO₄ or Na₂SO₄, preferably CaCl₂, for improving filterability. It has also been found that the addition of some other salts does not improve filterability (e.g. MgSO₄, K₂CO₃).

To the DMSO filtrate containing the remaining excessive 2-methylpiperazine, (±)-1-cyclopropyl-6-fluoro-1,4-dihydro-7-(3-methyl-1-piperazinyl)-8-methoxy-4-oxo-3-quinoline carboxylic acid, (±)-1-cyclopropyl-6-fluoro-1,4-dihydro-8-hydroxy-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinoline carboxylic acid, other impurities and especially 1-cyclopropyl-6,7-difluoro-1,4-dihydro-8-hydroxy-4-oxo-3-quinoline carboxylic acid, an equimolar amount of CaCl₂ is added for binding HF bound to amine nitrogen.

At the same time it has been surprisingly found that the filtration of 90-95% isolated pure 1-cyclopropyl-6,7-difluoro-1,4-dihydro-8-hydroxy-4-oxo-3-quinoline carboxylic acid at pH = 3-4 and the temperature of 0-25°C, preferably at the temperature of 0-
5°C, is incomparably more rapid than without the addition of CaCl₂. With the addition of CaCl₂ the filtration took 10-30 minutes and without the addition of CaCl₂ it was practically not finished even after 24 hours.

The suitably pure 1-cyclopropyl-6,7-difluoro-1,4-dihydro-8-hydroxy-4-oxo-3-quinoline carboxylic acid so prepared is methylated to 1-cyclopropyl-6,7-difluoro-1,4-dihydro-8-methoxy-4-oxo-3-quinoline carboxylic acid or its methyl ester. The latter is hydrolyzed to 1-cyclopropyl-6,7-difluoro-1,4-dihydro-4-oxo-3-quinoline carboxylic acid in an aqueous alkali metal carbonate solution, preferably potassium carbonate solution. The preparation of both compounds that may be isolated after regeneration is disclosed in EP 0 230 295 B1.

The process for the preparation of gatifloxacin from DMSO or a mixture of DMSO and water is characterized in that it includes the regeneration of the side product 1-cyclopropyl-6,7-difluoro-1,4-dihydro-8-hydroxy-4-oxo-3-quinoline carboxylic acid in such a way that to the filtrate a suitable salt (preferably CaCl₂, optionally KCl, CaSO₄, Na₂SO₄) is added and with this salt the filterability is surprisingly improved, the pH value is adjusted in the range between 3 and 4 and the precipitated degradation product is filtered and then regenerated with a suitable methylating agent to 1-cyclopropyl-6,7-difluoro-1,4-dihydro-4-oxo-3-quinoline carboxylic acid or 1-cyclopropyl-6,7-difluoro-1,4-dihydro-8-methoxy-4-oxo-3-quinoline carboxylic acid methyl ester.

As methylating agents dimethyl sulfate, methyl halides, e.g. methyl iodide, methyl bromide, or some other methylating agent well-known to someone skilled in the art may be used. Preferably dimethyl sulfate is used. By regulating the reaction time and using an excess of the methylating agent in the regeneration step, the methylation level may be adjusted in such a way that either 1-cyclopropyl-6,7-difluoro-1,4-dihydro-8-methoxy-4-oxo-3-quinoline carboxylic acid methyl ester or 1-cyclopropyl-6,7-difluoro-1,4-dihydro-4-oxo-3-quinoline carboxylic acid is isolated.
The process for the preparation of gatifloxacin is further characterized in that 1-cyclopropyl-6,7-difluoro-1,4-dihydro-8-methoxy-4-oxo-3-quinoline carboxylic acid methyl ester prepared by regeneration is hydrolyzed to 1-cyclopropyl-6,7-difluoro-1,4-dihydro-4-oxo-3-quinoline carboxylic acid and the latter is in the next step reacted with 2-methylpiperazine. If the regeneration was carried out to obtain 1-cyclopropyl-6,7-difluoro-1,4-dihydro-4-oxo-3-quinoline carboxylic acid, the step of the hydrolysis of the ester is not necessary.

The process for the preparation of gatifloxacin is characterized in that the process of purification of (±)-1-cyclopropyl-6-fluoro-1,4-dihydro-7-(3-methyl-1-piperazinyl)-8-methoxy-4-oxo-3-quinoline carboxylic acid is carried out by recrystallization in a MeOH/water mixture in a volume ratio from 8:2 to 9.5:0.5, preferably 9:1. Thus, in contrast to the use of pure MeOH, (±)-1-cyclopropyl-6-fluoro-1,4-dihydro-8-hydroxy-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinoline carboxylic acid and 1-cyclopropyl-6,7-difluoro-1,4-dihydro-8-hydroxy-4-oxo-3-quinoline carboxylic acid as well as all remaining impurities may be removed. Gatifloxacin sesquihydrate may be prepared according to EP 0 805 156 in an aqueous solution at 85°C.

The present process for the preparation of gatifloxacin is characterized by a product containing together less than 0.5% of impurities and not more than 0.2% of any single impurity. Preferably, the content of impurities of gatifloxacin sesquihydrate so prepared is less than 0.3% and no single impurity is present in a concentration of more than 0.1%.

One of the preferred features of the present invention is also the HPLC analysis method, which allows monitoring the conversion of the starting compound 1-cyclopropyl-6,7-difluoro-1,4-dihydro-8-methoxy-4-oxo-3-quinoline carboxylic acid to gatifloxacin. By the area percent method the starting compound 1-cyclopropyl-6,7-difluoro-1,4-dihydro-8-methoxy-4-oxo-3-quinoline carboxylic acid and the impurity
1-cyclopropyl-6,7-difluoro-1,4-dihydro-8-hydroxy-4-oxo-3-quinoline carboxylic acid are determined. They are detected at from 220 to 254 nm since at 292 nm there is a too weak response and at lower concentrations they cannot be seen.

The advantage of this HPLC method over the HPCL method disclosed in WO 2004/069825 A1 to TEVA Pharmaceutical Industries Ltd. resides in UV detection. The starting compound 1-cyclopropyl-6,7-difluoro-1,4-dihydro-8-methoxy-4-oxo-3-quinoline carboxylic acid and the impurity 1-cyclopropyl-6,7-difluoro-1,4-dihydro-8-hydroxy-4-oxo-3-quinoline carboxylic acid are detected at from 220 to 254 nm. In TEVA's case the detection is at 285 nm where the starting compound as well as the impurity exhibit a minimum absorption and therefore they cannot be correctly evaluated.

The present invention is illustrated by the following Examples.

**Examples:**

**Example 1:** Synthesis of crude gatifloxacin base ((±)-1-cyclopropyl-6-fluoro-1,4-dihydro-7-(3-methyl-1-piperazinyl)-8-methoxy-4-oxo-3-quinoline carboxylic acid)

Into a reactor with a working volume of 1000 mL equipped with a thermometer, a reflux condenser and a mechanical stirrer, DMSO (480 mL), 1-cyclopropyl-6,7-difluoro-1,4-dihydro-8-methoxy-4-oxo-3-quinoline carboxylic acid (138.0 g; 0.4675 mole) and 2-methylpiperazine (94.0 g; 0.9387 mole) were put at 25°C (20°C-30°C). The reaction mixture was stirred for 30 minutes at 25°C (20°C-30°C). Then it was heated in 50 minutes (45-60 minutes) to the temperature of 73°C. The reaction mixture was stirred at this temperature for 12 hours. After 12 hours at 73°C, the reaction mixture was cooled to 25°C in 45 minutes (40-50 minutes). The pH of the suspension was measured and adjusted to the pH value of 10.2 with a 15% HCl solution (27.5 mL of 15% HCl) and the suspension was stirred for 24 hours. The pH
of the suspension was periodically checked and adjusted to the desired value of 10.2 if necessary. When adjusting the pH vapours were formed, which were sucked off by underpressure and led through a trap with a solution of calcium hydroxide, which irreversibly bound fluoride ions. The product was then filtered over a filter MN 640 (black ribbon) and washed with methanol (165 mL). The product was thoroughly sucked off and the humidity was determined. Estimated yield of the dry gatifloxacin base: 52.0-54.7%.

The filtration lasted 3 minutes (2-5 minutes) and the washing and sucking-off lasted 90 minutes (60-120 minutes).

**Example 2:** First recrystallization of crude gatifloxacin base (±)-1-cyclopropyl-6-fluoro-1,4-dihydro-7-(3-methyl-1-piperazinyl)-8-methoxy-4-oxo-3-quinoline carboxylic acid)

Into a reactor with a working volume of 1000 mL equipped with a thermometer, a reflux condenser and a mechanical stirrer, the whole amount of the crude gatifloxacin base from Example 1, demineralized water (250 mL) and methanol (1000 mL) were put at 25°C (20°C-30°C). It was stirred for approximately 15 minutes in order to thoroughly homogenize the suspension. The temperature was slightly elevated thereby. The homogenized suspension was heated to reflux temperature (71°C) in 45 minutes and stirred at this temperature for 30 minutes. The obtained solution was cooled to 5°C in 120 minutes and stirred at this temperature for 30 minutes. It was filtered over a filter MN 640 (black ribbon) and washed with a methanol/water mixture (125 mL; 100:25, v/v). The product was thoroughly sucked off and the humidity was determined. The estimated overall yield of dry gatifloxacin base after the first recrystallization was 49.1-50.1%.

The filtration lasted 3 minutes (2-5 minutes) and the washing and sucking-off lasted 75 minutes (45-125 minutes).
Example 3: Second recrystallization of crude gatifloxacin base ((±)-1-cyclopropyl-6-fluoro-1,4-dihydro-7-(3-methyl-1-piperazinyl)-8-methoxy-4-oxo-3-quinoline carboxylic acid)

Into a reactor with a working volume of 1000 mL equipped with a thermometer, a reflux condenser and a mechanical stirrer, demineralized water (250 mL), still humid once recrystallized gatifloxacin base from the Example 2, EDTA (0.2 g) and methanol (1000 mL) were put at 25°C (20°C-30°C). It was stirred for approximately 15 minutes in order to thoroughly homogenize the suspension. The temperature was slightly elevated thereby. The homogenized suspension was heated in 45 minutes to the reflux temperature (71°C) and it was stirred at this temperature at the most until everything was dissolved (30 minutes). The solution had to be clear before filtering through a filter with dicalite applied thereon. The filtration was carried out as quickly as possible, the solution was returned to the reactor and again quickly heated to 71°C. The obtained solution was then cooled to 5°C in 120 minutes and stirred at this temperature for 30 minutes. It was filtered over a filter MN 640 (black ribbon) and washed with a methanol/water mixture (125 mL; 100:25, v/v). The product was thoroughly sucked off and the humidity was determined. The estimated overall yield of dry gatifloxacin base after the second recrystallization was 38.2-44.8%.

The filtration lasted 6 minutes (2-12 minutes) and the washing and sucking-off lasted 55 minutes (40-70 minutes).

Example 4: Formation of gatifloxacin sesquihydrate

Humid twice recrystallized gatifloxacin base was put into a reactor with a working volume of 1000 mL and demineralized water (710 mL) was added. It was stirred for 10 minutes to obtain a homogenous suspension, which was then heated in 75 minutes to 85°C. It was stirred for 30 minutes at 85°C and then cooled in 110 minutes to 25°C.
It was stirred for 15 minutes at 25°C, the stirring intensity was enhanced just before filtering, it was filtered over a filter MN 640 (black ribbon) and washed with demineralized water (71 mL). The filtration lasted 4 minutes (2-6 minutes) and the washing and sucking-off lasted 90 minutes (20-150 minutes). The product was thoroughly sucked off and dried in an air drier at 40-50°C for 60-120 minutes. The yield of the complete synthesis with regard to the weight of appropriately dried gatifloxacin sesquihydrate was 37.0-42.0%.

Example 5: Regeneration of 1-cyclopropyl-6,7-difluoro-1,4-dihydro-8-hydroxy-4-oxo-3-quinoline carboxylic acid

A volume of approximately 500 mL of DMSO filtrate after the step of nucleophilic substitution was put into a 1000 mL reactor and, under stirring, CaCl₂ (approximately 33 g) was added. The mixture was cooled under stirring to 0-5°C (-5°C-25°C) in 30 minutes. The pH was adjusted to the value of 4 with a 15% HCl aqueous solution and it was stirred for 3 hours under maintaining the temperature between 0 nad 5°C. The precipitated product was filtered, thoroughly washed with acetone and dried. Dry 1-cyclopropyl-6,7-difluoro-1,4-dihydro-8-hydroxy-4-oxo-3-quinoline carboxylic acid (approximately 35 g) with a purity over 90% was isolated.

Dry 1-cyclopropyl-6,7-difluoro-1,4-dihydro-8-hydroxy-4-oxo-3-quinoline carboxylic acid was added to acetone (approximately 160 mL) and potassium chloride (approximately 26 g) and dimethyl sulfate (18 mL) were added. Alternatively, 1,4-dioxan or tetrahydrofuran (THF) could be used as the solvent instead of acetone. The reaction mixture was heated to reflux temperature and was left to reflux until the completion of the reaction. After the completed reaction the suspension was cooled to room temperature and filtered. A mixture (58.4 g) of unreacted salts was isolated, which were added to an aqueous potassium carbonate solution, heated to reflux and the ester bond was hydrolyzed for from 30 minutes to some hours. The solution at reflux was cooled to room temperature and 1-cyclopropyl-6,7-difluoro-1,4-dihydro-4-
oxo-3-quinoline carboxylic acid formed was isolated. The yield of methylation and hydrolysis was approximately 17%.

**Example 6: Process monitoring in gatifloxacin synthesis**

The analysis took place on chromatographic column Inertsil ODS3, 3 μm, 150 mm x 4.0 mm I.D., at the column temperature of 40°C, by gradient elution. The solvent A was 0.03 M phosphoric acid, pH = 3 was adjusted with Et₃N, the solvent B was acetonitrile. The flow was approximately 1.2 mL/min. UV detection was used, the detection wavelengths were from 220 to 254 nm and 292 nm. The injection volume was 20 μL. The sample was prepared with the solvent: 0.03 M phosphoric acid (pH = 3) : acetonitrile = 87 : 13 (v/v).

Gradient time course:

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Change of a wavelength during the analysis:

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Claims

1. Process for the preparation of gatifloxacin having a content of impurities in the product of together less than 0.5% and of no single impurity of more than 0.2%, characterized in that
- in the isolation step to a suspension or a solution of gatifloxacin in DMSO an aqueous hydrochloric acid solution is added so that under stirring the pH value is maintained in a range of 9.5-11, preferably between 10.1 and 10.7, and the temperature range between 20°C and 35°C, preferably between 20°C and 30°C, and the product is filtered after a prolonged precipitation time of over 5 hours, preferably 24 hours.

2. Process according to claim 1 for the preparation of gatifloxacin, characterized in that the content of impurities in the product is together less than 0.3% and of no single impurity more than 0.1%.

3. Process for the preparation of gatifloxacin from DMSO or a mixture of DMSO and water in any ratio, characterized in that it includes a regeneration of the side product 1-cyclopropyl-6,7-difluoro-1,4-dihydro-8-hydroxy-4-oxo-3-quinoline carboxylic acid in such a way that to the filtrate a suitable salt is added, the pH value is adjusted in a range between 3 and 4 and the precipitated degradation product is filtered, which is then regenerated with a suitable methylating agent to 1-cyclopropyl-6,7-difluoro-1,4-dihydro-4-oxo-3-quinoline carboxylic acid.

4. Process according to claim 3, characterized in that the salt added for improving filterability is CaCl₂, KCl, CaSO₄ or Na₂SO₄, preferably CaCl₂.

5. Process for the preparation of gatifloxacin according to claim 1, characterized in that the process of purification is carried out by recrystallization in a MeOH/water mixture in a volume ratio of from 8:2 to 9.5:0.5, preferably 9:1.
6. HPLC chromatographic method for the determination of the rate of conversion of the starting compound 1-cyclopropyl-6,7-difluoro-1,4-dihydro-8-methoxy-4-oxo-3-quinoline carboxylic acid to gatifloxacin, characterized in that the starting compound 1-cyclopropyl-6,7-difluoro-1,4-dihydro-8-methoxy-4-oxo-3-quinoline carboxylic acid and the impurity 1-cyclopropyl-6,7-difluoro-1,4-dihydro-8-hydroxy-4-oxo-3-quinoline carboxylic acid are detected at from 220 to 254 nm.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
C07D215/56  C07D401/04

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

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 practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<td>A</td>
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Date of the actual completion of the international search
13 October 2005

Date of mailing of the international search report
30. 11. 05

Name and mailing address of the ISA
European Patent Office, P. B. 5818 Patentlaan 2 NL - 2280 HV Ridwijk
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Authorized officer
Seymour, L
**INTERNATIONAL SEARCH REPORT**

**Box II** Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
   because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
   because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
   because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box III** Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☑ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
    1-5

**Remark on Protest**

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.
This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-5
   process for the preparation of gatifloxacina

2. claim: 6
   method for monitoring the formation of gatifloxacina and its impurities
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