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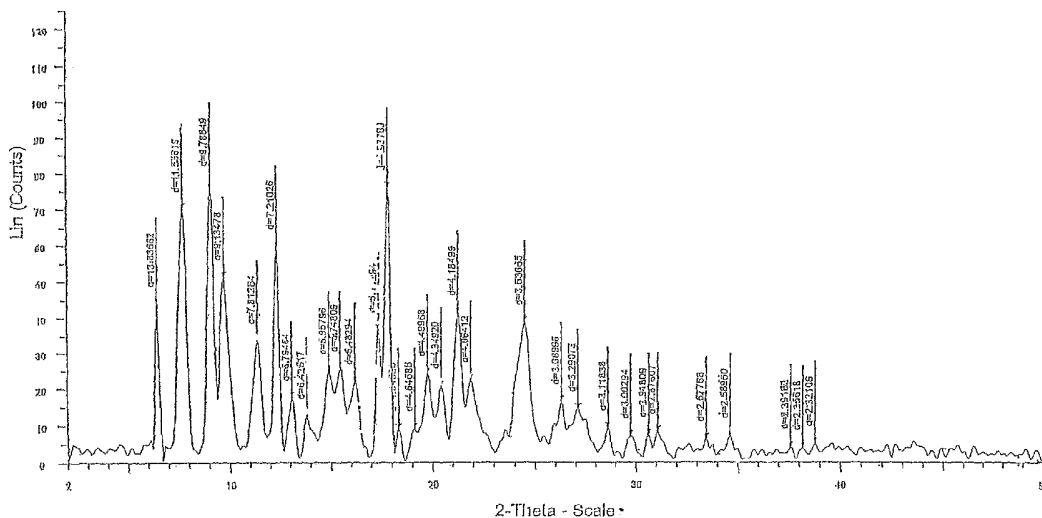
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[Continued on next page]

(54) Title: AN IMPROVED PROCESS FOR THE PREPARATION OF GATIFLOXACIN



(57) Abstract: The present invention relates to a process for the preparation of Gatifloxacin by reacting ethyl 1-cyclopropyl-6,7-difluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylate with aqueous hydrofluoroboric acid followed by condensation with 2-methyl piperazine in polar organic solvent resulting in an intermediate Cyclopropyl-7-(3-methylpiperazin-1-yl)-6-fluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylic acid boron difluoride chelate which upon hydrolysis yields Gatifloxacin.

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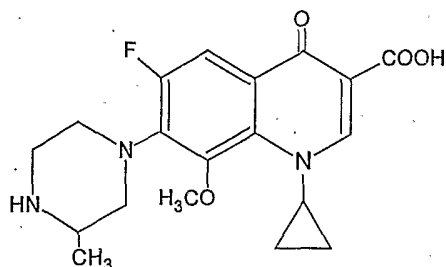
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**An improved process for the preparation of Gatifloxacin:**

The present invention relates to a process for the preparation of Gatifloxacin and its pharmaceutically acceptable salts and hydrates.

Gatifloxacin, chemically 1-Cyclopropyl-6-fluoro-7-(3-methyl piperazin-1-yl)-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylic acid, is represented by the following formula

**GATIFLOXACIN**

Gatifloxacin is a broad-spectrum fluoroquinolone antibiotic, which is disclosed in US Patent No. 5,043,450 as hemihydrate. For the preparation of Gatifloxacin there are few more methods reported in literature. US Patent No. 4,980,470 discloses the method for preparation of Gatifloxacin by condensation of 1-Cyclopropyl-6, 7-difluoro-8-methoxy-4-oxo-1, 4-dihydro-3-quinoline carboxylic acid with 2-methylpiperazine in anhydrous DMSO followed by column chromatographic purification and crystallization with methanol.

European Patent No EP 464,823 discloses a method for the preparation of Gatifloxacin by condensation of 2-methyl piperazine with (1-Cyclopropyl-6,7-difluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylic acid-O<sup>3</sup>,O<sup>4</sup>) bis (acetate-O)-borate followed by hydrolysis with triethylamine and crystallization with ethanol.

US patent No 5,880,283 discloses Gatifloxacin sesquihydrate and a process for its preparation by treating Gatifloxacin hemihydrate with water. US patent Application No 2002/0052379  
5 discloses several hydrates and claims Gatifloxacin pentahydrate. It also discloses the process for preparing Gatifloxacin pentahydrate by water equilibration of Gatifloxacin sesquihydrate or Gatifloxacin hemihydrate.

10 US Patent No 4,997,943 discloses the preparation of Gatifloxacin, which comprises:

- treating ethyl 1-cyclopropyl-6,7-difluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylate with hydrofluoroboric acid to give boron difluoride chelate derivative
- 15 • mixing the chelate derivative with 2-methyl piperazine (4.0 mol equiv.) in DMSO at room temperature for overnight
- evaporating the excess 2-methylpiperazine along with DMSO by vacuum
- washing the residue with diethyl ether
- 20 • separating the condensed chelate compound.
- dissolving the condensed chelate in a mixture of 80% aqueous ethanol, triethyl amine and maintaining at reflux temperature for 4 hrs
- cooling the reaction mass to RT and separating the insolubles  
25 by filtration,
- concentrating the filtrate under vacuum to separate the crystals and washing with ethanol.

Gatifloxacin crystals upon treating with hydrochloric acid in ethanol give Gatifloxacin hydrochloride in the overall yield of  
30 40%. The quality of Gatifloxacin or its hydrochloride salt was not disclosed.

The above method involves the exhaustive work-up resulting in exposure of Gatifloxacin to high temperature thereby enhancing

the possibilities of its degradation, use of diethyl ether, which is highly inflammable solvent. Further it involves the use of a large molar excess of 2-methyl piperazine vis-à-vis 1-cyclopropyl-6,7-difluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylic acid / or its boron difluoride chelate i.e. 4 : 1 there by increasing the consumptions of 2-methylpiperazine leading to the formation of impurities. It also involves the conversion to hydrochloride without isolation of Gatifloxacin.

10 In US patent No 4,980,470 the purification of crude Gatifloxacin involves the use of column chromatography, with the handling of solvents in very high volumes.

15 It has been a long felt need of the industry to provide commercially feasible and cost effective processes to yield high purity Gatifloxacin.

The main object of the present invention is to provide a process for the preparation of high pure Gatifloxacin hemihydrate.

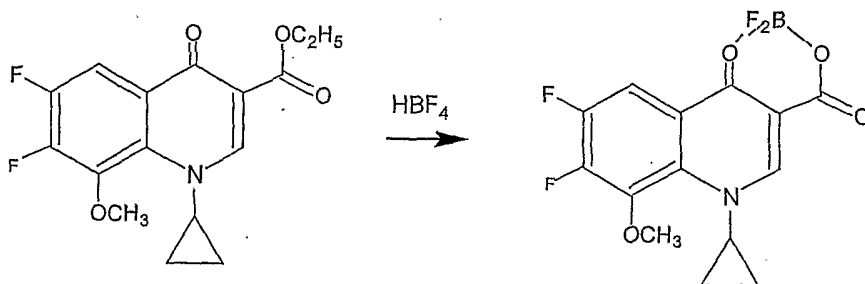
20 Another object of the invention is to provide a process for the preparation of Gatifloxacin without involving the exhaustive work-up.

25 Yet another object of the invention is to provide a process for the purification of 1-cyclopropyl-6-fluoro-7-(3-methyl piperazin-1-yl)-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylate boron difluoride chelate.

30 Accordingly, the present invention relates to a method for the preparation of Gatifloxacin hemihydrate from Ethyl-1-Cyclopropyl-6,7-difluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylate through boron difluoride chelate. Ethyl-1-cyclopropyl-6,7-difluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylate is

reacted with aqueous hydrofluoroboric acid followed by  
 condensation with 2-methyl piperazine in polar organic solvent  
 resulting in an intermediate 1-Cyclopropyl-7-(3-methyl piperazin-1-  
 yl)-6-fluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylic  
 5 acid boron difluoride chelate. This intermediate may be further  
 hydrolyzed to yield Gatifloxacin. Gatifloxacin so obtained may  
 needs purification to yield high purity product. However to obtain  
 directly high purity Gatifloxacin it is desirable to isolate the  
 intermediate by cooling to low temperatures. Treating with an  
 10 alcohol or mixture of alcohols purifies this intermediate. The  
 purified condensed chelate in aqueous ethanol on hydrolysis with  
 triethylamine followed by crystallization in methanol gives  
 Gatifloxacin hemihydrate with high purity.

15

**STAGE - I:**

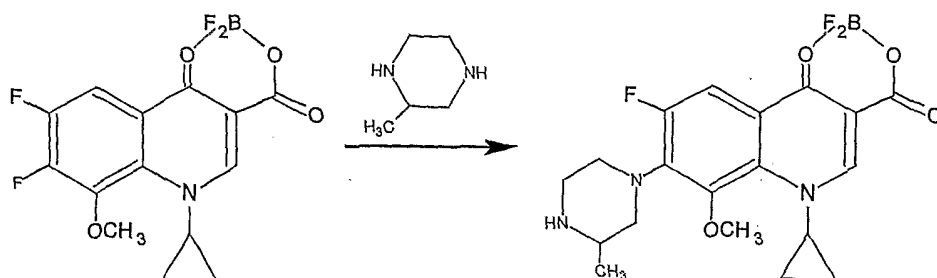
20 Ethyl 1-cyclopropyl-6,7-difluoro-8-methoxy  
 -4-oxo-1,4-dihydro-3-quinoline  
 carboxylate      1-Cyclopropyl-6,7-difluoro-8-methoxy  
 -4-oxo-1,4-dihydro-3-quinoline  
 carboxylic acid boron difluoride chelate

25

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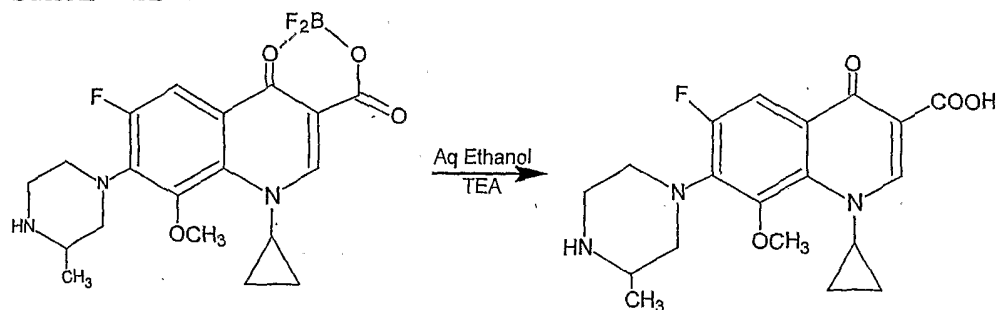
## STAGE - II:



5 1-Cyclopropyl-6,7-difluoro-8-methoxy  
-4-oxo-1,4-dihydro-3-quinoline  
carboxylicacid borondifluoride chelate

1-Cyclopropyl-7-(3-methylpiperazin-1-yl)  
6-fluoro-8-methoxy-4-oxo-1,4-dihydro-3-  
quinoline carboxylicacid borondifluoride  
chelate

## STAGE -III:



10 1-Cyclopropyl-7-(3-methylpiperazin-1-yl)  
-6-fluoro-8-methoxy-4-oxo-1,4-dihydro-3-  
quinoline carboxylicacid borondifluoride  
chelate

GATIFLOXACIN

15

## Brief description of the drawings:

20 Fig. 1: X-ray diffraction pattern of Gatifloxacin sesquihydrate

Fig. 2: FTIR spectrum of Gatifloxacin sesquihydrate

Fig. 3: FTIR spectrum of Gatifloxacin hemihydrate

25 Fig. 4: X-ray diffraction pattern of Gatifloxacin hemihydrate

The essential features of the present invention comprising steps:

- 30
- Reacting Ethyl 1-cyclopropyl-6,7-difluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylate with aq. hydrofluoroboricacid

- Isolating 1-Cyclopropyl-6,7-difluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylic acid boron difluoride chelate by addition of water followed by cooling
- 5 ▪ Condensing 1-Cyclopropyl-6,7-difluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylic acid boron difluoride chelate with 2-methyl piperazine in organic solvent(s)
- 10 ▪ Cooling the reaction mass to low temperature to crystallize the intermediate 1-Cyclopropyl-7-(3-methylpiperazin-1-yl)-6-fluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylic acid boron difluoride chelate
- Hydrolyzing 1-Cyclopropyl-7-(3-methylpiperazin-1-yl)-6-fluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylic acid boron difluoride chelate by treating with triethyl amine
- 15 ▪ Optionally isolating the intermediate 1-Cyclopropyl-7-(3-methylpiperazin-1-yl)-6-fluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylic acid boron difluoride chelate
- 20 ▪ Separating the impurities from 1-Cyclopropyl-7-(3-methylpiperazin-1-yl)-6-fluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylic acid boron difluoride chelate by treating with alcohol at selective temperature
- 25 ▪ Reacting 1-Cyclopropyl-7-(3-methylpiperazin-1-yl)-6-fluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylic acid boron difluoride chelate in aq. ethanol with triethylamine
- Removing aq. ethanol under vacuum followed by adding fresh ethanol
- Crystallizing the crude Gatifloxacin
- Treating the crystallized crude Gatifloxacin with hot methanol to give Gatifloxacin hemihydrate

30 The prepared Gatifloxacin is in the form of hemihydrate, and it is confirmed by its characteristic X-ray diffraction pattern and IR spectrum.



The starting materials Ethyl 1-cyclopropyl-6,7-difluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylate and 1-Cyclopropyl-6,7-difluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylic acid boron difluoride chelate are prepared by the  
5 literature reported methods.

Thus in accordance to the present invention condensation of 1-Cyclopropyl-6, 7-difluoro-8-methoxy-4-oxo-1, 4-dihydro-3-quinoline carboxylic acid boron difluoride chelate with molar  
10 excess 2-methyl piperazine is carried out in a organic solvent(s) such as acetonitrile, methylene chloride, ethylene chloride, methyl acetate, N-methyl-2-pyrrolidinone, methyl isobutyl ketone, ethylene glycol dimethyl ether (mono glyme), diethylene glycol dimethyl ether (diglyme), more selectively acetonitrile at temperature about  
15 of 30°C - 35°C and mixing for about 4 to about 8 hrs. Cooling the reaction mass to low temperature preferably below 0°C and more preferably to about -10°C to about -5°C followed by isolation of the 1-Cyclopropyl-7-(3-methylpiperazin-1-yl)-6-fluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylic acid boron difluoride  
20 chelate. However the intermediate need not be isolated and can be further hydrolyzed by treating with triethyl amine to yield Gatifloxacin.

The impurities from 1-Cyclopropyl-7-(3-methylpiperazin-1-yl)-  
25 6-fluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinolinecarboxylic acid boron difluoride chelate are separated by treating with an alcohol or mixture of alcohols such as methanol, ethanol, n-propanol, iso-propanol, butanol preferably methanol at selective temperature preferably at about 15°C to about 45°C for about 1 to about 4 hrs,  
30 followed by cooling the reaction mixture to low temperature preferably to 15°C, to 25°C. Treating the suspension of the 1-Cyclopropyl-7-(3-methylpiperazin-1-yl)-6-fluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylic acid boron difluoride chelate

with triethylamine in aqueous ethanol or in acetonitrile, at higher temperatures preferably at reflux temperature of the solvent for about 2 to 6 hrs, followed by removing the solvent and then adding fresh solvent, mixing and cooling to low temperatures preferably to below 0°C, more preferably to about -15°C to about -5°C to give the crude Gatifloxacin. Dissolving the crude Gatifloxacin in methanol at hot condition, removing insolubles if any, cooling the clear filtrate to low temperatures preferably to about -10°C to about 0°C followed by isolation and drying affords Gatifloxacin hemihydrate.

10

It may be noted that in the preferred embodiment of this invention the intermediate 1-Cyclopropyl-7-(3-methylpiperazin-1-yl)-6-fluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylic acid boron difluoride chelate is separated, purified and further treated to yield pure Gatifloxacin. In another embodiment of the invention the intermediate 1-Cyclopropyl-7-(3-methylpiperazin-1-yl)-6-fluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylic acid boron difluoride chelate is treated (without separation, isolation or purification) with triethylamine to yield Gatifloxacin, which requires purification to yield pure Gatifloxacin.

15

20

The invention can be further illustrated by the below non-limiting examples.

25

**Example-I:** Preparation of Gatifloxacin with isolation of intermediate (boron difluoride chelate derivative)

**Stage-1:** Preparation of 1-cyclopropyl-6,7-difluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylic acid boron difluoride chelate.

30

Ethyl-1-cyclopropyl-6,7-difluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylate (100g) is suspended in 40% aq. hydrofluoroboric acid (1000 ml). Temperature of the reaction mass is raised and

maintained at 95°C to 100°C for 5hrs followed by cooling to 30°C - 35°C. Water (400 ml) is added and maintained at 25°C - 30°C for 2hrs. Product is filtered, washed with water (500 ml) and dried at 40°C - 45°C to constant weight.

5 Dry weight of the product: 101.6 g (Yield: 95.8 %)

**Stage-2:** Preparation of 1- Cyclopropyl-7-(3-methylpiperazin-1-yl)-6-fluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylic acid boron difluoride chelate

10

100 g of Boron difluoride chelate derivative prepared as above in stage-1 is suspended in acetonitrile (800 ml), to that 2-methyl piperazine (44.0 g, 1.5 mole equiv.) is added and mixed for 15 min to obtain a clear solution. The reaction mass is maintained at 30°C - 35°C for 12 hrs followed by cooling to -10°C to -5°C. The reaction mass is maintained at -10°C to -5°C for 1 hr. The product is filtered and dried at 45°C - 50°C to constant weight.

15

Dry weight of the product: 116.0 g (Yield: 93.9 %).

20

The condensed chelate (100 g) prepared as above is suspended in methanol (1500 ml), maintained at 40°C - 45°C for 30 min. The reaction mass is gradually cooled, maintained for 1 hr at -5°C to 0°C. The product is filtered, washed with methanol (50 ml) and dried at 45°C - 50°C to constant weight.

25

Dry weight of the product: 80.0 g (Yield: 80.0 %)

**Stage -3:** Preparation of Gatifloxacin (Crude)

30

The pure condensed chelate (100.0 g) prepared as above in stage-2 is suspended in 20% aq. ethanol (1000 ml), the temperature is raised and maintained at 75°C to 80°C for 2 hrs. The reaction mass is cooled, filtered to remove insolubles, distilled under vacuum to remove solvent. Fresh ethanol (200 ml) is added and solvent is

removed under vacuum at temperature below 50°C. Ethanol (200 ml) is added to the residue and gradually cooled to -10°C to -5°C. The reaction mass is mixed at -10°C to -5°C for 1 hr and then filtered. The wet cake is washed with ethanol (25 ml) and dried at 45°C - 50°C to constant weight.

The dry weight of the Gatifloxacin is 83.3 g (Yield: 91.7 %)

**Stage- 4:** Purification of crude Gatifloxacin

Crude Gatifloxacin (100.0 g) prepared as above in stage-3 is suspended in methanol (4000 ml), the temperature is raised and maintained at 60°C to 65°C for 20 min. to get a clear solution. Activated carbon (5 g) is added, maintained for 30 min and the solution is filtered. The filtrate is concentrated to one third of its original volume under vacuum at temperature below 40°C. The reaction mass is gradually cooled and maintained at -10°C to -5°C for 2 hrs. The product is filtered, washed with methanol (50 ml) and dried at 45°C - 50°C to constant weight.

The dry weight of the pure Gatifloxacin is 76.0 g (Yield: 76.0 %)

**Example-II:** Preparation of Gatifloxacin without isolation of intermediate (boron difluoride chelate derivative)

**Stage-1:** Preparation of 1-cyclopropyl-6, 7-difluoro-8-methoxy-4-oxo-1, 4-dihydro-3-quinoline carboxylic acid boron difluoride chelate.

Ethyl-1-cyclopropyl-6, 7-difluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylate (100g) is suspended in 40% aq. hydrofluoroboric acid (1000 ml). Temperature of the reaction mass is raised and maintained at 95°C to 100°C for 5 hrs followed by cooling to 30°C - 35°C. 400 ml DM water is added, maintained at 25°C

- 30°C for 2hrs. The product is filtered, washed with DM water (500 ml) and dried at 40°C - 45°C to constant weight.

The dry wt is 102.5 g (Yield: 96.6 %)

5 **Stage - 2: Preparation of Gatifloxacin (Crude)**

The boron difluoride chelate derivative (100 g) prepared as above in stage-1 is suspended in acetonitrile (800 ml), 2-methyl piperazine (44 g, 1.5 mole equiv.) is added and mixed for 15 min to  
10 obtain a clear solution. The reaction mass is maintained at 30°C - 35°C for 12 hrs. Removed the solvent by vacuum distillation. 20% Aq. ethanol (1000 ml) is added, raised the temperature and maintained at 75°C to 80°C for 2 hrs. The reaction mass is cooled, filtered to remove insolubles. The filtrate is distilled under vacuum to remove  
15 solvent completely. Fresh ethanol (250 ml) is added and distilled under vacuum at temperature below 50°C. Fresh Ethanol (250 ml) is added to the residue and gradually cooled to -10°C to -5°C. The reaction mass is maintained at -10°C to -5°C for 1 hr and filtered. The wet cake is washed with ethanol (30 ml) and dried at 45°C - 50°C  
20 to constant weight.

The dry weight of the Gatifloxacin is 73.5 g (Yield: 65.4 %)

**Stage -3: Purification of crude Gatifloxacin**

25

Crude Gatifloxacin (80.0 g) prepared as above in stage-2 is suspended in methanol (2000 ml), the temperature is raised and maintained at 60°C to 65°C for 20 min. to get a clear solution. The reaction mixture is filtered. The filtrate is gradually cooled and  
30 maintained at -10°C to -5°C for 2 hrs. The product is filtered, washed with methanol (50 ml) and dried at 45°C - 50°C to constant weight.

The dry weight of the pure Gatifloxacin is 56.0 g (Yield: 70.0 %)

**We claim:**

1. A process for the preparation of Gatifloxacin comprising steps  
5 of:

- Reacting Ethyl 1-cyclopropyl-6,7-difluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylate with aq. hydrofluoroboric acid
- Isolating 1-Cyclopropyl-6,7-difluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylic acid boron difluoride chelate  
10 by addition of water followed by cooling
- Condensing 1-Cyclopropyl-6,7-difluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylic acid boron difluoride chelate with 2-methyl piperazine in organic solvent(s)
- Cooling the reaction mass to low temperature to crystallize  
15 the intermediate 1-Cyclopropyl-7-(3-methylpiperazin-1-yl)-6-fluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylic acid boron difluoride chelate
- Hydrolyzing 1-Cyclopropyl-7-(3-methylpiperazin-1-yl)-6-fluoro-  
20 8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylic acid boron difluoride chelate by treating with triethyl amine
- Optionally isolating the intermediate 1-Cyclopropyl-7-(3-methylpiperazin-1-yl)-6-fluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylic acid boron difluoride chelate
- Separating the impurities from 1-Cyclopropyl-7-(3-methylpiperazin-1-yl)-6-fluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylic acid boron difluoride chelate by treating  
25 with alcohol at selective temperature
- Reacting 1-Cyclopropyl-7-(3-methylpiperazin-1-yl)-6-fluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylic acid boron difluoride chelate in aq. ethanol with triethylamine  
30
- Removing aq. ethanol under vacuum followed by adding fresh ethanol

- Crystallizing the crude Gatifloxacin
  - Treating the crystallized crude Gatifloxacin with hot methanol
2. A process as claimed in claim 1, wherein the organic solvent(s)  
5 is acetonitrile or ethanol or methylene chloride or ethylene  
chloride or methyl isobutyl ketone or methyl acetate or N-methyl-  
2-pyrrolidinone or mono glyme or di glyme
  3. A process as claimed in claims 1 & 2, wherein the more preferred  
10 organic solvent is acetonitrile
  4. A process as claimed in claim 1, wherein the isolation of the  
intermediate 1-Cyclopropyl-7-(3-methylpiperazin-1-yl)-6-fluoro-8-  
methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylic acid boron  
15 difluoride chelate by cooling the reaction mass to temperature  
below 10<sup>0</sup>C preferably -10<sup>0</sup>C to 0<sup>0</sup>C
  5. A process as claimed in claim 1, wherein the alcohol is methanol  
or Ethanol or propanol or iso-propanol or butanol or mixtures  
20 thereof
  6. A process as claimed in claim 1 & 5 wherein the preferred  
alcohol is Methanol
  - 25 7. A process as claimed in claim 1, wherein the Gatifloxacin is  
crystallized at temperature below 10<sup>0</sup>C, preferably -10<sup>0</sup>C to 0<sup>0</sup>C

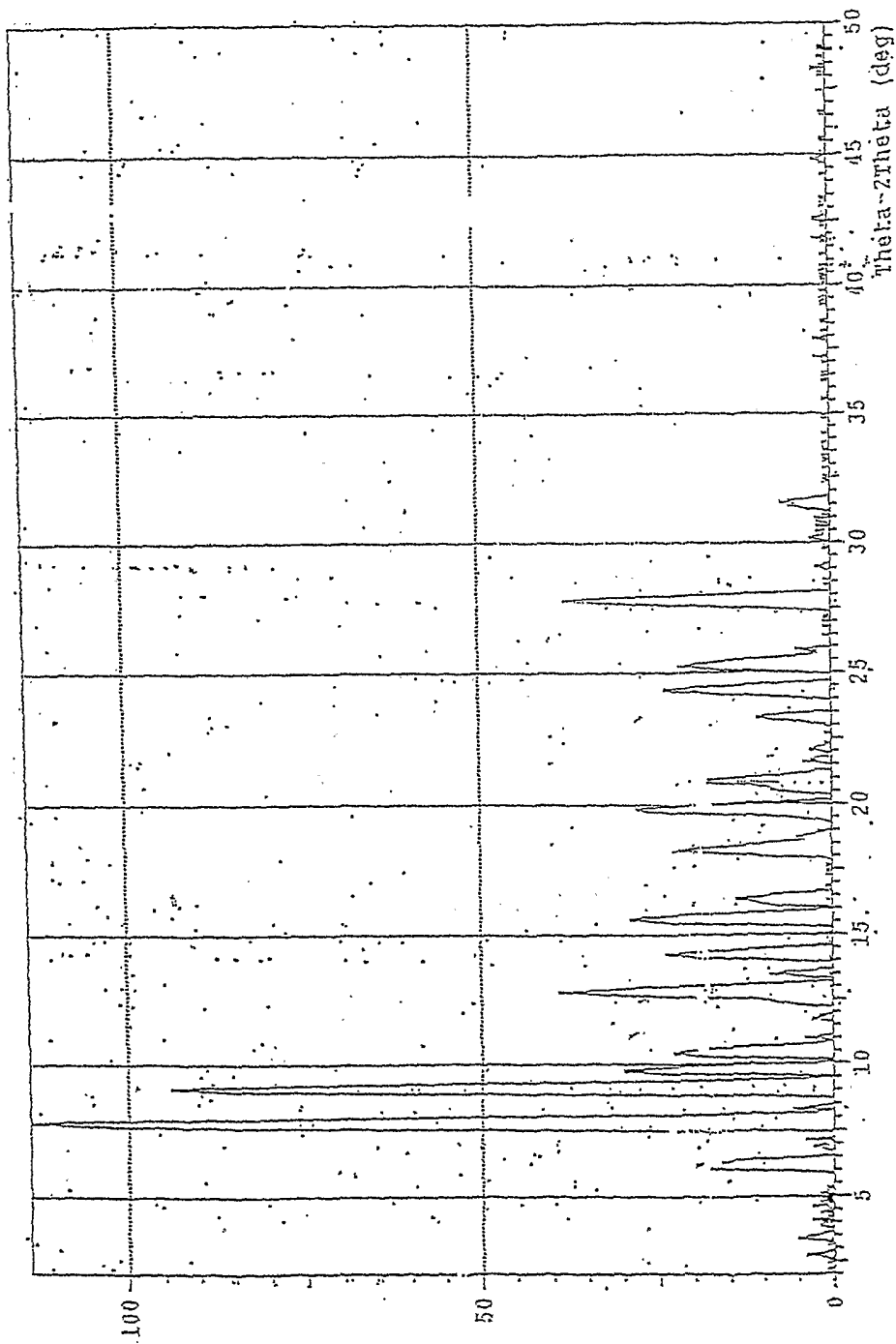


Figure-1



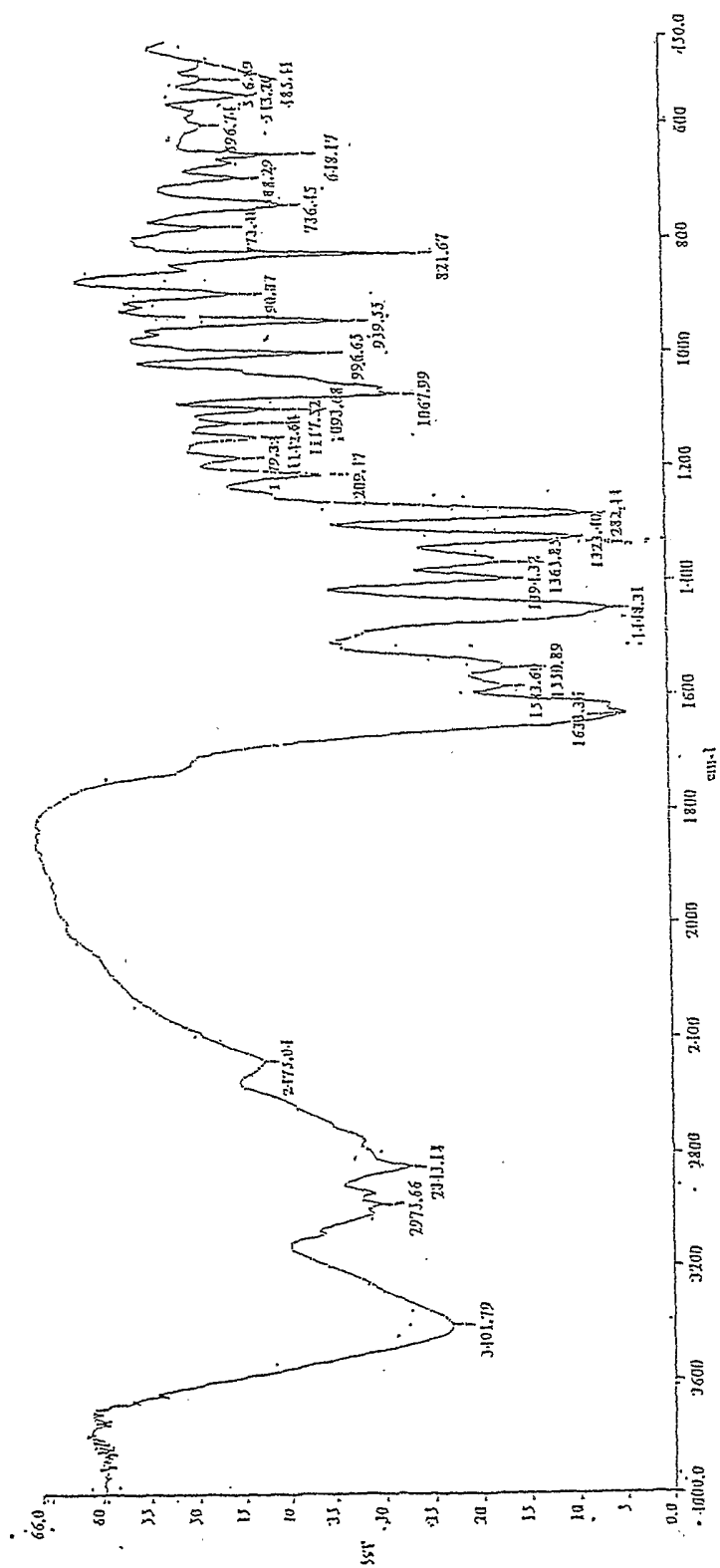


Figure-2

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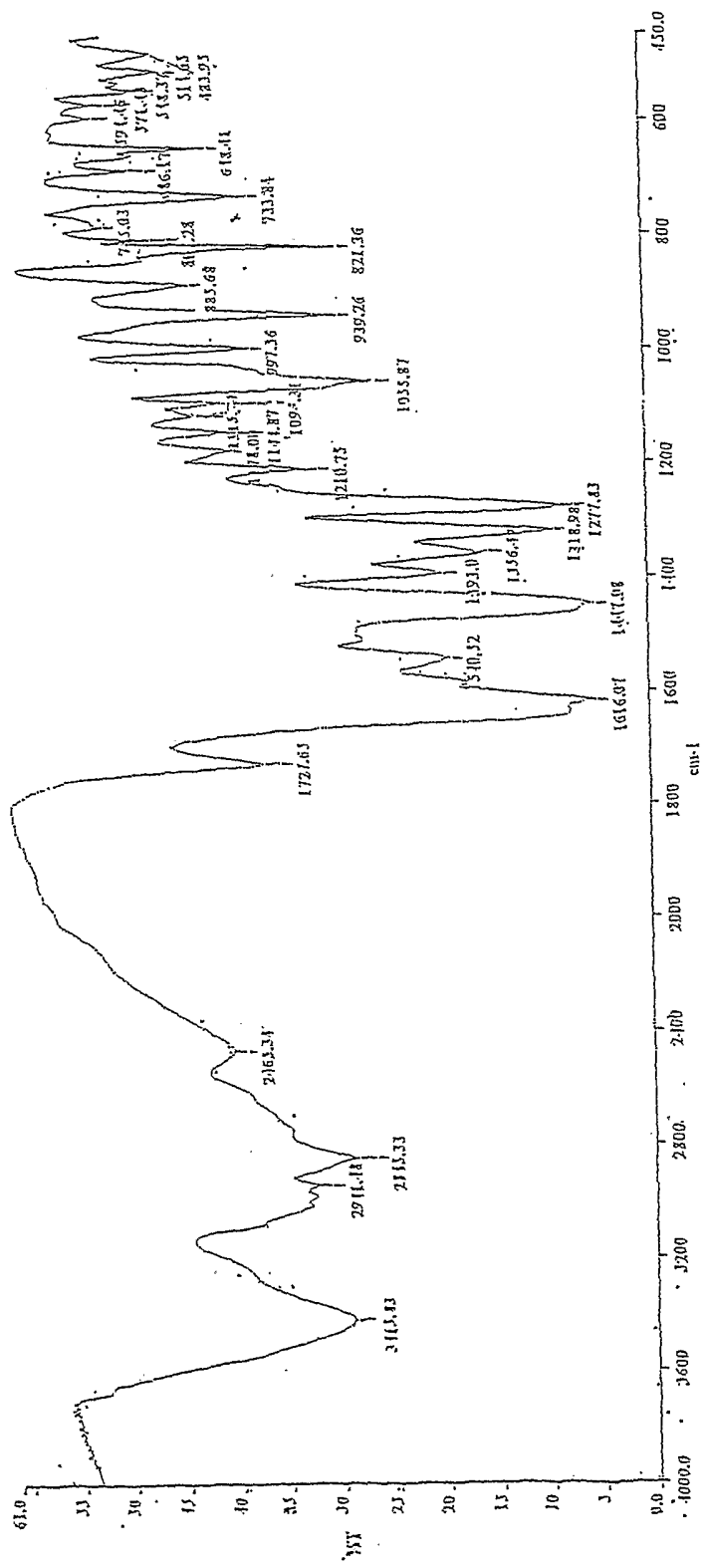


Figure-3

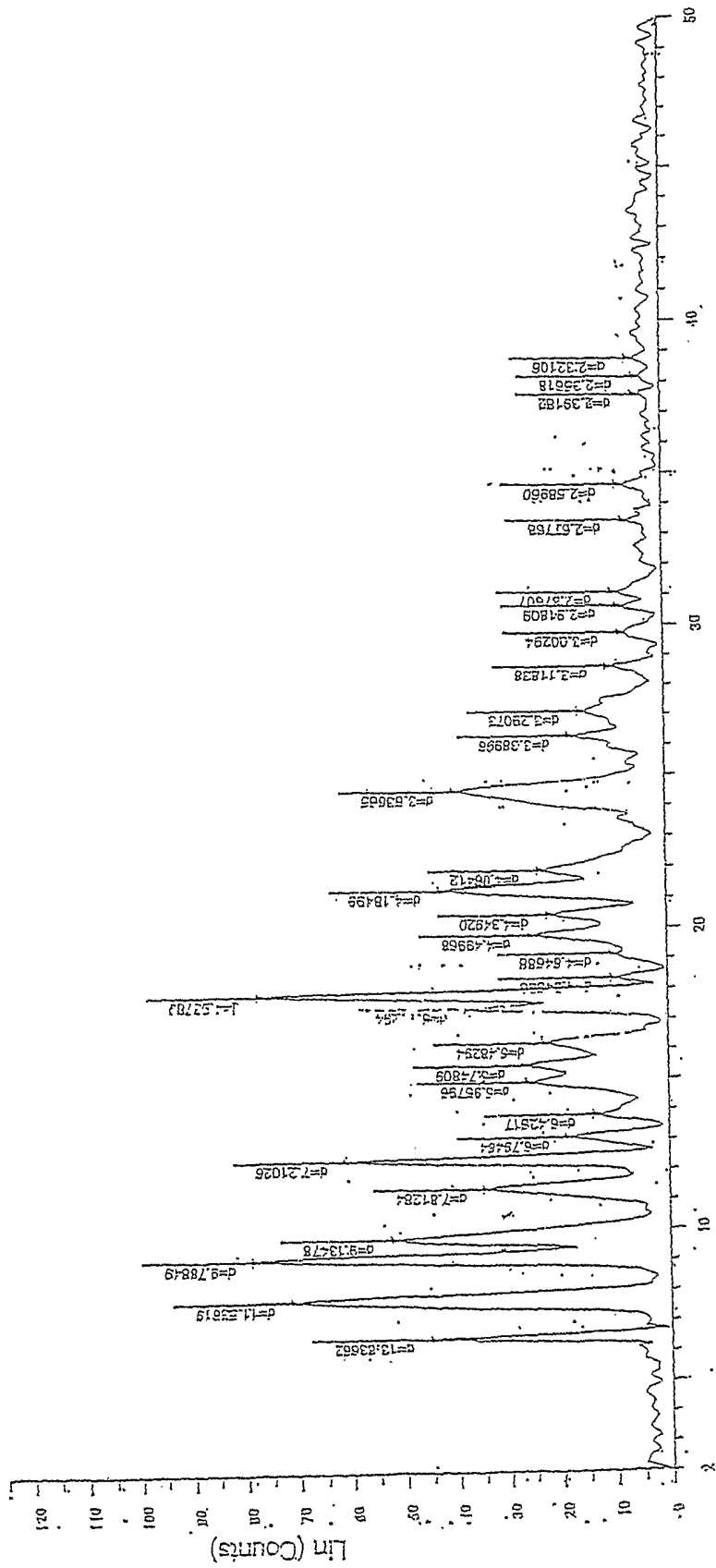


Figure-4

## INTERNATIONAL SEARCH REPORT

national application No.  
T/IN 2004/000221

A. CLASSIFICATION OF SUBJECT MATTER IPC <sup>7</sup> : C07D 215/56 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) IPC <sup>7</sup> : 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 practicable, search terms used) STN Karlsruhe: CAS: CA and REGISTRY, EPOQUE: EPODOC, WPI, Fulltext		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4997943 A (IWATA ET AL.) 5 March 1991 (05.03.1991) <i>reaction scheme A, preparation 7, example 22.</i>	1-7
	--	
A	EP 464823 A1 (KYORIN PHARMACEUTICAL CO.) 8 January 1992 (08.01.1992) <i>the whole document.</i>	1-7
	----	
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input checked="" type="checkbox"/> 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 12 November 2004 (12.11.2004)		Date of mailing of the international search report 26 November 2004 (26.11.2004)
Name and mailing address of the ISA/ AT <b>Austrian Patent Office</b> Dresdner Straße 87, A-1200 Vienna Facsimile No. +43 / 1 / 534 24 / 535		Authorized officer SLABY S. Telephone No. +43 / 1 / 534 24 / 348

INTERNATIONAL SEARCH REPORT

International application No.  
PCT/IN 2004/000221

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				DE	T	69131636T	2000-05-04
				HU	A	58747	1992-03-30
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				FI	A	871419	1987-10-01
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