

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
28 December 2006 (28.12.2006)

PCT

(10) International Publication Number
WO 2006/136919 A1

(51) International Patent Classification:
C07C 303/30 (2006.01) C07C 309/76 (2006.01)

(21) International Application Number:
PCT/IB2006/001676

(22) International Filing Date: 12 June 2006 (12.06.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
753/CHE/2005 20 June 2005 (20.06.2005) IN

(71) Applicant (for all designated States except US): **AUROBINDO PHARMA LIMITED** [IN/IN]; Aurobindo Pharma limited Plot No. 2, Maitrivihar Complex, Ameerpet, Hyderabad 500038 (IN).

(71) Applicant and

(72) Inventor: **KARURU, Mallikarjuna, Reddy** [IN/IN]; Aurobindo Pharma Limited Plot No. 2, Maitrivihar Complex, Ameerpet, Hyderabad 500038 (IN).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **GUPTA, Arun, Kumar** [IN/IN]; Aurobindo Pharma Limited Plot No. 2, Maitrivihar Complex, Ameerpet, Hyderabad 500038 (IN). **MEENAKSHISUNDERAM, Sivakumaran** [IN/IN]; Aurobindo Pharma Limited Plot No. 2, Maitrivihar Complex, Ameerpet, Hyderabad 500038 (IN).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declaration under Rule 4.17:

— of inventorship (Rule 4.17(iv))

Published:

— with international search report

— before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

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.

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

(57) Abstract: The present invention relates to a method for the preparation of Florfenicol from Fluoroamine compound, namely (1R,2S)-1-[4-(methylsulfonyl)phenyl]-2-amino-3-fluoro-1-propanol (II), by reaction with dihaloacetic acid ester in an organic solvent in presence of an inorganic base.



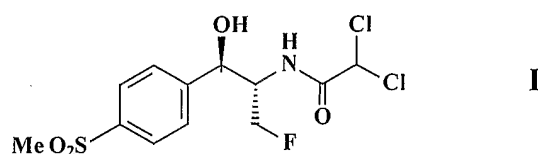
WO 2006/136919 A1

FIELD OF THE INVENTION

The present invention relates to an improved process for preparing Florfenicol.

5 BACKGROUND OF THE INVENTION

Florfenicol, the fluoro derivative of thiamphenicol, has the structure of Formula I



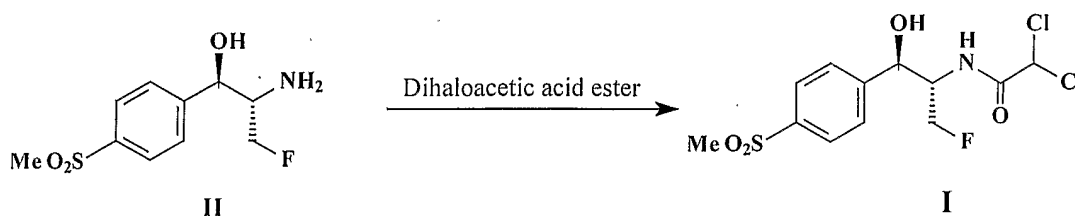
10

Florfenicol is a broad-spectrum antibiotic compound possessing activity against many Gram negative, Gram positive, and thiamphenicol-resistant microorganisms. Florfenicol, chemically known as (1*R*,2*S*)-2-dichloroacetamido-3-fluoro-1-[4-(methylsulfonyl)phenyl]-1-propanol, is of interest as a veterinary product.

15

Several prior-art references have described the process of preparing Florfenicol by acylating fluoro amine compound, (1*R*,2*S*)-1-[4-(methylsulfonyl)phenyl]-2-amino-3-fluoro-1-propanol (II) with dihaloacetic acid ester as shown below :

20



US Patent 4,235,892 describes a process of converting thiamphenicol into Florfenicol and other analogs. The process disclosed therein involves hydrolysis of thiamphenicol to produce aminodiol hydrochloride. Subsequently, amino group of aminodiol hydrochloride is protected with phthalic anhydride and

25

fluorination is carried out to produce a phthalimido-fluoro alcohol. Thereafter, removal of the protecting group with hydrazine hydrate followed by acylation of the resulting fluoro amine compound with methyl dichloroacetate results in Florfenicol. This process does not provide Florfenicol of high purity and
5 therefore further purification using column chromatography was carried out in the disclosed process.

US Patent 5,567,844 claims a process of acylation of Fluoro amine compound (II) with dihaloacetic acid in the presence of catalytic amounts of trialkylamine.
10 However, this process is not exemplified in this reference.

Subsequently, *Journal of Organic Chemistry*, **55**, 1990, 5291-5294, describes a commercial process for the production of Florfenicol wherein acylation of Fluoro amine compound (II) in methanol has been carried out with 5 mole equivalent of
15 methyl dichloroacetate in presence of 1 mole equivalent of triethylamine. This acylation reaction has been accomplished by stirring for 18 hours at room temperature.

The acylation reaction of Fluoro amine compound (II) with dihaloacetic acid or with methyl dihaloacetate does not go to completion even after prolonged stirring
20 and therefore extensive purification of Florfenicol is required to remove unreacted Fluoro amine. This results in lower yield, thereby adding on to the cost of Florfenicol.

In the instant invention, we have found that acylation of Fluoro amine compound with haloacetic acid ester can be conveniently carried out in presence of an
25 inorganic base.

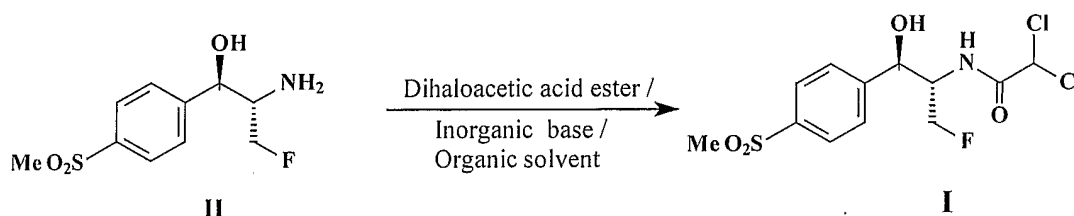
OBJECTIVE OF INVENTION

The main objective of the present invention is to provide an efficient and a simple process to produce Florfenicol (I) having high HPLC purity of greater than 99.5%.

SUMMARY OF THE INVENTION

Accordingly, the present invention relates to a method to convert Fluoro amine compound, namely (1*R*,2*S*)-1-[4-(methylsulfonyl)phenyl]-2-amino-3-fluoro-1-propanol (II) into Florfenicol (I) in an organic solvent by reacting with
5 dihaloacetic acid ester in presence of an inorganic base.

The Reaction Scheme is as given below:



DETAILED DESCRIPTION OF THE INVENTION

(1*R*,2*S*)-1-[4-(methylsulfonyl)phenyl]-2-amino-3-fluoro-1-propanol (II) is reacted with dihaloacetic acid ester in an organic solvent in the presence of an inorganic base to obtain Florfenicol (I), which is isolated by conventional methods known in
15 literature.

The starting material, (1*R*,2*S*)-1-[4-(methylsulfonyl)phenyl]-2-amino-3-fluoro-1-propanol (II) is prepared by methods reported in chemical literature.

In an embodiment of the invention, (1*R*,2*S*)-1-[4-(methylsulfonyl)phenyl]-2-amino-3-fluoro-1-propanol (II) is acylated with dihaloacetic acid ester in presence of catalytic amount of an anhydrous inorganic base, selected from sodium carbonate, sodium bicarbonate, potassium carbonate, potassium bicarbonate and preferably in presence of anhydrous sodium carbonate in an organic solvent, selected from methanol, ethanol, 2-propanol, butanol etc and preferably in methanol. The reaction is carried out at 60-65°C to accomplish the acylation in a
20 shorter period of 2 to 4 hours. Further, these acylation conditions require 2 to 2.5
25

mole equivalent of methyl dichloroacetate for completion of the acylation reaction. After completion of the acylation, the solvent is distilled off under vacuum and the product is precipitated out by addition of toluene and water. The Florfenicol thus produced can be crystallized from aqueous organic solvent
5 selected from methanol, ethanol, isopropanol, butanol etc and preferably from aqueous ethanol.

The major advantage realized in the process of the present invention is that the acylation is completed in 2 to 4 hours without using molar quantity of
10 triethylamine. Further, it requires 2 to 2.5 mole equivalent of methyl dichloroacetate to complete the acylation reaction.

The invention is now illustrated with a non-limiting example, which is provided for illustrative purpose and is not to be construed to limit the scope of the
15 invention.

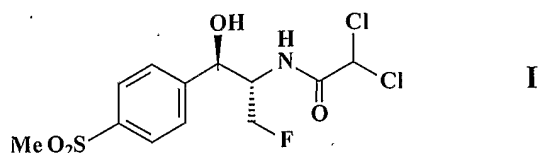
EXAMPLE

PREPARATION OF (1R,2S)-2-DICHLOROACETAMIDO-3-FLUORO-1-[4-(METHYLSULFONYL)PHENYL]-1-PROPANOL(FLORFENICOL)

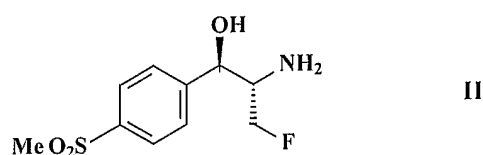
To a solution of (1R,2S)-1-[4-(methylsulfonyl)phenyl]-2-amino-3-fluoro-1-
20 propanol (10 g, 0.04 mole) in methanol (100 ml) was added methyl dichloroacetate (14.48 g; 0.10 mole) and anhydrous sodium carbonate (0.43 g, 0.004 mole) and contents were heated to reflux at 60-65°C for 2 hrs to complete the acylation reaction. After completion of the reaction, methanol was distilled off from the reaction mass under reduced pressure and Florfenicol was precipitated
25 by addition of toluene (75 ml) and water (10 ml). The product was isolated by filtration, and dried. This was crystallized from 20% v/v aqueous ethanol to give 11.50 g of Florfenicol having an HPLC purity of 99.73%.

WE CLAIM

1. A process for the preparation of Florfenicol of Formula I,



comprises reacting the Fluoro amine compound of Formula II



in an organic solvent with dihaloacetic acid ester in presence of an inorganic base.

2. The process as claimed in claim 1, wherein inorganic base is selected from sodium carbonate, sodium bicarbonate, potassium carbonate or potassium bicarbonate.
3. The process as claimed in claim 2, wherein the inorganic base is anhydrous sodium carbonate.
4. The process as claimed in claim 1, wherein the dihaloacetic acid ester is methyl dichloroacetate.
5. The process as claimed in claim 1, wherein organic solvent is methanol, ethanol, isopropanol, n-propanol or butanol.
6. The process as claimed in claim 5, wherein the organic solvent is methanol.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2006/001676

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07C303/30 C07C309/76

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)
C07C

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, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 130 633 A2 (ZAMBON SPA [IT]) 9 January 1985 (1985-01-09) page 11, line 21 - line 28 -----	1-6
A	D.P. SCHUMACHER ET.AL.: "An efficient synthesis of Florfenicol" J. ORG. CHEM., vol. 55, no. 18, 1990, pages 5291-5294, XP002403936 cited in the application Scheme 1, compound 11 (X=F) step (d); page 5294, left column, last paragraph; -----	1-6

☐ 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 document 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

20 October 2006

Date of mailing of the international search report

24/11/2006

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Kleidernigg, Oliver

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IB2006/001676

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 0130633	A2	09-01-1985	AT 143953 T	15-10-1996
			DE 3486438 D1	14-11-1996
			DE 3486438 T2	13-08-1998
			ES 8505927 A1	16-10-1985
			JP 8019085 B	28-02-1996
			JP 60069072 A	19-04-1985
			JP 2721959 B2	04-03-1998
			JP 8295678 A	12-11-1996