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Declarations under Rule 4.17:

— of inventorship (Rule 4.17(iv))

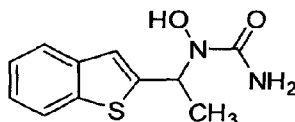
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— with international search report (Art. 21(3))

— before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))

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19 May 2011

(54) Title: IMPROVED PROCESS FOR PREPARATION OF (±)-1-(1-BENZO[B]THIEN-2-YLETHYL)-1-HYDROXYUREA



(I)

(57) Abstract: An improved process for the preparation of (±)-1-(1-Benzo[b]thien-2-ylethyl)-1-hydroxyurea compound of formula (I).



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INTERNATIONAL SEARCH REPORT

International application No.

PCT/IN2010/000640

A. CLASSIFICATION OF SUBJECT MATTER

See extra sheet

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: C07D; A61K

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)

WPI; EPODOC; CPRS; CNKI; CA; CAPlus: zileuton*; 142606-21-1; 143200-94-6; 111406-87-2; benzothienyl*

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	IT2008MI0888A1(DIPHARMA FRANCIS S.R.L. ITALY),15 Aug. 2008(15.08.2008), claim 15	16
A	IN2007KO01592A(LUPIN LIMITED INDIA), 05 June 2009(05.06.2009), pages 7-8 of description	1-18
A	RICHARD R. Copp et al., ACID-CATALYZED ADDITION OF N-HYDROXYUREA TO 1-ARYL ALCOHOL DERIVATIVES: A NEW SYNTHESIS OF ZILEUTON, SYNTHETIC COMMUNICATIONS, 2001, Vol. 31, No.20, pages 3081-3086	1-18

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

* Special categories of cited documents:	“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
“A” document defining the general state of the art which is not considered to be of particular relevance	“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
“E” earlier application or patent but published on or after the international filing date	“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
“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)	“&” document member of the same patent family
“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	

Date of the actual completion of the international search 22 Feb. 2011 (22.02.2011)	Date of mailing of the international search report 17 Mar. 2011 (17.03.2011)
Name and mailing address of the ISA/CN The State Intellectual Property Office, the P.R.China 6 Xitucheng Rd., Jimen Bridge, Haidian District, Beijing, China 100088 Facsimile No. 86-10-62019451	Authorized officer HE, Xiaoping Telephone No. (86-10)62084365

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IN2010/000640

Box No. 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 No. 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 extra 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 fees, this Authority did not invite payment of 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.:

Remark on protest

- The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IN2010/000640

CLASSIFICATION OF SUBJECT MATTER

C07D333/58 (2006.01) i

A61K 31/38 (2006.01) i

Continuation of Box No. III

The present claims 1-5, 8, 13-14 and 17-18(part) relate to processes for the preparation of zileuton which is a known compound (see prior arts such as IT2008MI0888A1, IN2007KO01592A, US4873259A and SYNTHETIC COMMUNICATIONS, 2001, Vol. 31, No.20, pages 3081-3086), the said processes comprise treating 1-(benzo[b]thiophen-2-yl) ethanone with NaBH₄ or ZnCl₂, then treating the obtained compound with N-hydroxy carbamate and finally treating the obtained compound with ammonia. The present claim 6 relates to 1-(benzo[b]thiophen-2-yl) ethyl(hydroxy)carbamates. The present claim 7 relates to ethyl 1-(benzo[b]thiophen-2-yl) ethyl(hydroxy)carbamate. The compounds of claims 6-7 are intermediate compounds of the processes of claims 1-5.

The present claim 9 relates to another process for the preparation of zileuton which comprises treating 1-(benzo[b]thiophen-2-yl) ethanone with hydroxylamine, then treating the obtained compound with borane-pyridine, and finally treating the obtained compound with urea.

The present claim 10 relates to a crystalline form of zileuton. The present claim 11 relates to another crystalline form of zileuton. The present claim 12 relates to a process for the purification/preparation of crystalline zileuton.

The present claims 15 and 17-18(part) relates to purifying the zileuton. The present claim 16 relates to zileuton.

Zileuton is a known compound. The method of the present claim 9 is quite different from that of claims 1-8, 13-14 and 17-18. The crystalline forms of zileuton of claims 10-12 are different from the technical solution of claims 1-9 and 13-18. So there is not a technical relationship among the claimed inventions involving one or more of the same or corresponding special technical features. Claims 1-18 do not comply with the requirement of unity in the sense of PCT Rules 13.1, 13.2 and 13.3.

The present application has at least 4 inventions or groups of inventions:

I: claims 1-8, 13-14, 16 and 17-18 (the part which refers to claims 13-14);

II: claim 9;

III: claims 10-12;

IV: claims 15, 17-18 (the part which refers to claim 15).

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IN2010/000640

Patent Documents referred in the Report	Publication Date	Patent Family	Publication Date
IN2007KO01592A	05.06.2009	None	
IT2008MI0888A1	15.08.2008	US20090286996A1	19.11.2009