Europäisches Patentamt | European Patent Office | Office européen des brevets

16. 05. 2003

REC'D 21 JUL 2003
WIPO PCT

Bescheinigung | Certificate | Attestation

Die angehefteten Unterlagen stimmen mit der ursprünglich eingereichten Fassung der auf dem nächsten Blatt bezeichneten europäischen Patentanmeldung überein.

The attached documents are exact copies of the European patent application described on the following page, as originally filed.

Les documents fixés à cette attestation sont conformes à la version initialement déposée de la demande de brevet européen spécifiée à la page suivante.

Patentanmeldung Nr. | Patent application No. | Demande de brevet n°

02076929.5

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

R C van Dijk

Anmeldung Nr:
Application no.: 02076929.5
Demande no:

Anmeldetag:
Date of filing: 16.05.02
Date de dépôt:

Anmelder/Applicant(s)/Demandeur(s):

Tibotec Pharmaceuticals Ltd.
Unit 4, Block 4B, Blanchardstown Corporate Park
Blanchardstown, Dublin 15
IRLANDE

Bezeichnung der Erfindung/Title of the invention/Titre de l'invention:
(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
If no title is shown please refer to the description.
Si aucun titre n'est indiqué se referer à la description.)

Pseudopolymorphic forms of a HIV protease inhibitor

In Anspruch genommene Priorität(en) / Priority(ies) claimed /Priorité(s) revendiquée(s)
Staat/Tag/Aktenzeichen/State/Date/File no./Pays/Date/Numéro de dépôt:

Internationale Patentklassifikation/International Patent Classification/
Classification internationale des brevets:

C07D493/00

Am Anmeldetag benannte Vertragstaaten/Contracting states designated at date of filing/Etats contractants désignées lors du dépôt:

AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE TR

PSEUDOPOLYMORPHIC FORMS OF A HIV PROTEASE INHIBITOR

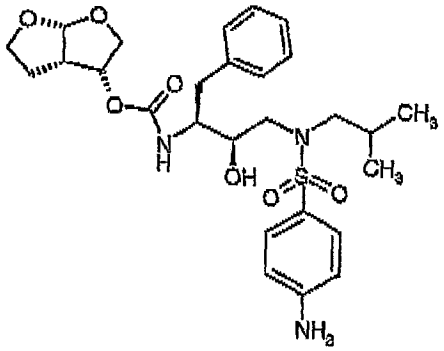
Technical Field

This invention relates to novel pseudopolymorphic forms of (3R,3aS,6aR)-hexahydrofuro [2,3-b] furan-3-yl (1S,2R)-3-[[(4-aminophenyl) sulfonyl] (isobutyl) amino]-1-benzyl-2-hydroxypropylcarbamate, a method for their preparation as well as their use as a medicament.

Background of the invention

Virus-encoded proteases, which are essential for viral replication, are required for the processing of viral protein precursors. Interference with the processing of protein precursors inhibits the formation of infectious virions. Accordingly, inhibitors of viral proteases may be used to prevent or treat chronic and acute viral infections. (3R,3aS,6aR)-hexahydrofuro [2,3-b] furan-3-yl (1S,2R)-3-[[(4-aminophenyl) sulfonyl] (isobutyl) amino]-1-benzyl-2-hydroxypropylcarbamate has HIV protease inhibitory activity and is particularly well suited for inhibiting HIV-1 and HIV-2 viruses.

The structure of (3R,3aS,6aR)-hexahydrofuro [2,3-b] furan-3-yl (1S,2R)-3-[[(4-aminophenyl) sulfonyl] (isobutyl) amino]-1-benzyl-2-hydroxypropylcarbamate, is shown below:



Formula (X)

Compound of formula (X) and processes for its preparation are disclosed in EP 715618, WO 99/67417, US 6,248,775, and in Bioorganic and Chemistry Letters, Vol. 8, pp. 687-690, 1998, "Potent HIV protease inhibitors incorporating high-affinity P_2-ligands and (*R*)-(hydroxyethylamino)sulfonamide isostere", all of which are incorporated herein by reference.

Drugs utilized in the preparation of pharmaceutical formulations must meet certain

standards, including GMP (Good Manufacturing Practices) and ICH (International Conference on Harmonization). Such standards include technical requirements that encompass a heterogeneous and wide range of physical, chemical and pharmaceutical parameters. It is this variety of parameters to consider, which make pharmaceutical formulations a complex technical discipline.

For instance, and as example, a drug utilized for the preparation of pharmaceutical formulations should meet an acceptable purity. There are established guidelines that define the limits and qualification of impurities in new drug substances produced by chemical synthesis, i.e. actual and potential impurities most likely to arise during the synthesis, purification, and storage of the new drug substance. Guidelines are instituted for the amount of allowed degradation products of the drug substance, or reaction products of the drug substance with an excipient and/or immediate container/closure system.

Stability is also a parameter considered in creating pharmaceutical formulations. An optimal stability will ensure that the desired chemical integrity of drug substances is maintained during the shelf-life of the pharmaceutical formulation, which is the time frame over which a product can be relied upon to retain its quality characteristics when stored under expected or directed storage conditions. During this period the drug may be administered with little or no risk, as the presence of potentially dangerous degradation products does not pose any prejudicial consequences to the health of the receiver, nor the lower content of the active ingredient could cause under medication.

Different factors, such as light radiation, temperature, oxygen, humidity, pH sensitivity in solutions, may play a negative role for stability and may bring difficulties to drugs in maintaining a determined shelf life.

Bioavailability is also a parameter to consider in drug delivery design of pharmaceutical acceptable formulations. Bioavailability is concerned with the quantity and rate at which the intact form of a particular drug appears in the systemic circulation following administration of the drug. The bioavailability exhibited by a drug is thus of relevance in determining whether a therapeutically effective concentration is achieved at the site(s) of action of the drug.

Physico-chemical factors and the pharmaco-technical formulation can have a great repercussion in the bioavailability of the drug. As such, several properties of the drug such as dissociation constant, dissolution rate, solubility, polymorphic form, particle size, play a crucial role in bioavailability.

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.