Señor Jefe

DIVISION DE NUEVAS CREACIONES

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Santa Fe de Bogotá, D.C.

Re.: Expediente No. 000-50.944

Solicitud Patente

SMITHKLINE BEECHAM CORPORATION

Debidamente traducida, adjunto acompaño la copia oficial de la solicitud de patente básica ***Estadounidense No. 60/143.100,*** *la cual le solicito agregar a este expediente para los efectos legales respectivos.*

De Usted atentamente,

GERMAN CASTILLO GRAU

T.P.#2.978 del C.S.J.

ESTADOS UNIDOS DE AMÉRICA

A TODOS A QUIENES LLEGUE EL PRESENTE:

DEPARTAMENTO DE COMERCIO DE LOS ESTADOS UNIDOS

Oficina de Marcas y Patentes

22 de junio de 2000.

LA PRESENTE CERTIFICA QUE LA ADJUNTA ES UNA COPIA TOMADA DE LOS REGISTROS DE LA OFICINA DE MARCAS Y PATENTES DE LOS ESTADOS UNIDOS, DE LOS DOCUMENTOS DE LA SOLICITUD DE PATENTE ABAJO IDENTIFICADA Y LA CUAL CUMPLE CON LOS REQUISITOS PARA QUE LE SEA CONFERIDA UNA FECHA DE RADICACIÓN SEGÚN 35 USC 111.

NÚMERO DE SOLICITUD *60/143,110*

FECHA DE RADICACIÓN: *19 de julio de 1999*

Por Autoridad del

COMISIONADO DE MARCAS Y PATENTES

(FIRMA) N. WOODSON

Oficial de Certificaciones

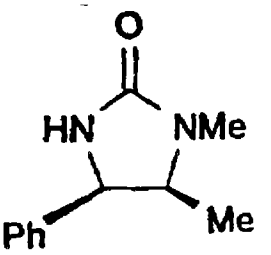
(SELLO DORADO DE OBLEA)

* * * *

PROCESO

REIVINDICACIONES:

1. Un proceso para la preparación de un compuesto de la Fórmula (I):



1

que consiste en calentar L-efedina y urea en la presencia de una sal amonio no volátil.

PA 265083

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

June 22, 2000

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE UNDER 35 USC 111.

APPLICATION NUMBER: ***60/143,110***
FILING DATE: ***July 09, 1999***

By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS

N. WOODSON
Certifying Officer

A/PROV

"EXPRESS MAIL CERTIFICATE"

"Express Mail" Mailing Label Number EL085630906US

Date Of Deposit: July 9, 1999

I Hereby Certify That This Paper Or Fee Is Being Deposited With The United States Postal Service "Express Mail Post Office To Addressee" Service Under 37 CFR 1.10 On The Date Indicated Above And Is Addressed To: Assistant Commissioner for Patents, Washington, D.C. 20231.

Name Of Person Mailing Paper Or Fee
(Type Or Print) L. Smith

Signature

07/09/99 JC841 U.S. PTO 60/143110

PROVISIONAL APPLICATION COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION for PATENT under 37 CFR 1.53(c).

Docket No.	P50960P		

INVENTOR(s) / APPLICANT(s)

Last Name	First Name	Middle Initial	Residence (City and Either State or Foreign Country)
PRIDGEN	Lendon	N.	Collegeville, Pennsylvania

TITLE OF THE INVENTION (280 characters max)

PROCESS

CORRESPONDENCE ADDRESS

SMITHKLINE BEECHAM CORPORATION
Corporate Intellectual Property - UW2220
709 Swedeland Road
King of Prussia

Telephone No. 610-270-5016
Facsimile No. 610-270-5090

State	PA	Zip Code	19406-2799	Country	United States of America

ENCLOSED APPLICATION PARTS (check all that apply)

☒ Specification	Number of Pages	4	☐ Small Entity Statement	
☐ Drawings	Number of Sheets		☒ Other (specify) **Abstract – 1 page**	

METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT

☐ The Commissioner is hereby authorized to charge filing fees and credit Deposit Account No. **19-2570**	PROVISIONAL FILING FEE AMOUNT ($)	**$150.00**

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

☒ No.

☐ Yes, the name of the U.S. Government agency and the Government contract number are:_____.

Respectfully submitted,
Signature: Linda E Hall
Linda E. Hall

Date: July 9, 1999
Registration No.: 31,763

☐ Additional inventors are being named on separately numbered sheets attached hereto.

PROVISIONAL APPLICATION FILING ONLY

SEND TO: Assistant Commissioner for Patents, Box Provisional Application, Washington, D.C. 20231.

N:\LEH\CASES\P50960P\provis.doc

PROCESS

FIELD OF THE INVENTION

The present invention relates to any improvement in the process to prepare aromatic ring-fused cyclopentane derivatives, specifically indane-2-carboxylates and cyclopentano[b]pyridino-2-carboxylates. This improvement relates to the process for preparing important chiral intermediates used in the preparation of indanes and cyclopentano[b]pyridines. This chiral intermediate is (4R,5S)-1,5-dimethyl-4-phenyl-imidizolidin-2-one.

BACKGROUND OF THE INVENTION

Certain indane-2-carboxylic acids and cyclopentano[6]pyridines are useful endothelin receptor antagonists; see U.S. Patent Nos. 5,817,693 5,716,984 and 5,389,620. The racemates of these compounds have important pharmaceutical activity; however, the entanimers have improved activity. For example, (+)(1S,1R,3S)-3-[2-hydroxyeth-1-yloxy)-4-methoxyphenyl]-1-[3,4-methylenedioxyphenyl)-5-propoxylindane-2-carboxylic acid and (+)(1S,2R,3S)3-(2-carboxymethoxy-4-methoxyphenyl-1-(3,4-methylene dioxyphenyl)-5-propoxylindane-2-carboxylic acid are under development and are potential commercial products.

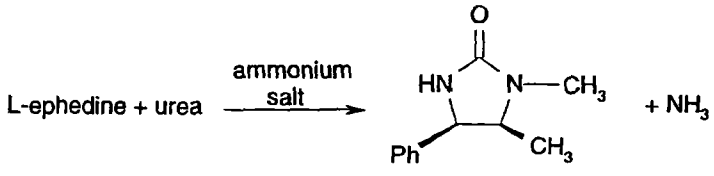
In a PCT application published on May 15, 1997 under International Publication No. WO 97/17342, an improved process for preparing these entanimers is described. The imidizolidin-2-one chiral intermediate was disclosed as an important chiral auxiliary intermediate in this process.

Synthesis of this intermediate is reported in the literature by condensing urea with epedrine; see Close, ***J. Org. Chem., 15***, 1131 (1950) and Drewes et al., ***Chem Ber. 126***, 2663 (1993). This literature procedure has several problems associated with it. The yield is lower than is desired for a commercial process. The process also gives an undesirable oxazolidin-2-one impurity as 25-30% of the crude isolated product. Purification is required before the product can be used. In addition, certain by-products, such as ammonium chloride, cyanimic acid and ammonia form solid particulates that tend to block risers in certain fixed vessels and poses a safety hazard. Thus an improvement in the process for preparing this compound was desired. I have found discovered and disclose in this application an improved process which overcomes the problems associated with the know method.

SUMMARY OF THE INVENTION

The compound (4R,5S)-1,5-dimethyl-4-phenylimidazolidin-2-one (compound 1) is referred to as the most preferred chiral auxiliary in WO 97/17342. The term chiral auxiliary meant a non-racemic functional group that imparts a diastereoselective reaction at a remote prochiral center of a molecule. Compound 1 is a critical intermediate in the stereoselective process disclosed and claimed in WO 97/17342 and which entire published application is incorporated by reference into this application.

The process of this invention involves the following process:



The process is carried out in the presence of a non-volatile ammonium salt at a temperature of 90° to 190°. Suitable ammonium salts include, but not limited to, ammonium sulfamate ammonium sulfate, and ammonium dihydrogen phosphate that would work. The reaction is run at the beginning in an inert organic solvent with a boiling point greater than 75°C in order to provide efficient stirring of the melting reactants. Examples of suitable solvents include, but not limited to, benzene, toluene, xylene mesitylene, chlorobenzene and the like. The ratio of reactants L-ephedine:urea:ammonium salt is 3:1:1 equivalents.

After the reaction is heated to about 100° or the boiling point of the solvent, the solvent is allowed to distil off and the reaction melt is heated to 160-190°C, preferably 165-180°C, until the reaction is completed. The most preferred temperature range is 175-179°C.

Work-up with water results in compound 1 in greater than 99.9% enantiomeric purity and an overall yield improvement of 10-25% over published processes. In addition, the oxazolidinone impurity obtained with the older published procedure is produced in less than 1%.

Compound 1 can be used directly as obtained in the process to prepare the desired pharmaceutically important compounds, for example, as used within the process disclosed in WO 97/17432.

The reaction vessel is purged with nitrogen before heating is begun. During the reaction, ammonia begins to evolve when the reaction mixture reaches a temperature of about 140°. Ammonia can be collected by use of an acid scrubber. Evolution of the ammonia should be monitored and controlled at a reasonable rate by the rate of heating of the reaction mixture.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description and the Examples that follow, utilize the present invention to its fullest extent. The following Examples are to be construed as merely illustrative and not a limitation of the scope of the present invention.

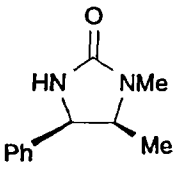
EXAMPLE

(4R,5S)-1,5-Dimethyl-4-phenyl-imidazolidin-2-one

To a 20 gallon glass-lined reactor was added toluene (36 L), urea (16.4 kg, 273.3 moles, 3 equiv), ammonium sulfamate (10.35 kg, 92.3 moles, 1 equiv) and ephedrine (14.36 kg, 86.9 moles). The reaction vessel was purged with nitrogen then was heated to 98°C to remove the toluene. After 40 minutes, all 36 L of toluene was distilled. The reaction was heated to 175°C. Ammonia begins to evolve at ~140°C. After 1.5 hours at 175°C to 180°C, HPLC indicated that the reaction had proceeded to completion. The reaction vessel was cooled to about 105°C and quenched with 27 L of water. At 57°C, 3 L of ethanol was added. The reaction, as a slurry, was stirred at ambient temperature for 4 hours then was transferred to a basket centrifuge and collected. The centrifuged wet cake was rinsed with 60 L of water and collected to yield 11.65 kg of wet cake. The wet cake was dried under vacuum at 20 – 25 °C for 14 hours. The final dry weight of crude product was 10.7 kg (56.25 moles, 65% crude yield). This material was recrystallized from acetonitrile:water (93:7): m.p. 174-175°C;][α]25/D –96.3° (c 1.0, CH_2C1_2); [α]25/D –46° (c 1.0, MeOH).

What is claimed is:

1. A process for the preparation of a compound of Formula 1:



1

which comprises heating L-ephedine and urea together in the presence of a non-volatile ammonium salt.

ABSTRACT OF THE DISCLOSURE

An improved process to make an important chiral auxilary is disclosed and claimed.