

Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

DIVISION DE NUEVAS CREACIONES

E. _____ S _____

Re: P1.-ELI LILLY AND COMPANY .- Solicitud de Patente de
Invención para "PREPARACION DE PIPERIDIN-4-ONAS
SUSTITUIDAS".-Clase A61.-Expediente número 00-
048.059 .-

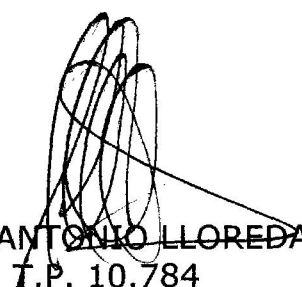
1. Me refiero a mi solicitud de patente de fecha 27 de Junio de 2000.
2. Anexos me permito presentar a usted:
 - (1) Copia autentica, debidamente certificada de la solicitud de patente presentada para el invento arriba nombrado **respecto de la cual reclamo prioridad**, a saber la solicitud estadinense número 60/141.478 de 29 de Junio de 1999, junto con su traducción correspondiente a las legalizaciones y reivindicaciones de dicho documento;
 - (2) Copia debidamente autenticada por el Notario Sexto del Circulo de Bogotá, de los documentos que acreditan la calidad de Traductor Oficial de la señora María Luisa Brigard de Restrepo quien elaboró la traducción de la legalizaciones de la solicitud estadinense número 60/141.478 de 29 de Junio de 1999.
 - (3) Documentos que acreditan el traspaso que los autores del invento de la referencia hacen a favor de mi poderdante, de sus derechos sobre el mismo, debidamente legalizados hasta por el Ministerio de Relaciones Exteriores de Colombia bajo el número 303765 de 25 de Julio de 2000.
 - (4) Traducción Oficial No. 204, debidamente legalizada hasta por el Ministerio de Relaciones Exteriores de Colombia bajo el número

5280

307732 de 28 de Julio de 2000, correspondiente a las partes pertinentes de dicho documento de traspaso.

3. Ruego a usted tomar atenta nota de lo anterior y proceder de conformidad.

Señor Superintendente,



JOSE ANTONIO LLORED A
T.P. 10.784
Código 231

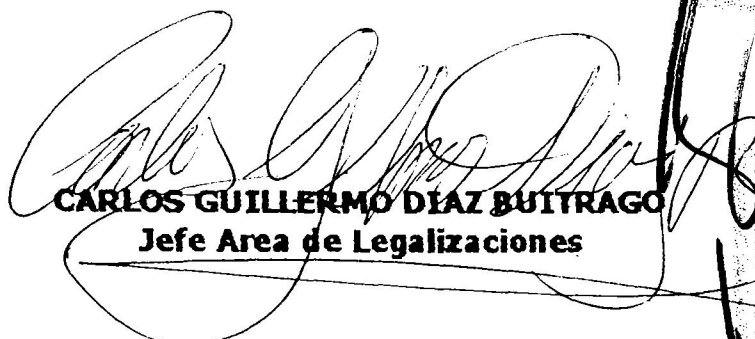
**EL SUSCRITO JEFE DEL AREA DE
LEGALIZACIONES DEL MINISTERIO DE
RELACIONES EXTERIORES**

CERTIFICA

Que revisados los registros que se llevan en la oficina de Legalizaciones aparece la firma de la señora **MARIA LUISA DE BRIGARD DE RESTREPO**, como traductora e intérprete oficial para los idiomas **INGLES - ESPAÑOL, ESPAÑOL-INGLES**, según resolución 0793 del 21 de marzo de 1958

La anterior certificación se expide a solicitud de la interesada **quien se identifica** con cédula de ciudadanía No. 20.024.691 expedida en Santa Fe de Bogotá

Dada en Santa Fe de Bogotá, D.C. a los veinticinco (25) días de marzo de 1999


CARLOS GUILLERMO DIAZ BUITRAGO
Jefe Area de Legalizaciones

3628
COMO NOTARIO SEYTO ENCARGADO DEL CIRCUITO DE SANTA FE DE BOGOTA, HAGO CONSTAR QUE LA COPIA FOTOSTATICA COINCIDE CON LA FOTOCOPIA AUTENTICA QUE HE TENIDO A LA VISTA.

PASLO MENDEZ BARAJAS

COMO NOTARIO SEYTO ENCARGADO DEL CIRCUITO DE SANTA FE DE BOGOTA, HAGO CONSTAR QUE LA COPIA FOTOSTATICA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA.

13 ABR 1999

PASLO MENDEZ BARAJAS

25 ABR. 2000

El. 611431
00.048059

TRADUCCION OFICIAL No. 5.741

de un documento escrito en INGLES, el cual para su identificación se sella con el sello del Traductor al mismo tiempo que la presente. -

ESTADOS UNIDOS DE AMERICA

A CUANTOS LLEGAREN LAS PRESENTES:

DEPARTAMENTO DE COMERCIO DE LOS ESTADOS UNIDOS

Oficina de Patentes y Marcas de Fábrica de los Estados Unidos

TRADUCCION OFICIAL No. 5.741
14 de julio del 2000
Maria Luisa B. [Signature]
Interprete Oficial
del Depto. del Comercio de los Estados Unidos

POR LA PRESENTE SE CERTIFICA QUE ANEXA AQUI SE ENCUENTRA UNA COPIA FIEL , TOMADA DE LOS REGISTROS DE LA OFICINA DE PATENTES Y MARCAS DE FABRICA DE LOS ESTADOS UNIDOS, DE LOS DOCUMENTOS DE LA SOLICITUD DE PATENTE IDENTIFICADA ABAJO QUE SATISFACEN LOS REQUISITOS PARA QUE SEA OTORGADA UNA FECHA DE REGISTRO SEGUN 35 USC 111.

NUMERO DE SOLICITUD: 60/141,478

FECHA DE REGISTRO: 29 de junio de 1999.

Por Autorización del

COMISIONADO DE PATENTES Y MARCAS DE FABRICA

(Firma)

H. L. JACKSON

38

Funcionario Certificador

**Sello: OFICINA DE PATENTES Y MARCAS DE FABRICA - ESTADOS UNIDOS
DE AMERICA -**

ANEXO:

SOLICITUD PROVISIONAL PARA HOJA DE CUBIERTA DE PATENTE

Esta es una solicitud de registro de una SOLICITUD PROVISIONAL DE PATENTE ^{5.741}
según 37 CFR 1.53 (c)

TRADUCCION OFICIAL NO.
Escríban el signo más (+) en esta casilla

Número del Expediente	P-12998	Escríban el signo más (+) en esta casilla
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INVENTOR(ES)/SOLICITANTE(S)			
APELLIDO	PRIMER NOMBRE	NOMBRE DEL MEDIO	RESIDENCIA (CIUDAD Y ESTADO O PAIS EXTRANJERO)
Rizzo Staszac Zhang	John Michael Tony	Robert Alexander Yantao	Indianapolis, Indiana Indianapolis, Indiana Indianapolis, Indiana
TITULO DE LA INVENCION			
PREPARACION DE PIPERIDIN-4-ONAS SUSTITUIDAS			
DIRECCION DE CORRESPONDENCIA			

39

Eli Lilly and Company División de Patentes/D.C. 1104 Lilly Corporate Center Indianapolis, Indiana 46285					
ESTADO	IN	CODIGO ZIP	46285	PAIS	EE.UU.A.
PARTES DE SOLICITUD INCLUIDAS					
X Especificaciones		Número de Páginas 14			
METODO DE PAGO					
X El Comisionado Auxiliar es autorizado por la presente para cobrar los derechos de registro y acreditarlos a la Cuenta de Depósito Número 05-0840			MONTO DE LOS DERECHOS DE REGISTRO PROVISIONAL (\$)		\$150.00

5741
\$150.00
Maria Lenta
Interesate Oficial
No. 0702 del Min. de Justicia

¿La invención fué hecha por una agencia del Gobierno de los Estados Unidos o bajo un contrato con una agencia del Gobierno de los Estados Unidos?
X No.

Presentada respetuosamente,
FIRMA (Firma)

Fecha 29/6/99

NO. DE REGISTRO: 38,537

NOMBRE EN LETRA DE IMPRENTA: NELSEN L. LENTZ

SOLICITUD PROVISIONAL SOLAMENTE PARA REGISTRO DE PATENTE

Enviar por "Correo Expreso" número de rótulo EL042029402 US
Fecha de Depósito 29 de junio de 1999

Por el presente certifico que este documento o estos derechos se están depositando en la "Oficina de Correo Expreso para el Destinatario" del servicio Postal de los Estados Unidos según 37 C.F.R. 1.10 en la fecha indicada arriba y son dirigidos al Comisionado Auxiliar de Patentes, Washington, D.C., 20231.

Olga M. Franz
Nombre impreso

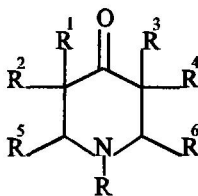
(Fdo) Olga M. Franz
Firma

ANEXO:

P-12998

LO QUE SE REIVINDICA ES:

1. Un procedimiento para la preparación de un compuesto de la fórmula I



fórmula I

TRANSMISION OFICIAL No. 5741
 María Luisa Briceño de Restrepo
 Intermediaria Oficial
 MA 0702 del MIN de Justicia

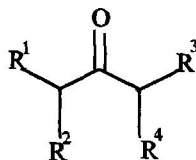
en donde R es hidrógeno, alquilo C₁-C₆, halo-alquilo(C₁-C₆), fenilo, bencilo, o fenilo sustituido con 1 a 3 sustitutos escogidos entre el grupo, constituido por F, Cl, Br, I, alquilo C₁-C₆, alcoxi C₁-C₆, halo-alquilo(C₁-C₆), fenilo, NO₂ y CN;

R¹, R², R³, R⁴, R⁵, y R⁶, son, cada uno independientemente, hidrógeno, alquilo C₁-C₆, halo-alquilo(C₁-C₆), fenilo, o fenilo sustituido con 1 a 3 sustitutos escogidos entre el grupo, constituido por F, Cl, Br, I, alquilo C₁-C₆, alcoxi C₁-C₆, -S(alquilo (C₁-C₆), -S(fenilo), halo-alquilo(C₁-C₆), fenilo, NO₂ y CN;

o la sal farmacéuticamente aceptable del mismo,

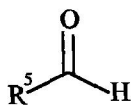
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que consiste en combinar un compuesto de la fórmula II:



fórmula II

en donde R¹, R², R³ y R⁴ corresponden a las definiciones que anteceden,
un compuesto de la fórmula III:



TRABAJOS OFICIALES No. 5741
fórmula III
María Luisa Briceño de Rodríguez
Intérprete Oficial
Calle 17 de Mayo No. 100 de Lima

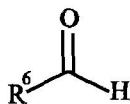
en donde R⁵ corresponde a la definición que antecede,
y un compuesto de la fórmula IV:



fórmula IV

en donde R corresponde a la definición que antecede,
en la presencia de un ácido adecuado,

y luego adicionar una base adecuada y un compuesto de la fórmula V:



fórmula V

en donde R⁶ corresponde a la definición que antecede.

2. El procedimiento acorde con la reivindicación 1 en el que la base adecuada es diisopropiletilamina.

3. El procedimiento acorde con la reivindicación 2 en el que el ácido adecuado es HCl.

4. El procedimiento acorde con la reivindicación 3 en el que R¹, R², R³, R⁴, R⁵, y R⁶, son, cada uno independientemente, hidrógeno, alquilo C₁-C₆, fenilo o bencilo.

5. El procedimiento acorde con la reivindicación 4 en el que R³ y R⁴ son alquilo C₁-C₆.

6. El procedimiento acorde con la reivindicación 4 en el que R⁵ es alquilo C₁-C₆ y R⁶ es hidrógeno.

7. El procedimiento acorde con la reivindicación 5 en el que R³ y R⁴ son metilo.

8. El procedimiento acorde con la reivindicación 6 en el que R⁵ es metilo.

9. El procedimiento acorde con la reivindicación 7 en el que R⁵ y R⁶ son hidrógeno.

MANUFACTURER. OFFICIAL No. 5741
Instituto de Patentes de Colombia
No. 0783 del 2001

43²¹⁶

10. El procedimiento acorde con la reivindicación 9 en el que R¹ y R² son hidrógeno.

11. El procedimiento acorde con la reivindicación 10 en el que R es hidrógeno.

12. El procedimiento acorde con la reivindicación 10 en el que R es bencilo.

ES TRADUCCION FIEL Y COMPLETA, de la cual queda copia en los archivos de esta oficina de traducciones, para su confrontación y a la que me remito.

Derechos de Traducción: \$63.000.00

BOGOTA, 1º DE AGOSTO DEL 2000.

TRADUCCION OFICIAL No. 5741

Maria Luisa Brigard de Restrepo

Maria Luisa Brigard de Restrepo

Intérprete Oficial

No. 0762 del Min. de Justicia

PA 272934

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

July 14, 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: 60/141,478

FILING DATE: June 29, 1999



By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS

H. L. Jackson

H. L. JACKSON

Certifying Officer

7/PROV US 48

PROVISIONAL APPLICATION FOR PATENT COVER SHEET

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

Docket Number	P-12998	Type a plus sign (+) inside this box -->	+
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INVENTOR(s)/APPLICANT(s)			
LAST NAME	FIRST NAME	MIDDLE NAME	RESIDENCE (CITY AND EITHER STATE OR FOREIGN COUNTRY)
Rizzo	John	Robert	Indianapolis, Indiana
Staszak	Michael	Alexander	Indianapolis, Indiana
Zhang	Tony	Yantao	Indianapolis, Indiana

TITLE OF THE INVENTION (280 characters max)

PREPARATION OF SUBSTITUTED PIPERIDIN-4-ONES

CORRESPONDENCE ADDRESS

Eli Lilly and Company
Patent Division/D.C. 1104
Lilly Corporate Center
Indianapolis, Indiana 46285

STATE	IN	ZIP CODE	46285	COUNTRY	USA
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ENCLOSED APPLICATION PARTS (check all that apply)

☒ Specification	Number of pages	14	☐ Small Entity Statement
☐ Drawing(s)	Number of Sheets		☐ Other (Specify)

METHOD OF PAYMENT (check one)

☐ A check or money order is enclosed to cover the Provisional filing fees	PROVISIONAL FILING FEE AMOUNT (\$)	\$150.00
☒ The Assistant Commissioner is hereby authorized to charge filing fees and credit Deposit Account Number: 05-0840		

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



Date 6 / 29 / 99

TYPED or PRINTED NAME NELSEN L. LENTZ

REGISTRATION NO. (if appropriate)

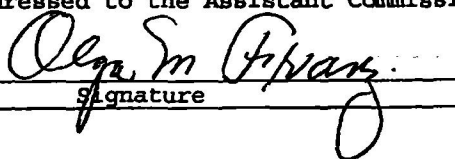
38,537

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

PROVISIONAL APPLICATION FOR PATENT FILING ONLY

"Express Mail" mailing label number EL 042029402 US Date of Deposit June 29, 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 C.F.R. 1.10 on the date indicated above and is addressed to the Assistant Commissioner for Patents, Washington, D.C., 20231.

Olga M. Franz
Printed Name


Signature

46#

PREPARATION OF SUBSTITUTED PIPERIDIN-4-ONESFIELD OF THE INVENTION

5 The present invention provides a novel process for the preparation of substituted piperidin-4-ones useful as intermediates in the preparation of pharmaceuticals.

BACKGROUND OF THE INVENTION

10 G.T. Katvalyan and E.A. Mistryukov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 11, 2575 (2436 transl.) (1968) disclose a multistep synthesis of 1-methyl-3,3-dimethyl-piperidin-4-one starting with methylamine and isobutyraldehyde. In addition, I.V. Micovic, et al., *J. Chem. Soc., Perkin Trans.*, 1, 2041 (1996) disclose a multistep synthesis of 1-benzyl-3,3-gem-dimethyl-piperidine-4-one
15 starting with benzylamine and methyl acrylate.

 It has now been discovered that 3-substituted piperidones can be prepared simply and efficiently following the one-pot procedure of the present invention, thus obviating the traditionally lengthy syntheses such as those requiring a Dieckmann condensation.

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SUMMARY OF THE INVENTION

 The present invention provides a process for the preparation of a compound of formula I:

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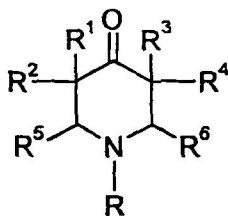
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Olga M. Franz
Printed Name

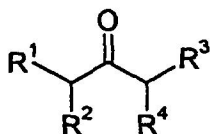
Olga M. Franz
Signature

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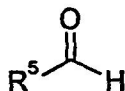
formula I

- wherein R is hydrogen, C₁-C₆ alkyl, halo(C₁-C₆)alkyl, phenyl, benzyl, or phenyl substituted with from 1 to 3 substituents selected from the group consisting of F, Cl, Br, I, C₁-C₆ alkyl, C₁-C₆ alkoxy, halo(C₁-C₆)alkyl, phenyl, NO₂, and CN;
- 5 R¹, R², R³, R⁴, R⁵ and R⁶ are each independently hydrogen, C₁-C₆ alkyl, halo(C₁-C₆)alkyl, phenyl, or phenyl substituted with from 1 to 3 substituents selected from the group consisting of F, Cl, Br, I, C₁-C₆ alkyl, C₁-C₆ alkoxy, -S(C₁-C₆ alkyl), -S(phenyl), halo(C₁-C₆)alkyl, phenyl, NO₂, and CN;
- 10 or the pharmaceutically acceptable salt thereof;
- comprising combining a compound of formula II:



formula II

wherein R¹, R², R³, and R⁴ are defined as above, a compound of formula III:

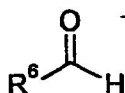


formula III

- 15 wherein R⁵ is defined as above, and a compound of formula IV:



wherein R is defined as above, in the presence of a suitable acid;
followed by addition of a suitable base and a compound of formula V:



formula V

- 20 wherein R⁶ is defined as above.

DETAILED DESCRIPTION OF THE INVENTION

As used herein, the terms "Halo", "Halide" or "Hal" refers to a chlorine, bromine, iodine or fluorine atom, unless otherwise specified herein.

As used herein, the term "Me" refers to a methyl group, the term "Et" refers to an ethyl group, the term "Pr" refers to a propyl group, the term "iPr" refers to an isopropyl group, the term "Bu" refers to a butyl group, the term "Ph" refers to a phenyl group, the term "benzyl" refers to a -CH₂phenyl group.

As used herein the term "C₁-C₄ alkyl" refers to a straight or branched, monovalent, saturated aliphatic chain of 1 to 4 carbon atoms and includes, but is not limited to methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl and the like.

As used herein the term "C₁-C₆ alkyl" refers to a straight or branched, monovalent, saturated aliphatic chain of 1 to 6 carbon atoms and includes, but is not limited to methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, t-butyl, n-pentyl, n-hexyl, and the like. The term "C₁-C₆ alkyl" includes within its scope "C₁-C₄ alkyl".

As used herein the term "C₁-C₆ alkoxy" refers to a straight or branched alkyl chain having from one to six carbon atoms attached to an oxygen atom. Typical C₁-C₆ alkoxy groups include methoxy, ethoxy, propoxy, isopropoxy, butoxy, t-butoxy, pentoxy and the like. The term "C₁-C₆ alkoxy" includes within its definition the term "C₁-C₄ alkoxy".

As used herein the term "-S(C₁-C₆ alkyl)" refers to a straight or branched alkyl chain having from one to six carbon atoms attached to a sulfur atom such as -SCH₃, -SCH₂CH₃, -SCH₂CH₂CH₃, -SCH₂CH₂CH₂CH₃, and the like.

As used herein the term "halo(C₁-C₆)alkyl" refers to a straight or branched alkyl chain having from one to six carbon atoms with 1, 2 or 3 halogen atoms attached to it. Typical halo(C₁-C₆)alkyl groups include chloromethyl, 2-bromoethyl, 1-chloroisopropyl, 3-fluoropropyl, 2,3-dibromobutyl, 3-chloroisobutyl, iodo-t-butyl, trifluoromethyl and the like. The term "halo(C₁-C₆)alkyl" includes within its definition the term "halo(C₁-C₄)alkyl".

This invention includes the hydrates and the pharmaceutically acceptable salts of the compounds of formula I. A compound of this invention can possess

a sufficiently basic functional group which can react with any of a number of inorganic and organic acids, to form a pharmaceutically acceptable salt.

The term "pharmaceutically acceptable salt" as used herein, refers to salts of the compounds of formula I which are substantially non-toxic to living organisms. Typical pharmaceutically acceptable salts include those salts prepared by reaction of the compounds of the present invention with a pharmaceutically acceptable mineral or organic acid. Such salts are also known as acid addition salts.

Acids commonly employed to form acid addition salts are inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, phosphoric acid, and the like, and organic acids such as p-toluenesulfonic, methanesulfonic acid, oxalic acid, p-bromophenylsulfonic acid, carbonic acid, succinic acid, citric acid, benzoic acid, acetic acid, and the like. Examples of such pharmaceutically acceptable salts are the sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, bromide, iodide, acetate, propionate, decanoate, caprylate, acrylate, formate, hydrochloride, dihydrochloride, isobutyrate, caproate, heptanoate, propiolate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, butyne-1,4-dioate, hexyne-1,6-dioate, benzoate, chlorobenzoate, methylbenzoate, hydroxybenzoate, methoxybenzoate, phthalate, xylenesulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, g-hydroxybutyrate, glycolate, tartrate, methanesulfonate, propanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, mandelate and the like. Preferred pharmaceutically acceptable acid addition salts are those formed with mineral acids such as hydrochloric acid and hydrobromic acid, and those formed with organic acids such as maleic acid, oxalic acid and methanesulfonic acid.

It should be recognized that the particular counterion forming a part of any salt of this invention is usually not of a critical nature, so long as the salt as a whole is pharmacologically acceptable and as long as the counterion does not contribute undesired qualities to the salt as a whole. It is further understood that such salts may exist as a hydrate.

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The designation "  " refers to a bond that protrudes backward out of the plane of the page.

5 As used herein, the term "stereoisomer" refers to a compound made up of the same atoms bonded by the same bonds but having different three-dimensional structures which are not interchangeable. The three-dimensional structures are called configurations. As used herein, the term "enantiomer" refers to two stereoisomers whose molecules are nonsuperimposable mirror
10 images of one another. The term "chiral center" refers to a carbon atom to which four different groups are attached. As used herein, the term "diastereomers" refers to stereoisomers which are not enantiomers. In addition, two diastereomers which have a different configuration at only one chiral center are referred to herein as "epimers". The terms "racemate", "racemic mixture" or
15 "racemic modification" refer to a mixture of equal parts of enantiomers.

 The term "enantiomeric enrichment" as used herein refers to the increase in the amount of one enantiomer as compared to the other. A convenient method of expressing the enantiomeric enrichment achieved is the concept of enantiomeric excess, or "ee", which is found using the following equation:

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$$ee = \frac{E^1 - E^2}{E^1 + E^2} \times 100$$

 wherein E^1 is the amount of the first enantiomer and E^2 is the amount of the
25 second enantiomer. Thus, if the initial ratio of the two enantiomers is 50:50, such as is present in a racemic mixture, and an enantiomeric enrichment sufficient to produce a final ratio of 50:30 is achieved, the ee with respect to the first enantiomer is 25%. However, if the final ratio is 90:10, the ee with respect to the first enantiomer is 80%. An ee of greater than 90% is preferred, an ee of
30 greater than 95% is most preferred and an ee of greater than 99% is most especially preferred. Enantiomeric enrichment is readily determined by one of ordinary skill in the art using standard techniques and procedures, such as gas or high performance liquid chromatography with a chiral column. Choice of the

51 8

appropriate chiral column, eluent and conditions necessary to effect separation of the enantiomeric pair is well within the knowledge of one of ordinary skill in the art. In addition, the enantiomers of compounds of formula I can be resolved by one of ordinary skill in the art using standard techniques well known in the art, such as those described by J. Jacques, et al., "Enantiomers, Racemates, and Resolutions", John Wiley and Sons, Inc., 1981.

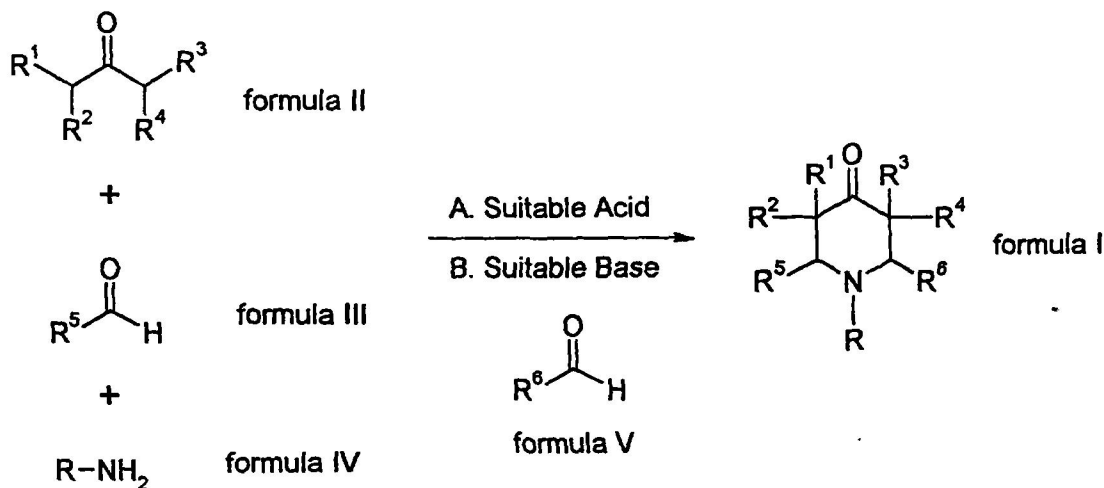
Some of the compounds of the present invention have one or more chiral centers and may exist in a variety of stereoisomeric configurations. As a consequence of these chiral centers, the compounds of the present invention occur as racemates, mixtures of enantiomers and as individual enantiomers, as well as diastereomers and mixtures of diastereomers. All such racemates, enantiomers, and diastereomers are within the scope of the present invention.

The terms "R" and "S" are used herein as commonly used in organic chemistry to denote specific configuration of a chiral center. The term "R" (rectus) refers to that configuration of a chiral center with a clockwise relationship of group priorities (highest to second lowest) when viewed along the bond toward the lowest priority group. The term "S" (sinister) refers to that configuration of a chiral center with a counterclockwise relationship of group priorities (highest to second lowest) when viewed along the bond toward the lowest priority group. The priority of groups is based upon their atomic number (in order of decreasing atomic number). A partial list of priorities and a discussion of stereochemistry is contained in "Nomenclature of Organic Compounds: Principles and Practice", (J.H. Fletcher, et al., eds., 1974) at pages 103-120.

The specific stereoisomers and enantiomers of compounds of formula (I) can be prepared by one of ordinary skill in the art utilizing well known techniques and processes, such as those disclosed by Eliel and Wilen, "Stereochemistry of Organic Compounds", John Wiley & Sons, Inc., 1994, Chapter 7 Separation of Stereoisomers. Resolution. Racemization, and by Collet and Wilen, "Enantiomers, Racemates, and Resolutions", John Wiley & Sons, Inc., 1981. For example, the specific stereoisomers and enantiomers can be prepared by stereospecific syntheses using enantiomerically and geometrically pure, or

enantiomerically or geometrically enriched starting materials. In addition, the specific stereoisomers and enantiomers can be resolved and recovered by techniques such as chromatography on chiral stationary phases, enzymatic resolution or fractional recrystallization of addition salts formed by reagents used
5 for that purpose.

Compounds of formula I can be prepared by following the procedures as set forth in Scheme I. This scheme is not intended to limit the scope of the invention in any way. All substituents, unless otherwise indicated, are previously defined. The reagents and starting materials are readily available to one of
10 ordinary skill in the art.

Scheme I

- 5 In Scheme I, step A, the compound of formula IV is combined with the compound of formula III in a suitable organic solvent, such as ethanol and the mixture is further combined with a compound of formula II in the presence of a suitable acid. Examples of a suitable acid are inorganic or organic Bronsted acids, which include, but are not limited to, hydrochloric acid, sulfuric acid, phosphoric acid, methanesulfonic acid, formic acid, trifluoroacetic acid, acetic acid, chloroacetic acid, and the like.
- 10

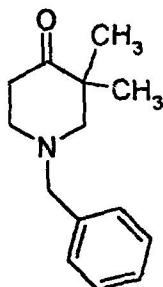
- For example, about 2.25 equivalents of a compound of formula III is combined with a compound of formula IV in ethanol. This solution is slowly added to a solution of about 1.05 equivalents of compound of formula II in ethanol with about 1.0 to 1.2 equivalents of hydrochloric acid at a temperature of from about 50 °C to about 90 °C, preferably at reflux. After 8 hours to about 24 hours, preferably about 18 hours, in Step B, a suitable base is added followed by addition of about 1 equivalent of compound of formula V. Examples of a suitable base are inorganic or organic bases well known in the art, which include but are not limited to, trialkylamines, such as triethylamine, tributylamine, diisopropylethylamine, isopropyldiethylamine, potassium hydroxide, sodium hydroxide, potassium carbonate, sodium carbonate, potassium phosphate tribasic, and the like. Alternatively, when $R^5 = R^6$, all of the aldehyde can be
- 15
- 20

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added in one portion. The reaction is stirred at a temperature of from about 50 °C to about 80 °C, preferably reflux, for about 2 hours to about 16 hours.

The compound of formula I is then isolated and purified using techniques and procedures well known in the art. For example, the reaction mixture is cooled to about 5°C and treated with about one equivalent of base, such as potassium hydroxide dissolved in water. The mixture is then extracted with a suitable organic solvent, such as heptane and MTBE. The organic extracts are then combined, dried over anhydrous magnesium sulfate, filtered and concentrated under vacuum to provide the compound of formula I. The compound of formula I is then purified by recrystallization or flash chromatography on silica gel with a suitable eluent, such as ethyl acetate/hexane to provide purified compound of formula I. Alternatively, the salt of the product can be isolated using standard techniques well known in the art without treating with base.

The following examples represent the process of the present invention as described generally above in Scheme I. These examples are illustrative only and are not intended to limit the invention in any way. The reagents and starting materials are readily available to one of ordinary skill in the art. As used herein, the following terms have the meanings indicated: "eq" or "equiv." refers to equivalents; "g" refers to grams; "mg" refers to milligrams; "L" refers to liters; "mL" refers to milliliters; "μL" refers to microliters; "mol" refers to moles; "mmol" refers to millimoles; "psi" refers to pounds per square inch; "mm Hg" refers to millimeters of mercury; "min" refers to minutes; "h" or "hr" refers to hours; "°C" refers to degrees Celsius; "TLC" refers to thin layer chromatography; "HPLC" refers to high performance liquid chromatography; "R_t" refers to retention factor; "R_t" refers to retention time; "δ" refers to part per million down-field from tetramethylsilane; "THF" refers to tetrahydrofuran; "DMF" refers to N,N-dimethylformamide; "DMSO" refers to methyl sulfoxide; "LDA" refers to lithium diisopropylamide; "aq" refers to aqueous; "EtOAc" refers to ethyl acetate; "iPrOAc" refers to isopropyl acetate; "MeOH" refers to methanol; "MTBE" refers to tert-butyl methyl ether; "TMEDA" refers to N,N,N',N'-tetramethylethylenediamine, and "RT" refers to room temperature.

Example 1Preparation of N-Benzyl-3,3-dimethyl-piperidin-4-one.

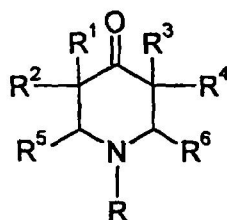
- 5 Scheme I: Benzylamine (214 g, 2 mol) is combined with formaldehyde (37% in water, 375 g, 4.5 mol) in ethanol (1 L) with occasional cooling. This biphasic mixture is added over a period of 90 minutes to a refluxing solution of 2-methyl-3-butanone (182 g, 2.11 mol) in anhydrous ethanol (1L) and hydrochloric acid (209 g of 37% solution, 2.1 mol). The brownish solution is heated at reflux
- 10 for an additional 18 hours. Then triethylamine (310 mL, 223.8 g, 2.21 mol) and formaldehyde (50 g, 36%, 0.6 mol) are added sequentially and the reaction mixture is heated at reflux for 24 hours. The reaction mixture is then cooled to 5°C and treated with potassium hydroxide (117.6 g, 2.1 mol, dissolved in 200 mL of water). The reaction mixture is then extracted with heptane (2 X 500 mL) and
- 15 MTBE (2 X 500 mL). The organic extracts is then combined, dried over anhydrous sodium sulfate, filtered and concentrated under vacuum to provide the title compound, (339.36 g after 18% by volume of the above combined organic extracts was removed prior to concentration). This material was purified by chromatography on silica gel (methylene chloride/ethanol, 100:1) to provide
- 20 purified title compound.
- ¹H NMR (CDCl₃) δ 1.14 (s, 6H), 2.41 (s, 2H), 2.52 (t, 2H), 2.72 (t, 2H), 3.57 (s, 2H), 7.2-7.4 (m, 5H).

Example 2Alternative Preparation of N-Benzyl-3,3-dimethyl-piperidin-4-one.

- In a 1 liter 3-necked flask equipped with mechanical stirring, addition
5 funnel and a calcium chloride drying tube is added a 37% weight solution of
formaldehyde (168.5 mL, 2.25 mole) dissolved in 500 mL of absolute ethanol.
The resulting solution is cooled in an ice-water bath to 10°C, and benzylamine
(109 mL, 1mole) is added dropwise over a one hour period. In a separate 3 liter
3-necked flask equipped with mechanical stirring, addition funnel and two
10 condensers is added 3-methyl-2-butanone (113 mL, 1.06mole) dissolved in
500ml of absolute ethanol and concentrated hydrogen chloride (92 mL,
1.11mole). The resulting solution is brought to reflux and the
formaldehyde/benzylamine solution is added dropwise over a 2 hour period. This
solution is refluxed overnight, and then cooled to ambient temperature.
15 Diisopropylethylamine (142.2 g, 1.1 mole) and formaldehyde (22.46 mL,
0.3mole) are added and the resulting solution is heated to reflux for six hours,
and then cooled to ambient temperature. The solution is quenched with
potassium hydroxide (61.6 g, 1.1 mole) in 200 mL of water, and then extracted
with 500 mL ethyl acetate three times. The organics are concentrated under
20 vacuum to give 225 g of red oil. The crude oil is dissolved in 1 liter of methylene
chloride. This solution is carefully poured over 1 kg of silica gel on a sintered
glass filter. The silica gel is washed with 4 L of methylene chloride. The
methylene chloride is concentrated under vacuum to provide 142 g of a yellow
oil which crystallizes in the freezer overnight. Yield=65.4%.
- 25 While the foregoing specification teaches the principles of the present
invention, with examples provided for the purpose of illustration, it will be
understood by one of the ordinary skill in the art, that the practice of the
invention encompasses all of the usual variations, adaptations, or modifications,
as come within the scope of the following claims and its equivalents.

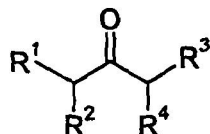
WHAT IS CLAIMED IS:

1. A process for the preparation of a compound of formula I:



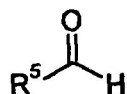
formula I

- 5 wherein R is hydrogen, C₁-C₆ alkyl, halo(C₁-C₆)alkyl, phenyl, benzyl, or phenyl substituted with from 1 to 3 substituents selected from the group consisting of F, Cl, Br, I, C₁-C₆ alkyl, C₁-C₆ alkoxy, halo(C₁-C₆)alkyl, phenyl, NO₂, and CN; R¹, R², R³, R⁴, R⁵ and R⁶ are each independently hydrogen, C₁-C₆ alkyl, halo(C₁-C₆)alkyl, phenyl, or phenyl substituted with from 1 to 3 substituents selected from the group consisting of F, Cl, Br, I, C₁-C₆ alkyl, C₁-C₆ alkoxy, -S(C₁-C₆ alkyl), -S(phenyl), halo(C₁-C₆)alkyl, phenyl, NO₂, and CN, or the pharmaceutically acceptable salt thereof; comprising combining a compound of formula II:



formula II

- 15 wherein R¹, R², R³, and R⁴ are defined as above, a compound of formula III:



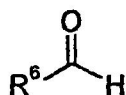
formula III

wherein R⁵ is defined as above, and a compound of formula IV:



wherein R is defined as above, in the presence of a suitable acid;

- 20 followed by addition of a suitable base and a compound of formula V:



formula V

wherein R⁶ is defined as above.

2. The process according to claim 1 wherein the suitable base is diisopropylethylamine.

3. The process according to claim 2 wherein the suitable acid is HCl.

4. The process according to claim 3 wherein R^1 , R^2 , R^3 , R^4 , R^5 and R^6 are each independently hydrogen, C_1 - C_6 alkyl, phenyl or benzyl.

5. The process according to claim 4 wherein R^3 and R^4 are C_1 - C_6 alkyl.

6. The process according to claim 4 wherein R^5 is C_1 - C_6 alkyl and R^6 is hydrogen.

7. The process according to claim 5 wherein R^3 and R^4 are methyl.

8. The process according to 6 wherein R^5 is methyl.

9. The process according to claim 7 wherein R^5 and R^6 are hydrogen.

10. The process according to claim 9 wherein R^1 and R^2 are hydrogen.

11. The process according to claim 10 wherein R is hydrogen.

12. The process according to claim 10 wherein R is benzyl.

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ABSTRACT

The present invention provides a novel process for the preparation of substituted piperidin-4-ones useful as intermediates in the preparation of
5 pharmaceuticals.

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TRADUCCION OFICIAL No. 204

TRADUCCION DE UN DOCUMENTO PRESENTADO SIMULTANEAMENTE EN INGLÉS Y ESPAÑOL. LEGALIZACION TRASPASO DE LA INVENCION DENOMINADA PREPARACION DE PIPERIDIN-4-ONAS SUSTITUIDAS A FAVOR DE ELI LILLY AND COMPANY.

TRASPASO

COLOMBIA

CASO: X-12998

INVENCION: PREPARACION DE PIPERIDIN-4-ONAS SUSTITUIDAS

Firmado: John Robert Rizzo

Firmado: Michael Alexander Staszak

Firmado: Tony Yantao Zhang


ESTADO DE COLOMBIA
INSTRUMENTO DE
REG. INSTRUMENTOS 111

61/6

CERTIFICADO NOTARIAL

ESTADO: Indiana
CONDADO: Marion

El 1º junio de 2000, comparecieron personalmente ante mí **John Robert Rizzo, Michael Alexander Staszak, y Tony Yantao Zhang**, quienes reconocieron que firmaron el documento anterior como un acto voluntario suyo para los propósitos en él establecidos.

Firmado: **Catherine Michel**
NOTARIO PUBLICO

Catherine Michel
Mi comisión expira octubre 21, 2000
Residencia: Condado de Johnson

Sello del Notario Público de Indiana
Sello del Consulado General de Colombia en Chicago

ESTADOS UNIDOS DE AMERICA CERTIFICADO DE OFICIO ESTADO DE INDIANA

Certificación del Secretario de Estado de Indiana **Sue Anne Gilroy** sobre el cargo y las funciones de **Catherine Michel**, como Notario Público del Condado de Johnson, en la fecha de expedición del documento adjunto, expedido el 21 de junio del 2000.

Firmado: **Sue Anne Gilroy**


SUE ANNE GILROY
SECRETARY OF STATE
OFFICE OF THE SECRETARY
OF STATE
INDIANAPOLIS, INDIANA 46204-0001

Secretario de Estado

Firmado: **Mary Reeve**

Delegado

Sello en papel dorado del Estado de Indiana

Sello del Consulado General de Colombia en Chicago

CONSULADO DE COLOMBIA

Chicago, Illinois 60611

No. 2173

CERTIFICA la firma y funciones de la señora **Sue Anne Gilroy** como Secretaria del Estado de Indiana

Fecha: Julio 12, 2000.

Firmado: **VICTORIA EUGENIA CARDENAS GERLEIN**

Cónsul

Hay sello del Consulado de Colombia en Chicago


VICTORIA EUGENIA CARDENAS GERLEIN
Cónsul General de Colombia
en Chicago, Illinois

MINISTERIO DE RELACIONES EXTERIORES

SANTA FE DE BOGOTA

N°303765

CERTIFICA la firma y el cargo del funcionario consular **José Fernando Gómez**, el día 25 de julio, 2000.

(Firma) Ilegible

JEFE DE LEGALIZACIONES
Santafé de Bogotá, D.C.

Kashida

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 [Signature]
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ASSIGNMENT

The undersigned
John Robert Rizzo, Michael Alexander Staszak,
and Tony Yantao Zhang

domiciled in
2037 Glendora Drive, Indianapolis, Indiana 46214,
4515 North Lakeridge Drive, Indianapolis, Indiana 46234, and
12345 Moon River Court, Indianapolis, Indiana 46236
(respectively)

hereby state under oath to be the
sole and true inventor(s) of
**PREPARATION OF SUBSTITUTED
PIPERIDIN-4-ONES**

states as well that he/they
assign, without reservations or
limitation, in favor of

ELI LILLY AND COMPANY

a corporation organized and
existing under the laws of the
State of Indiana, United States
of America

domiciled in Lilly Corporate Center
Indianapolis, Indiana 46285
United States of America

All rights inherent to said
invention, and that the above
mentioned corporation hereby to
apply, in its name, for the cor-
responding patent in the Republic
of Colombia.



John Robert Rizzo



Michael Alexander Staszak



Tony Yantao Zhang

TRASPASO

abajo firmado

John Robert Rizzo, Michael Alexander
Staszak, y Tony Yantao Zhang

domiciliado en
2037 Glendora Drive, Indianapolis, Indiana 46214,
4515 North Lakeridge Drive, Indianapolis, Indiana
46234, y 12345 Moon River Court, Indianapolis
Indiana 46236
(respectivamente)

decia bajo juramnto ser único
y verdadero inventor de
PREPARACION DE PIPERIDIN-4-ONAS SUSTITUIDAS

Declaramos asimismo que cedemos
y transf sin reserva ni limitacion,
a favor de la sociedad

ELI LILLY AND COMPANY

organizada y existente de
conformidad con las leyes del
Estado de Indiana, Estados Unidos
América

domiciliada en Lilly Corporate Center
Indianapolis, Indiana 46285
Estados Unidos de América

todos los derechos inherentes a
dicha invención y que la citada
sociedad queda facultada para
solicitar en su nombre la patente
correspondiente en la República de
Colombia.



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UNITED STATES OF AMERICA
CERTIFICATE OF OFFICE
STATE OF INDIANA

I, Sue Anne Gilroy, Secretary of State of Indiana, DO HEREBY CERTIFY: That,
according to records on file in my office, Catherine Michel was duly elected or
annointed to the office of Notary Public in and for County of Johnson and that the



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Consulado General de Colombia

500 NORTH MICHIGAN AVENUE, SUITE 2040
CHICAGO, ILLINOIS 60611

TEL.(312)923-1196 FAX(312)923-1197

No. 2173

Chicago,

JUL 1 2000

La suscrita Cónsul de Colombia, CERTIFICA que el señor Sue Anne Gilroy quien autoriza el presente documento, ejercía legalmente, en la fecha allí expresada, las funciones de Secretario de Estado de Indiana, y que la firma y sello que en el documento aparecen como suyos son los que usa y acostumbra en sus actos oficiales.

La Cónsul no asume responsabilidad alguna por el contenido de documento.

PAGADO IMPUESTO DE TIMBRE DERECHOS CONSULARES
(VEINTIDOS DOLARES US\$22.00)

Victoria Eugenia Cardenas
VICTORIA EUGENIA CARDENAS GERLEIN
Cónsul



MINISTERIO DE RELACIONES
EXTERIORES
303765
C. Cardenas
FIRMA APTA EN EL
DOCUMENTO DE PENA
LAS FUNCIONES INDICADAS

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