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PROCESO MEJORADO PARA HIDROXIZAPIRONAS

51. CLASIFICACION INTERNACIONAL

A61K31/495; A61K31/50

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BRISTOL - MYERS SQUIBB COMPANY

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PRINCETON, NEW JERSEY, ESTADOS UNIDOS DE AMERICA

74. APODERADO

HECTOR GOMEZ MEJIA

22. SANTAFE DE BOGOTA, D.C.

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1

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☒ Patente de Invención.☐ Patente de Modelo de Utilidad.☐ Capítulo I.☒ Capítulo II.

2

SOLICITANTE
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Nombre: BRISTOL - MYERS SQUIBB COMPANY

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Estados Unidos de América

Nacionalidad o Domicilio: Estados Unidos

Lugar de Constitución: Estados Unidos

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3

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08536, US; 315 North Cherrywood Drive, Lafayette, CO 80026, Estados Unidos de América
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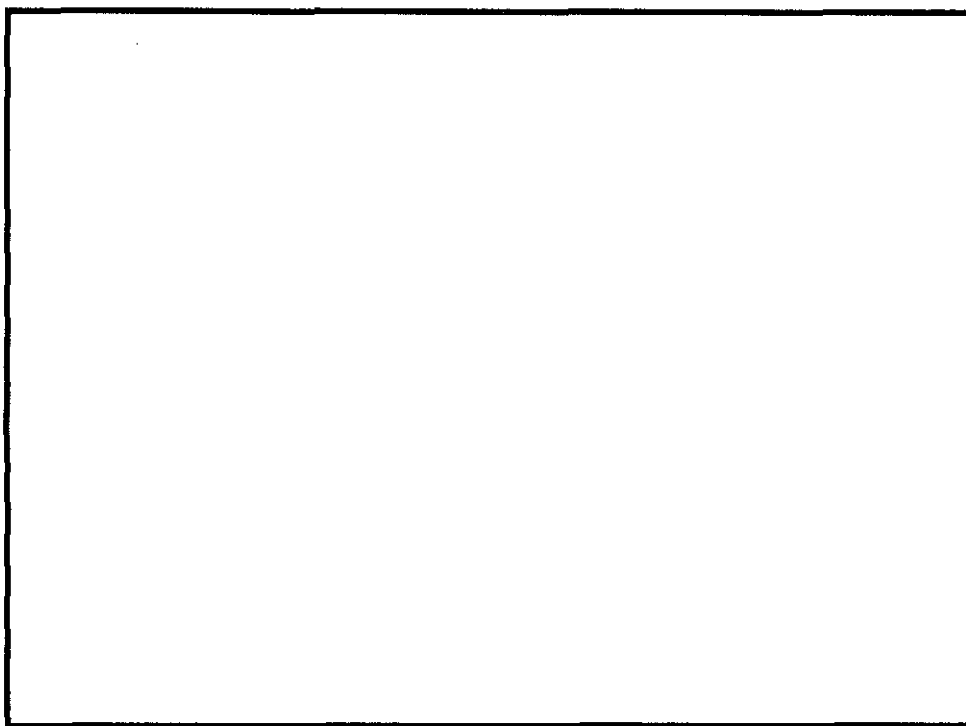
Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página.

10

ANEXOS

- ☒ Comprobante de pago de la tasa de presentación de la solicitud. \$443.000
- ☐ Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- ☒ Poderes, si fuere el caso. **Fotocopia autenticada**
- ☒ Documento de cesión del inventor al solicitante o a su causante.
- ☐ Declaraciones
- ☒ Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Copia del examen preliminar efectuado por la IPEA.
- ☒ Traducción del examen preliminar efectuado por la IPEA.
- ☐ De ser el caso, copia del contrato de acceso.
- ☐ De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- ☐ De ser el caso, certificado de depósito del material biológico.
- ☐ Arte final 12x12.
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- ☒ Otros - Tarjeta de Propietarios

11 FIGURA CARACTERÍSTICA:



12 Solicito la concesión de la patente.

NOMBRE: HECTOR GOMEZ MEJIA

FIRMA: *Hector Gomez Mejia*

C.C. 22720 de Bogotá T.P. 19486 del C.S.J.

Instrucciones para la presentación de los anexos, ver reverso de esta página.

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***** C O N C E P T O *****

CANT. RENTISTICO	CONCEPTO	TOTAL CONCEPTO
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	TOTAL :	\$ 443,000.00

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(74) Agents: EPPERSON, James et al.; Bristol-Myers Squibb
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(54) Title: IMPROVED PROCESS FOR HYDROXYAZAPIRONES

(57) Abstract: This invention describes a process for preparing hydroxyazapirones of Formula (I) from azapirones of Formula (II). The process comprises treating azapirones with a strong base, monitoring enolate formation of the azapirone by IR spectroscopy, and reacting the enolate with a source of molecular oxygen in the presence of a reductant. The process is suitable for large scale production of hydroxyazapirones.

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INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 31/495, 31/50, 31/00

US CL : 514/252.18, 629

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)

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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)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01/45687 A2 (FABRE/KRAMER PHARMACEUTICALS, INC.) 28 June 2001 (28.06.2001), see full text, especially page 11.	1-22
X	WO 02/16347 A1 (AKZO NOBEL N.V.) 28 February 2002 (28.02.2002), see full text, especially pages 6-7.	1-22
X, P	US 6,593,331 B2 (CAMBORDE et al) 15 July 2003 (15.07.2003), see full text, especially column 5-6.	1-22

☐ 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

"B" earlier application or patent 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)

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"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 considered with one or more other such documents, such combination being obvious to a person skilled in the art

"A" document member of the same patent family

Date of the actual completion of the international search

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46

Continuation of B. FIELDS SEARCHED Item 3:
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- (51) International Patent Classification⁷: A61K (74) Agents: EPPERSON, James et al.; Bristol-Myers Squibb Company, P.O. Box 4000, Princeton, NJ 08543-4000 (US).
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- (71) Applicant (*for all designated States except US*): BRISTOL-MYERS SQUIBB COMPANY [US/US]; P. O. Box 4000, Route 206 and Provinceline Road, Princeton, NJ 08543-4000 (US).
- (72) Inventors; and
- (75) Inventors/Applicants (*for US only*): DEPUE, Jeffrey [US/US]; 6 John Hancock Avenue, Hillsborough, NJ 08844 (US). KOTNIS, Atul, S. [IN/US]; 16 Oxford Court, Kendall Park, NJ 08824 (US). LEUNG, Simon [CN/US]; 238 Vasser Drive, Piscataway, NJ 08854 (US). DOWDY, Eric, D. [US/US]; 25-01 Ravens Crest Drive, Plainsboro, NJ 08536 (US). WATSON, Daniel, J. [GB/US]; 105 Olympic Court #9, Princeton, NJ 08540 (US).
- Published:
— *without international search report and to be republished upon receipt of that report*
- 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: IMPROVED PROCESS FOR HYDROXYAZAPIRONES

(57) Abstract: This invention describes a process for preparing hydroxyazapirones of Formula I from azapirones of Formula II. The process comprises treating azapirones with a strong base, monitoring enolate formation of the azapirone by IR spectroscopy, and reacting the enolate with a source of molecular oxygen in the presence of a reductant. The process is suitable for large scale production of hydroxyazapirones.

WO 2004/014309 A2

IMPROVED PROCESS FOR HYDROXYAZAPIRONES

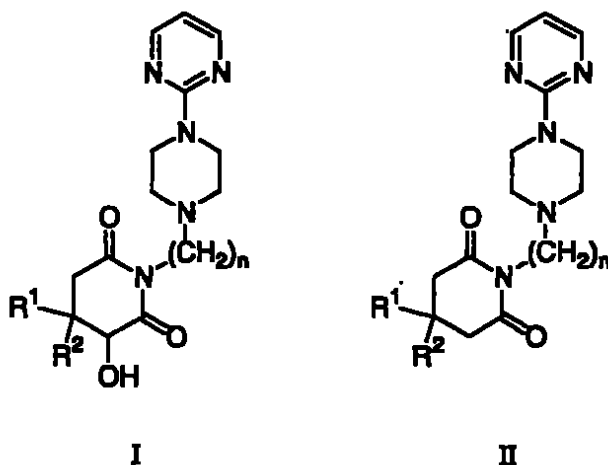
BACKGROUND OF THE INVENTION

5 Certain azapirones, such as the compounds of Formula II, have been shown to have therapeutic potential when hydroxylated to form hydroxyazapirones of Formula I. Two examples of hydroxyazapirones are 6-hydroxybuspirone (R^1 and R^2 are 1,4-butandiyl and n is 4) and 3-hydroxygepirone (R^1 and R^2 are methyl and n is 4). Initially discovered as metabolites (see Mayol et al. *Clin. Pharmacol. Ther.* 1985

10 37, 210 and Kerns et al. *J. Pharmaceut and Biomedical Analysis* 1999 20, 115-128), these compounds are now believed to be biologically active and their use in treating anxiety disorders and depression has been disclosed (Mayol, R. F. U.S. patent 6,150,365, 2000; Rider, P.H. PCT appl. WO 02/16347, 2002). As these compounds

show promise in therapy, improved methods for their production would be of benefit.

15

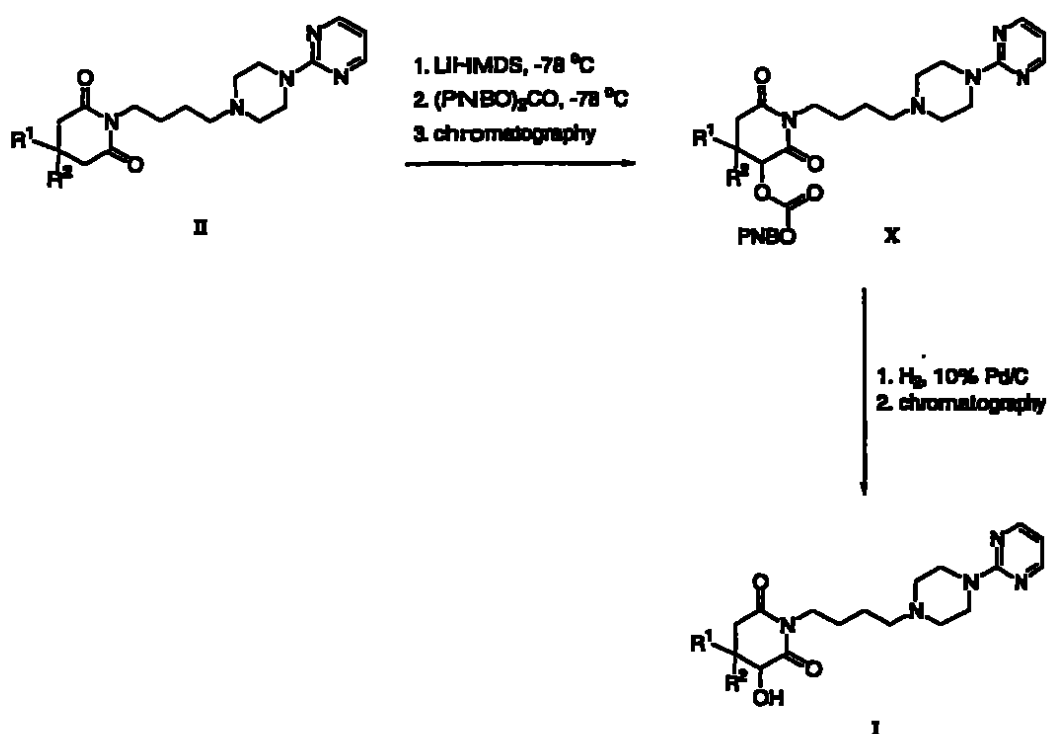


Processes which selectively hydroxylate Formula II azapirones into Formula I hydroxyazapirones have been disclosed (Mayol, R. F. U.S. patent 6,150,365, 2000;

20 Rider, P.H. PCT appl. WO 02/16347, 2002). One process for hydroxylating both buspirone and gepirone is illustrated in Scheme 1. In this process, the imide enolate derived from imide II was generated and trapped by di-4-nitrobenzyl peroxydicarbonate [(PNBOCO)₂] to produce intermediate X. After chromatographic purification, hydrogenation of intermediate X afforded the Formula I compound.

25

Scheme 1.

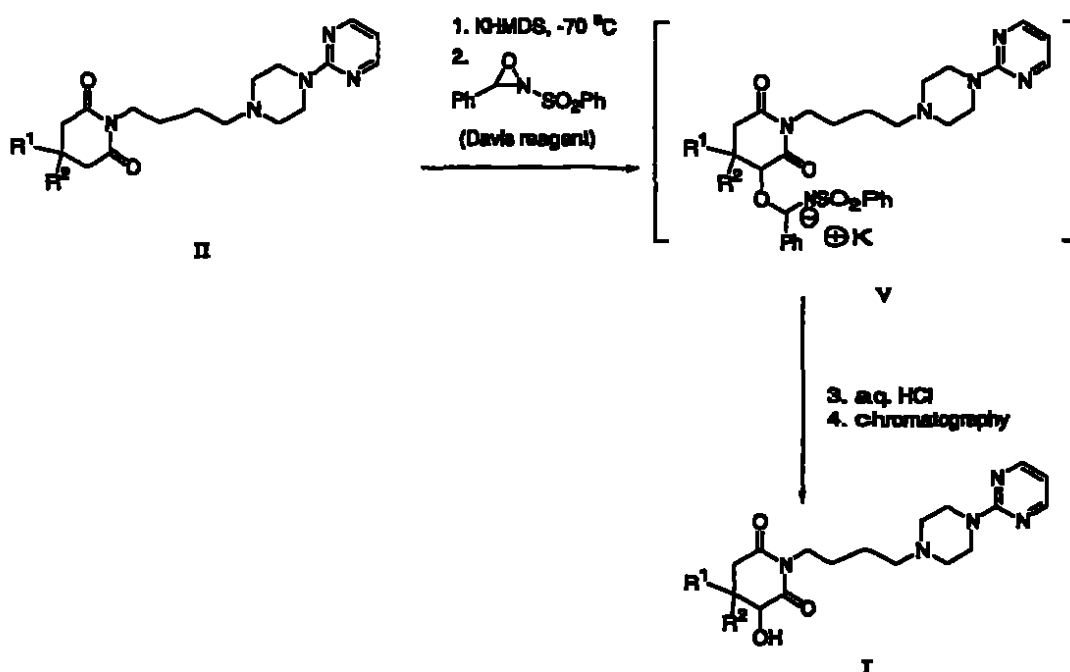


A second process, shown in scheme 2, was employed for buspirone hydroxylation.

5 In this process, the imide enolate derived from II was reacted with 2-(phenylsulfonyl)-3-phenyloxaziridine (the Davis reagent) to form the postulated intermediate V. Acidic workup provided the Formula I product.

10 Drawbacks of both these processes include the requirement to synthesize the starting reagents and the necessity of chromatographically purifying the products.

Scheme 2.



A third process involving enzymatic conversion in certain mammalian liver
5 microsomes was not amenable to large-scale synthesis.

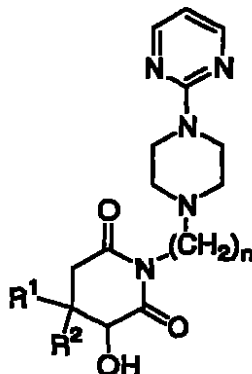
By contrast, the invention disclosed below improves upon these processes by
employing a one step procedure using commercially available reagents and air. The
process also provides direct crystallization of the product rather than
10 chromatographic purification.

SUMMARY OF THE INVENTION

This invention describes an improved one-pot process for hydroxylation of certain
15 useful azapirone psychotropic agents, such as buspirone and gepirone. The process
uses commercially available reagents and air. The pure product is crystallized directly
from the reaction mixture, and the process is amenable to large-scale synthesis.

✓
11**DETAILED DESCRIPTION OF THE INVENTION**

The invention provides a process for the preparation of hydroxyazapirones of Formula I,

**I**

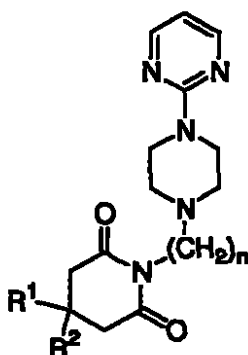
wherein

R^1 and R^2 are independently hydrogen or C_{1-6} alkyl, or where

R^1 and R^2 taken together are $-CH_2(CH_2)_{0-5}CH_2-$, and

n is an integer from 2 to 5,

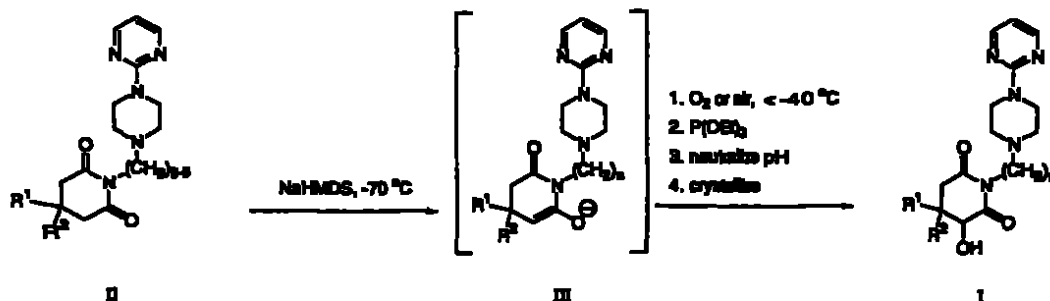
from azapirones of Formula II.

**II**

The process is shown in scheme 3. Briefly, a Formula II azapirone compound is dissolved in an appropriate solvent containing 1-5 equivalents of a suitable reductant. A strong base is added, generating an imide enolate of Formula III. A source of oxygen is added until the generation of Formula I compound is complete. In the

course of the experimental workup, the product is crystallized and isolated. This process is described in detail below.

Scheme 3.



A Formula II compound is dissolved in a suitable aprotic solvent to a preferred ratio of 10-20 mL/g. Suitable solvents for enolate generation include ethereal solvents such as diethylether, 1,2-dimethoxyethane, dioxane, and 2-methyltetrahydrofuran.

10 Tetrahydrofuran (THF) is a preferred solvent for this reaction. A suitable reductant in the range of 1-5 equivalents is added to the solution. Suitable reductants are those that reduce organic hydroperoxides to alcohols. These reductants include tri(C₁₋₈)alkylphosphites as well as other reductants such as triarylphosphites, triaryl- and trialkyl phosphines, thiourea, sodium borohydride, copper (II) chloride with iron
15 (II) sulfate, iron (III) chloride, titanium isopropoxide, dimethyl sulfide, diethyldisulfide, sodium sulfite, sodium thiosulfate, zinc and acetic acid, and 1-propene. While the reductant may be added at any convenient stage of the process, it is preferably present when the oxygenation reaction proceeds. The solution is cooled to -40 to -100 °C, preferably to a range of -68 to -75 °C, and allowed to
20 completely stabilize.

About one equivalent of an appropriate strong base is added. The base mediates deprotonation and formation of an imide enolate anion (III). Preferred bases suitable for this type of deprotonation include disilazanes, such as lithium bis(trimethylsilyl)amide, sodium bis(trimethylsilyl)amide, and potassium bis(trimethylsilyl)amide. Other strong bases which may be used include dialkylamide bases (such as lithium diisopropylamide), metal hydrides, and metal alkoxides.

X 13

Generation of a stoichiometric amount of enolate is critical for optimizing the process—undergeneration of enolate resulted in poor conversion and recovered starting material, while overaddition of base resulted in the production of dihydroxylated side products. The use of reaction monitoring, in particular employing FTIR, to directly observe conversion of the starting imide to the corresponding enolate solved this issue. Direct observation of anion generation allowed the base to be charged until the IR signal for starting material no longer declined, indicating complete consumption of the starting material. Starting material was then incrementally charged until a steady IR signal of starting material was observed, indicating no excess base was present. This provided a solution of enolate with a slight excess of starting material (1% to 3%). Because excess starting material was easier to purge than dihydroxylated side products (the impurities that resulted when excess base was present), this was the preferred situation. Variations in the base titer, water content, and phosphite quality were automatically corrected because the phosphite was charged before the base.

In general, the enolate compound of Formula III was formed *in situ* and reacted immediately with an electrophile. However, the invention includes stable enol compounds which can later be reactivated. For example, enol acetates and enolsilanes are suitable substrates for the process.

After enolate generation, air or oxygen was sparged into the reaction mixture, controlling the initial rate of sparging to maintain the temperature of the reaction mixture less than -40 °C. The sparging was continued until the reaction was complete as indicated by HPLC. Although air and oxygen gas are preferred sources of molecular oxygen, other oxygen sources can be used including gaseous mixtures containing molecular oxygen, liquid oxygen, and solutions containing liquid oxygen.

The mixture was diluted with a suitable solvent such as methyl *tert*-butylether (MTBE), ethyl acetate, or 2-methyl-THF, warmed to room temperature, and neutralized with 1M hydrochloric acid until the pH was 6.0 to 7.0, preferably 6.5 to 6.9. Other acids can be used and the final pH can also be adjusted with various bases including sodium phosphate. The reaction mixture was then partitioned, and the

organic layer separated. The organic solvents were replaced by isopropanol, and the solution was cooled to crystallize the product. The product was normally isolated in 64-90% with greater than 95% purity.

- 5 Occasionally the reaction product contained recovered starting material or a 6,10-dihydroxylated side product. In these cases, one of two crystallization procedures improved the purity. These procedures are described in the Specific Embodiments section.

10 **DESCRIPTION OF THE SPECIFIC EMBODIMENTS**

EXAMPLE 1

6-Hydroxybuspirone

- 15 Buspirone (8-[4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl]-8-azaspiro(4.5)-decane-7,9-dione) (246.5 g, 639.6 mmol) was charged to a 12 L flask equipped with a mechanical stirrer and a React-IR probe under inert gas. Tetrahydrofuran (4.383 kg, 60.8 mol, 4.930 L, 20 mL/g) was charged and the mixture agitated at ambient temperature until homogeneous. Triethyl phosphite (371.9 g, 2.238 mol, 383.8 mL, 20 3.5 eq) was added and the mixture was cooled to -68 to -75 °C. The mixture was agitated at this temperature for at least 10 minutes to allow the React-IR signal to stabilize. 1.0 M Sodium bis(trimethylsilyl)amide in THF (600.4 g, 664.1 mmol, 664.1 mL, 1.00 eq) was charged to the mixture at such a rate so as to maintain the temperature less than -60 °C. Small amounts of sodium bis(trimethylsilyl)amide 25 were charged to the mixture until the IR signal for buspirone reached a minimum indicating complete deprotonation of buspirone. Additional buspirone in THF (10-20 mL/g) was then charged to the reaction mixture in small increments until the IR signal indicated a 0.5 % to 5 % excess of buspirone. Air was sparged into the reaction mixture, controlling the initial rate of sparging so as to maintain the temperature of 30 the reaction mixture less than -60 °C. The sparging was continued until the reaction was complete as indicated by HPLC. Methyl *tert*-butyl ether (384.8 g, 4.365 mol, 520.0 mL) was added followed by 1M hydrochloric acid (1350.8 g, 1.328 mmol,

1615

1328 mL) and the solution was warmed to ambient temperature. The pH was adjusted to between 6.5 and 6.9 using hydrochloric acid and Na_3PO_4 . The phases were separated and the organic phase was washed twice with brine (542.3 g, 493 mL). The solvent of the rich organic layer was then replaced by isopropyl alcohol and the solution was cooled to crystallize the reaction product. There is an option to seed with 0.01 to 5 % buspirone at approximately 54 to 56 °C. The crystalline slurry was then filtered and the wet cake was washed with isopropyl alcohol and dried to provide 6-hydroxybuspirone (220.0 g, 82%), mp 109.5 °C.

Alternatively the product can be crystallized by either of these two methods: (a) concentration and solvent replacement into heptane or hexanes, or (b) solvent replacement into EtOAc and crystallization by the combination of cooling and addition of heptane or hexanes.

EXAMPLE 2

Crystallization of 6-hydroxybuspirone to reduce 6,10-dihydroxybuspirone and buspirone.

6-hydroxybuspirone (35.0 g, 90.8 mmol) was slurried with anisole (385 mL, 1.1 mL/g, 10-15 mL/g may be used). The mixture was heated to 80-100 °C and stirred to obtain a clear solution. The solution was then cooled to 75-85 °C before 6,10-dihydroxybuspirone seeds (87.5 mg, 0.25 wt%, 0-2 wt% may be used) were added. The mixture was then cooled to ambient temperature over 2-6 h and stirred overnight. The resulting slurry was filtered and the filtrate was concentrated to approximately half its initial volume. Heptane (400 mL) was then added over 1 h and the resulting slurry was stirred at ambient temperature overnight. The slurry was filtered and the resulting filter cake was washed with heptane. After drying, 23.04 g of 6-hydroxybuspirone was obtained (66% recovery). In some experiments, this recrystallization reduced 6,10-dihydroxybuspirone from ~9% to ~1.5%.

EXAMPLE 3

Crystallization of 6-hydroxybuspirone to reduce buspirone.

16
X

6-hydroxybuspirone (220.0 g, 547.9 mmol) was slurried with absolute ethyl alcohol or isopropyl alcohol (2.20 L, 10 mL/g, 10-20 mL/g may be used) in a 3-necked round bottom flask equipped with a mechanical stirrer. The mixture was heated from ambient temperature to form a solution (55-70 °C). The resulting solution was then cooled to form a slurry. The solid was filtered, washed, and dried to provide purified 6-hydroxybuspirone (165.0 g, 75% recovery). In some experiments, this recrystallization reduced buspirone from ~3% to ~1.4%.

10

EXAMPLE 4**Alternate protocol for 6-hydroxybuspirone**

Buspirone (350.0 g, 0.908 mol) was dissolved in THF (6.9 L) in a 10 L vessel under argon. The mixture was cooled to -70 °C using a dry ice/IPA bath. A THF solution of NaHMDS (0.908 mol, 1.00 equiv [0.762 mol titrated to be 0.953 M and 0.146 mol titrated to be 0.91 M]) was added over 12 min while maintaining the temperature below -40 °C. Triethylphosphite (3.18 mol, 3.5 equiv) was added in one portion over approximately one min. The solution was stirred at -60 °C for approximately 45 min. The solution was then cooled to -70 °C. Oxygen (ultra high purity [UHP]) was bubbled into the reaction mixture using a gas dispersion tube. (Note: the bubbler and a Nitrogen inlet were configured so that nitrogen passed through the vessel during the entire reaction). An exotherm of approximately 5 °C was observed and the rate of oxygen sparging was controlled so as to maintain the temperature below -64.6 °C. The reaction was monitored using HPLC by taking aliquots of the reaction mixture and quenching into the organic mobile phase. When the AP of the starting material no longer declined (AP approximately 2), the reaction was quenched with HCl (6 M, 0.5 L, the pH was measured to be approximately 3 at approximately -10 °C) and allowed to warm to room temperature overnight. The pH was adjusted to approximately 2.0 by the addition of NaOH (2 N, 40 mL) and the solution was observed to be cloudy and somewhat heterogeneous. HPLC analysis indicated 6-hydroxybuspirone (92.6 AP) and buspirone (1.27 AP). The mixture was transferred to a 22 L, jacketed 3-neck flask equipped with mechanical stirrer, gas

7/2

adapter, reflux condenser, and thermocouple. Water was added (650 mL) and the mixture was heated. At approximately 35 °C, the mixture became homogeneous. (Note: alternatively one can add 2.5 M HCl instead of 6 M HCl and water to adjust the pH to 2.0). The mixture was then warmed to approximately 58 °C for a total of approximately 30 h and held at ambient temperature for approximately 124 h. During the heating, samples were periodically taken for ³¹P NMR and HPLC analysis (monitoring for extent of hydrolysis of diethylphosphite to HP(O)(OH)(OEt) and HPLC analysis of 6-hydroxybuspirone).

The solution was then neutralized to a pH of 6.84 by the slow addition (25 min) of a NaOH/saturated brine solution (3.5 N, 1.0 L [700 mL of 10.0 N NaOH and saturated brine added until the volume reached 2.0 L]). MTBE (650 mL) and saturated brine (500 mL) were added in order to assist the phase split. The aqueous layer (2900 mL) was removed and saved for analysis and a sample of the organic layer was saved for analysis as well. To the organic layer was added saturated brine (650 mL) and MTBE (150 mL) and the phases were allowed to separate. The second aqueous layer was removed (800 mL) and saved for analysis. Samples of the phases were analyzed via ³¹P NMR (monitoring for diethylphosphite content) and HPLC (monitoring the amount of 6-hydroxybuspirone within a given phase).

A 4 L cylindrical, glass reactor equipped with mechanical stirrer, condenser, and thermocouples (for both batch and distillate temperature) was charged with 3800 mL of the solution. Distillation was conducted under reduced pressure (the pressure ranged from -19.5 to -20 in Hg) until the volume was approximately 500 mL. The remaining product-rich organic phase was added and distillation resumed, reducing the volume to approximately 1000 mL. IPA was added (2000 mL) and distillation at reduced pressure was resumed until the volume was reduced to approximately 1000 mL. An additional 1000 mL of IPA was added bringing the volume to approximately 2000 mL (no THF was detectable via GC and the water content was measured to be 0.13%). The mixture was heated to 75 °C to dissolve all solids and then subdivided into two batches detailed in A and B below.

15/8

Batch A. Approximately 1000 mL was transferred to a vessel equipped with a magnetic stirrer and water was added (15 mL, Karl Fischer titration indicated 3.94% water). This solution was then slowly cooled to ambient temperature while stirring, and seeded with 6-hydroxybuspirone (approximately 20 mg). The mixture was
5 filtered seven days later on a 4-6 micron glass sintered filter and the mother liquor saved for analysis (740 mL). The off-white solid was subsequently washed with IPA (2 x 260 mL). The white solid was suctioned dried for 1 h and then placed into a an oven at 45 °C (27 in Hg with an N₂ bleed for 69 h). 6-Hydroxybuspirone was
10 obtained as an off-white solid (166.0 g, purity = 99 AP, buspirone AP = 0.35, and a trans-diol side product AP = 0.54).

Batch B. The remainder of the solution (water content 0.13%) was allowed to cool to ambient temperature and seeded with 6-hydroxybuspirone (20 mg) at approximately 56 °C. The mixture was filtered seven days later on a 4-6 micron glass
15 sintered filter and the reactor rinsed (four times with the mother liquor in order to recover all solids). The mother liquor was saved for analysis (620 mL). The off-white solid was subsequently washed with IPA (2 x 260 mL). The white solid was suctioned dried for 1 h and then placed into a an oven at 45 °C (27 in Hg with an N₂ bleed for 69 hours). 6-Hydroxybuspirone was obtained as an off-white solid
20 (156.6 g, AP = 99, buspirone AP = 0.35, and a trans-diol side product AP = 0.54).

EXAMPLE 5

3-Hydroxygepirone

25 Gepirone (4,4-dimethyl-1-[4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl]-2,6-piperidinedione) (10.0 g, 27.8 mmol) was charged to a 500 mL flask equipped with a mechanical stirrer and a React-IR probe under inert gas. Tetrahydrofuran (250 mL, 25 mL/g) was charged and the mixture agitated at ambient temperature until homogeneous. Triethyl phosphite (28.9 g, 174 mmol, 29.8 mL, 6.25 eq) was added
30 and the mixture was cooled to -65 to -80 °C. The mixture was agitated at this temperature for at least 10 minutes to allow the React-IR signal to stabilize. 1.0 M Sodium bis(trimethylsilyl)amide in THF (27.8 mL, 27.8 mmol, 1.00 eq) was charged

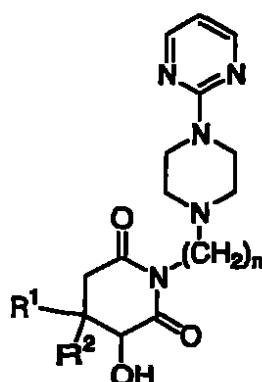
B19

to the mixture at such a rate so as to maintain the temperature less than -60°C . Small amounts of sodium bis(trimethylsilyl)amide were charged to the mixture until the IR signal for buspirone reached a minimum indicating complete deprotonation of gepirone. Additional gepirone in THF (25 mL/g) was then charged to the reaction mixture in small increments until the IR signal indicated a 3.24 % excess of gepirone. Air was sparged into the reaction mixture, controlling the initial rate of sparging so as to maintain the temperature of the reaction mixture less than -60°C . The sparging was continued until the reaction was complete as indicated by HPLC. Methyl *tert*-butyl ether (40.0 mL) was added followed by 1M hydrochloric acid (45.0 mL) and the solution was warmed to ambient temperature. The pH (9.48 at 20.6°C) was adjusted to between 6.5 and 6.9 using hydrochloric acid and Na_3PO_4 (pH = 6.95 at 22.7°C). The phases were separated and the organic phase was washed twice with 25 wt % brine (40.0 mL). The solvent of the rich organic layer was then replaced by isopropyl alcohol and the solution was cooled to ambient temperature to crystallize the reaction product. The crystalline slurry was then filtered and the wet cake was washed twice with isopropyl alcohol (15.0 mL) and dried to provide 3-hydroxygepirone (9.32 g, 89%), mp 128°C .


CLAIMS

We claim:

1. A process for preparing hydroxyazapirones of Formula I,



I

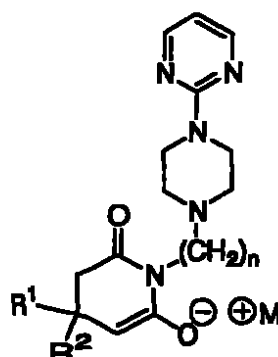
5 wherein

R^1 and R^2 are independently hydrogen, C_{1-6} alkyl, or

R^1 and R^2 taken together are $-CH_2(CH_2)_{0-5}CH_2-$, and

n is an integer from 2 to 5,

comprising reacting a compound of Formula III



III

10

wherein $M^{\oplus}$ is an alkali or alkaline earth metal cation

with molecular oxygen in the presence of a reductant to provide a Formula I product.

15

2. The process of claim 1 wherein the source of molecular oxygen is air or oxygen gas.

3. The process of claim 1 wherein the reductant is selected from the group consisting of triarylphosphites, trialkyl- and triaryl phosphines, thiourea, sodium

borohydride, copper (II) chloride with iron (II) sulfate, iron (III) chloride, titanium isopropoxide, dimethyl sulfide, diethyldisulfide, sodium sulfite, sodium thiosulfate, zinc and acetic acid, and 1-propene.

4. The process of claim 1 wherein the reductant is tri(C₁₋₃)alkylphosphite.

5. The process of claim 4 wherein the reductant is triethyl phosphite.

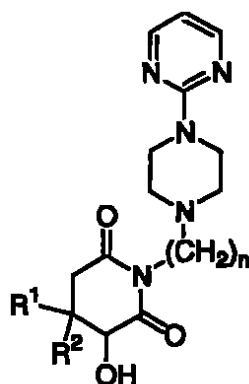
6. The process of claim 1 where R¹ and R² are independently selected from hydrogen and C₁₋₆alkyl.

7. The process of claim 6 where R¹ and R² are methyl and n is 4.

8. The process of claim 1 where R¹ and R² taken together are -CH₂(CH₂)₀₋₅CH₂-.

9. The process of claim 8 where R¹ and R² taken together are -CH₂CH₂CH₂CH₂- and n is 4.

10. A process for preparing hydroxyazapirones of Formula I,



I

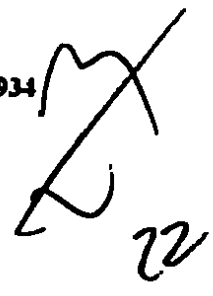
wherein

R¹ and R² are independently hydrogen, C₁₋₆alkyl, or where

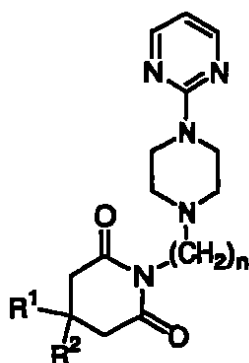
R¹ and R² taken together are -CH₂(CH₂)₀₋₅CH₂-, and

n is an integer from 2 to 5,

comprising

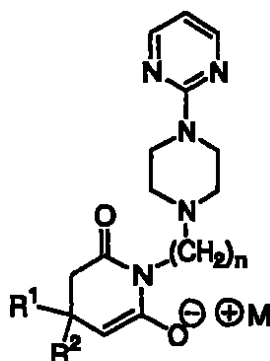


(a) reacting an azapirone compound of Formula II



II

with a strong base to form an intermediate imide enolate anion of Formula III



III

5

(b) reacting the imide enolate III with molecular oxygen in the presence of a reductant.

11. The process of claim 10 wherein the source of molecular oxygen is air or oxygen gas.

12. The process of claim 10 wherein the strong base is selected from the group consisting of lithium bis(trimethylsilyl)amide, sodium bis(trimethylsilyl)amide, potassium bis(trimethylsilyl)amide, lithium dialkylamide, sodium dialkylamide, potassium dialkylamide, sodamide, lithium alkoxide, sodium alkoxide, potassium alkoxide, lithium hydride, sodium hydride, and potassium hydride.

13. The process of claim 12 wherein the base is sodium bis(trimethylsilyl)amide.

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14. The process of claim 10 wherein the imide enolate anion III formation is maximized by the use of spectroscopy to monitor conversion of II to III.

5 15. The process of claim 14 wherein IR spectroscopy is used to monitor conversion of II to III.

10 16. The process of claim 10 wherein the reductant is selected from the group consisting of triarylphosphites, trialkyl- and triaryl phosphines, thiourea, sodium borohydride, copper (II) chloride with iron (II) sulfate, iron (III) chloride, titanium isopropoxide, dimethyl sulfide, diethyldisulfide, sodium sulfite, sodium thiosulfate, zinc and acetic acid, and 1-propene.

15 17. The process of claim 10 wherein the reductant is tri(C₁₋₈)alkylphosphite.

18. The process of claim 17 wherein the reductant is triethyl phosphite.

20 19. The process of claim 1 where R¹ and R² are independently selected from hydrogen and C₁₋₆alkyl.

20. The process of claim 19 where R¹ and R² are methyl and n is 4.

25 21. The process of claim 10 where R¹ and R² taken together are -CH₂(CH₂)₀₋₅CH₂-.

22. The process of claim 21 where R¹ and R² taken together are -CH₂CH₂CH₂CH₂- and n is 4.

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(54) Título: PROCESO MEJORADO PARA HIDROXIAZAPIRONAS

(57) Resumen: La presente invención se refiere a un proceso para preparar hidroxiazapironas de Fórmula I, a partir de azapironas de Fórmula II. El proceso comprende tratar azapironas con una base fuerte, monitorear la formación de enolato de la azapirona por espectroscopía de IR, y hacer reaccionar el enolato con una fuente de oxígeno molecular en la presencia de un agente reductor. El proceso es adecuado para producción a gran escala de hidroxiazapironas

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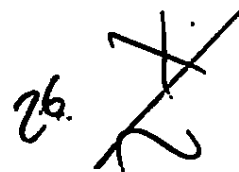
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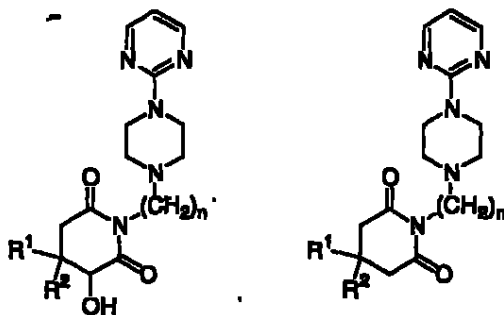
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(57) Resumen: La presente invención se refiere a un proceso para preparar hidroxiazapironas de Fórmula I, a partir de azapironas de Fórmula II. El proceso comprende tratar azapironas con una base fuerte, monitorear la formación de enolato de la azapirona por espectroscopía de IR, y hacer reaccionar el enolato con una fuente de oxígeno molecular en la presencia de un agente reductor. El proceso es adecuado para producción a gran escala de hidroxiazapironas

26. **PROCESO MEJORADO PARA HIDROXIAZAPIRONAS****ANTECEDENTES DE LA INVENCION**

Ciertas azapironas, tales como los compuestos de
5 Fórmula II, han sido mostradas por tener potencial
terapéutico cuando son hidroxiladas para formar
hidroxiazapironas de Fórmula I. Dos ejemplos de
hidroxiazapironas son 6-hidroxibuspirona (R^1 y R^2 son 1,4-
butandiilo y n es 4) y 3-hidroxigepirona (R^1 y R^2 son metilo y
10 n es 4). Inicialmente descubiertos como metabolitos (véase
Mayol et al. *Clin. Pharmacol. Ther.* 1985 37, 210 y Kerns et
al. *J. Pharmaceut and Biomedical Analysis* 1999 20, 115-128),
estos compuestos se cree ahora que son biológicamente activos
y se ha descrito su uso en trastornos de ansiedad y depresión
15 (Mayol, R.F., Patente estadounidense 6,150,365, 2000; Rider,
P.H. Solicitud PCT WO 02/16347, 2002). Como estos compuestos
muestran promesa en terapia, podrían ser de beneficio,
métodos mejorados para su producción.

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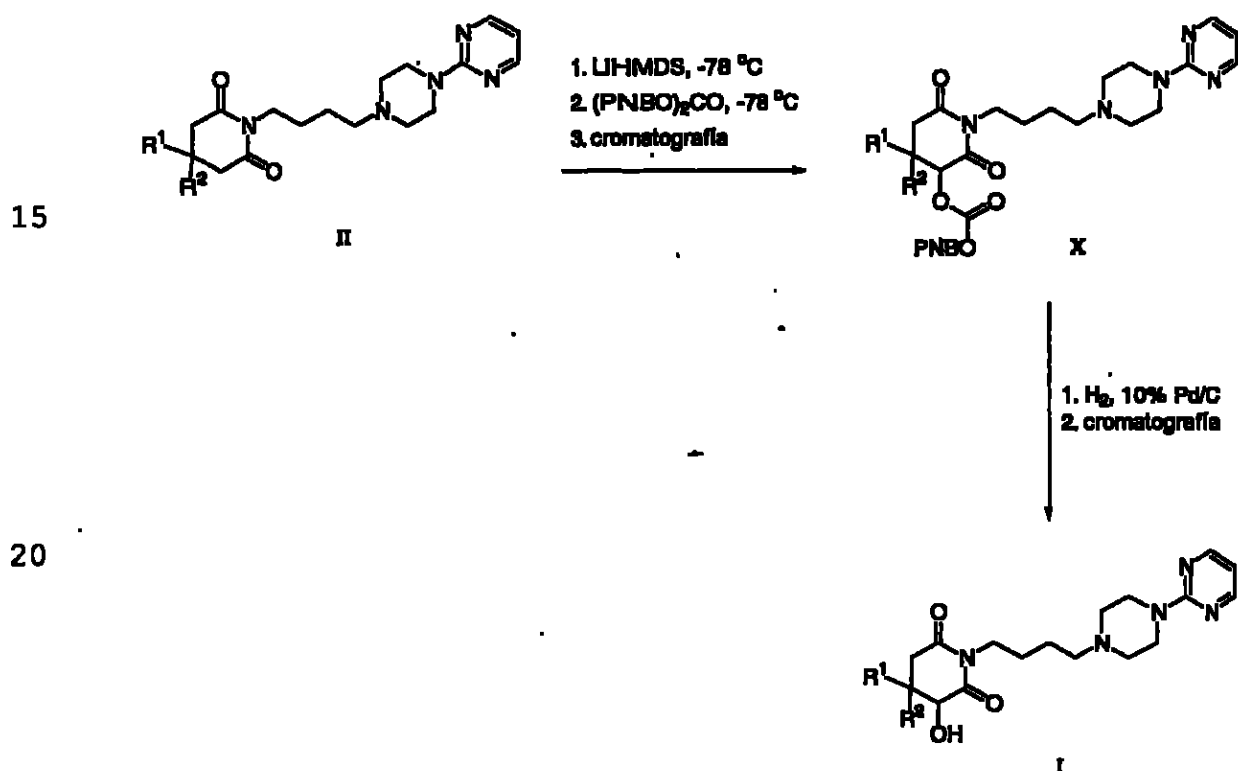
I

II

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Se han descrito procesos los cuales selectivamente hidroxilan azapironas de Fórmula II en hidroxiazapironas de Fórmula I (Mayol, R.F. Patente estadounidense 6,150,365, 2000; Rider, P.H. Solicitud PCT WO 02/16347, 2002). Un proceso para hidroxilar tanto bupiriona como gepirona se ilustra en el Esquema de Reacción 1. En este proceso, el enolato de imida derivado de imida II se generó y atrapó por peroxidicarbonato de di-4-nitrobencilo [(PNBOCO)₂], para producir el intermediario X. Después de la purificación cromatográfica, la hidrogenación del intermediario X proporcionó el compuesto de Fórmula I.

Esquema de Reacción 1.

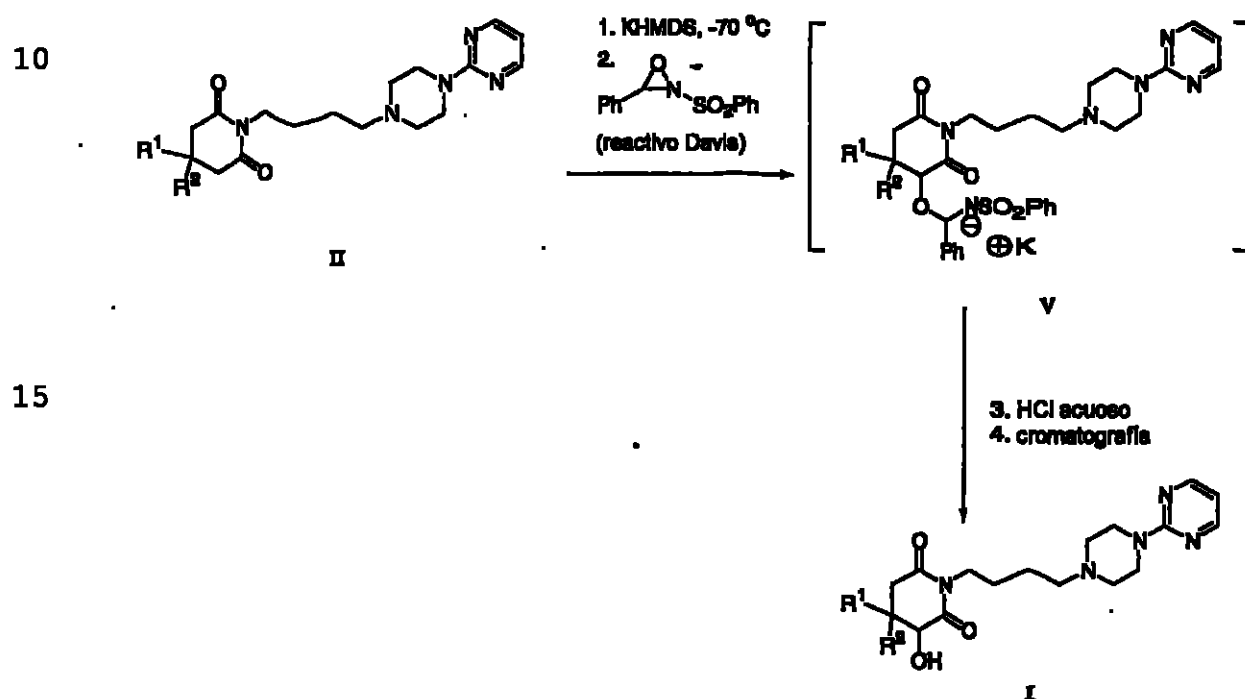


Un segundo proceso, mostrado en el esquema de reacción 2, se empleó para hidroxilación de bupiriona. En

este proceso, el enolato de imida derivado de II, se hizo reaccionar con 2-(fenilsulfonil)-3-feniloxaziridina (el reactivo Davis) para formar el intermediario V postulado. El funcionamiento ácido proporciona el producto de Fórmula I.

5 Las desventajas de ambos de estos procesos, incluyen el requerimiento para sintetizar los reactivos iniciadores y la necesidad de purificar cromatográficamente los productos.

Esquema de Reacción 2.



Un tercer proceso que involucra una conversión enzimática en ciertos microsomas de hígado de mamífero, no es receptivo para la síntesis a gran escala.

Por el contrario, la invención descrita abajo,
25 mejora después de estos procesos empleando un procedimiento

29

de una etapa usando reactivos y aire comercialmente disponibles. El proceso también proporciona cristalización directa del producto, preferentemente, purificación cromatográfica.

5

SUMARIO DE LA INVENCION

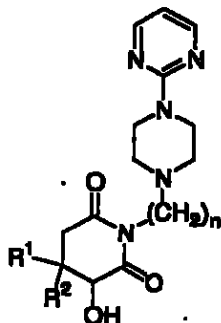
Esta invención describe un proceso de un envase mejorado por hidroxilación, de ciertos agentes psicotrópicos de azapirona útiles, tales como buspirona y gepirona. El proceso usa reactivos y aire comercialmente disponibles. El producto puro es directamente cristalizado de la mezcla de reacción, y el proceso es receptivo para la síntesis a gran escala.

10

DESCRIPCIÓN DETALLADA DE LA INVENCION

La presente invención proporciona un proceso para la preparación de hidroxiazapironas de Fórmula I,

15



20

I

en donde

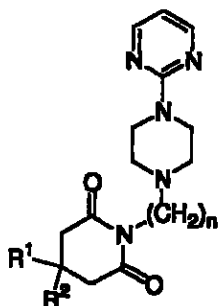
R¹ y R² son independientemente hidrógeno o alquilo C₁₋₆, o en donde

25 R¹ y R² tomados en conjunto son -CH₂(CH₂)₀₋₅CH₂-, y

30
M

n es un número entero de 2 a 5,
de azapironas de Fórmula II.

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II

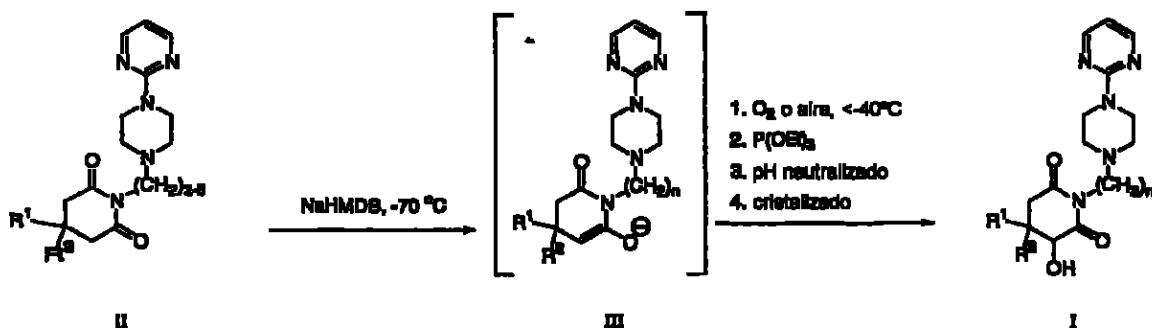
10

El proceso se muestra en el esquema de reacción 3. Brevemente, un compuesto de azapirona de Fórmula II se disuelve en un solvente apropiado que contiene de 1-5 equivalentes de un agente reductor adecuado. Se agrega una base fuerte, generando un enolato de imida de Fórmula III. Se agrega una fuente de oxígeno hasta que la generación del compuesto de Fórmula I se completa. En el curso del levantamiento experimental, el producto es cristalizado y aislado. Este proceso se describe en detalle abajo.

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Esquema de Reacción 3.

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Se disolvió un compuesto de Fórmula II en un solvente aprótico adecuado a una relación preferida de 10-20 mL/g. Solventes adecuados para la generación de enolato incluyen solventes etéreos tales como dietiléter, 1,2-
5 dimetoxietano, dioxano y 2-metiltetrahidrofurano. Tetrahidrofurano (THF), es un solvente preferido para esta reacción. Un agente reductor adecuado en el intervalo de 1-5 equivalentes se agrega a la solución. Los agentes reductores adecuados son aquellos que reducen hidroperóxidos orgánicos a
10 alcoholes. Estos agentes reductores incluyen trialkilfosfitos (C_1-8), así como también otros agentes reductores tales como triarilfosfitos, triaril y trialkil fosfinas, tiourea, borohidruro de sodio, cloruro de cobre(II) con sulfato de hierro (II), cloruro de hierro (III),
15 isopropóxido de titanio, dimetilsulfuro, dietildisulfuro, sulfito de sodio, tiosulfato de sodio, zinc y ácido acético, y 1-propeno. Mientras el agente reductor puede ser agregado en cualquier etapa conveniente del proceso, está preferiblemente presente cuando la reacción de oxigenación
20 procede. La solución es enfriada de -40 hasta -100°C , preferiblemente a un intervalo de -68 a 76°C , y se deja estabilizar completamente.

Se agrega aproximadamente un equivalente de una base fuerte apropiada. La base media la desprotonación y
25 formación de un anión enolato de imida (III). Las bases

preferidas adecuadas para este tipo de desprotonación incluyen disilazanos, tales como bis(trimetilsilil)amida de litio, bis(trimetilsilil)amida de sodio, y bis(trimetilsilil)amida de potasio. Otras bases fuertes las
5 cuales pueden ser usadas incluyen, bases de dialquilamida (tal como diisopropilamida de litio), hidruros metálicos y alcóxidos metálicos.

La generación de una cantidad estequiométrica de enolato es crítica para optimizar el proceso de sobre
10 generación de enolato que resulta en escasa conversión y material iniciador recuperado, mientras la adición excesiva de base resulta en la producción de productos colaterales dihidroxilados. El uso de monitoreo de reacción, en particular, empleando FTIR, para observar directamente la
15 conversión de la imida iniciadora al enolato correspondiente, soluciona este tema. La observación directa de la generación de anión, permite a la base ser cargada hasta que la señal IR para el material iniciador no declina más, indicando completo consumo del material iniciador. El material iniciador fue
20 entonces incrementadamente cargado hasta que se observó una señal IR lista de material iniciador, indicando que no estuvo presente exceso de base. Esto proporcionó una solución del enolato con un ligero exceso de material iniciador (1% a 3%). Debido a que el exceso de material iniciador fue más fácil de
25 purgar que los productos colaterales dihidroxilados (las



impurezas que resultan cuando estuvo presente el exceso de base), esta fue entonces la situación preferida. Variaciones en el titulador base, contenido de agua, y calidad de fosfito, fueron automáticamente corregidas debido a que el

5 fosfito se cargó antes de la base.

En general, el compuesto enolato de Fórmula III, fue formado *in situ* y se hizo reaccionar inmediatamente con electrófilo. Sin embargo, la invención incluye compuestos de enol estables, los cuales pueden ser después reactivados. Por

10 ejemplo, acetatos de enol y enolsilanos, son sustratos adecuados para el proceso.

Después de la generación del enolato, el aire u oxígeno se roció en la mezcla de reacción, controlando la relación inicial de rociado para mantener la temperatura de

15 la mezcla de reacción menos de -40°C . El rociado se continuó hasta que la reacción fue completa como se indica por CLAR. Aunque el gas de oxígeno y aire son fuentes preferidas de oxígeno molecular, pueden ser usadas otras fuentes de oxígeno incluyendo, mezclas gaseosas que contienen oxígeno molecular,

20 oxígeno líquido y soluciones que contienen oxígeno líquido.

La mezcla fue diluida con un solvente adecuado tal como terc-butiléter metílico (MTBE), acetato de etilo, o 2-metil-THF, calentada a temperatura ambiente, y neutralizada con 1M de ácido clorhídrico, hasta que el pH fue de 6.0 a

25 7.0, preferiblemente 6.5 a 6.9. Otros ácidos pueden ser

24

usados y el pH final puede también ser ajustado con varias bases que incluyen fosfato de sodio. La mezcla de reacción entonces fue dividida, y la capa orgánica separada. Los solventes orgánicos fueron reemplazados por isopropanol, y la solución se enfrió para cristalizar el producto. El producto fue normalmente aislado en 64-90% con más de 95% de pureza.

Ocasionalmente, el producto de reacción contiene el material iniciador recuperado, o un producto colateral 6,10-dihidroxiado. En estos casos, uno de los dos procedimientos de cristalización mejoró la pureza. Estos procedimientos se describen en la sección de Modalidades Específicas.

DESCRIPCIÓN DE LAS MODALIDADES ESPECÍFICAS

EJEMPLO 1

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6-Hidroxibuspirona

Se cargó buspirona (8-[4-[4-(2-pirimidinil)-1-piperazinil]butil]-8-azaespiro(4.5)-decan-7,9-diona) (246.5 g, 639.6 mmol), a un matraz de 12L equipado con un agitador mecánico y una sonda Reac-IR bajo gas inerte. Se cargó tetrahidrofurano (4.383 kg, 60.8 mol, 4.930 L, 20 mL/g), y la mezcla se agitó a temperatura ambiente con homogeneidad. Se agregó trietilfosfito (371.9 g, 2.238 mol, 383.8 mL, 3.5 equivalentes) y la mezcla se dejó enfriar de -68 hasta -75°C. La mezcla fue agitada a esta temperatura por al menos 10 minutos para dejar estabilizar la señal Reac-IR. Se cargó a

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M

la mezcla, 1.0M de bis(trimetilsilil)amida de sodio en THF (600.4 g, 664.1 mmol, 664.1 mL, 1.00 equivalentes), a tal relación para mantener la temperatura menos de -60°C. Se cargaron pequeñas cantidades de bis(trimetilsilil)amida de sodio a la mezcla, hasta que la señal IR para buspirona alcanzó un mínimo, indicando la completa desprotonación de buspirona. Se cargó entonces a la mezcla de reacción, buspirona adicional en THF (10-20 mL/g) en incrementos menores hasta que la señal IR indicó un 0.5% a 5% de exceso de buspirona. Se roció aire en la mezcla de reacción, controlando la relación inicial de rociado para mantener la temperatura de la mezcla de reacción menos de -60°C. El rociado se continuó hasta que la reacción fue completa como se indica por CLAR. Se agregó terc-butil éter metílico (384.8 g, 4.365 mol, 520.0 mL), seguido por ácido clorhídrico 1M (1350.8 g, 1.328 mmol, 1328 mL), y la solución se calentó a temperatura ambiente. El pH se ajustó entre 6.5 y 6.9 usando ácido clorhídrico y Na_3PO_4 . Las fases fueron separadas y la fase orgánica fue lavada dos veces con salmuera (542.3 g, 493 mL). El solvente de la capa orgánica rica, fue entonces reemplazado por alcohol isopropílico y la solución se enfrió para cristalizar el producto de reacción. Hubo una opción para impregnar con 0.01 a 5% de buspirona a aproximadamente 54 a 56°C. La suspensión cristaliza fue entonces filtrada y la pasta húmeda fue lavada con alcohol isopropílico y secada para proporcionar 6-hidroxibuspirona (220.0 g, 82%), pf 109.5°C.

Alternativamente, el producto puede ser
cristalizado ya sea por estos dos métodos: (a) concentración
y reemplazo de solvente en heptano o hexanos, o (b) reemplazo
de solvente en EtOAc y cristalización por la combinación de
5 enfriamiento y adición de heptano o hexanos.

EJEMPLO 2

Cristalización de 6-hidroxibuspirona para reducir 6,10- dihidroxibuspirona y buspirona

Se formó en suspensión 6-hidroxibuspirona (35.0 g,
10 90.8 mmol) con anisol (385 mL, 11 mL/g, pueden ser usados 10-
15 mL/g). La mezcla se calentó a 80-100°C y se agitó para
obtener una solución clara. La solución entonces se enfrió a
75-85°C antes fueron agregadas impregnaciones de 6,10-
dihidroxibuspirona (87.5 mg, 0.25% p, pueden ser usados 0-2%
15 en p). La mezcla fue entonces enfriada a temperatura ambiente
durante 2-6 horas y se agitó durante la noche. La suspensión
resultante fue filtrada y lo filtrado se concentró a
aproximadamente la mitad de su volumen inicial. Se agregó
entonces heptano (400 mL) durante 1 hora y la suspensión
20 resultante se agitó a temperatura ambiente durante la noche.
La suspensión fue filtrada y la pasa de filtro resultante fue
lavada con heptano. Después de secar, se obtuvo 23.04 g de 6-
hidroxibuspirona (66% de recuperación). En algunos
experimentos, esta recristalización redujo 6,10-
25 dihidroxibuspirona de ~9% a ~1.5%.

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EJEMPLO 3

Cristalización de 6-hidroxibuspirona para reducir buspirona

Se formó en suspensión 6-hidroxibuspirona (220.0 g, 547.9 mmol) con alcohol etílico absoluto o alcohol isopropílico (2.20 L, 10 mL/g, pueden ser usados 10-20 mL/g), en un matraz de bola de 3 cuellos, equipado con un agitador mecánico. La mezcla fue calentada de temperatura ambiente para formar una solución (55-70°C). La solución resultante fue entonces enfriada para formar una suspensión. El sólido se filtró, se lavó y se secó para proporcionar 6-hidroxibuspirona purificada (165.0 g, 75% de recuperación). En algunos experimentos, esta recristalización reduce la buspirona de ~3% a ~1.4%.

EJEMPLO 4

Protocolo alternativo para 6-hidroxibuspirona

Se disolvió buspirona (350.0 g, 0.908 mol) en THF (6.9 L) en un recipiente de 10L bajo argón. La mezcla se enfrió a -70°C usando un baño de hielo seco/IPA. Se agregó una solución de THF de NaHMDS (0.908 mol, 1.00 equivalentes [0.762 ml, titulada para ser 0.953 M y 0.146 mol, titulada para ser 0.91 M]) durante 12 minutos, mientras se mantiene la temperatura por debajo de -40°C. Se agregó trietilfosfito (3.18 mol, 3.5 equivalentes) en una porción durante aproximadamente un minuto. La solución se agitó a -60°C por aproximadamente 45 minutos. La solución fue entonces enfriada

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a -70°C . Se burbujeó oxígeno (pureza ultra alta [UHP]) en la mezcla de reacción usando un tubo de dispersión de gas. (Nota: el burbujeador y una entrada de Nitrógeno fueron configurados de manera que el nitrógeno pasa a través del recipiente durante la reacción completa). Un exoterma de aproximadamente 5°C fue observado y la relación de rociado de oxígeno fue controlada para mantener la temperatura por debajo de -64.6°C . La reacción se monitoreó usando CLAR tomando alícuotas de la mezcla de reacción y enfriándola en la fase móvil orgánica. Cuando el AP del material iniciador no declinó más (AP aproximadamente 2), la reacción se enfrió rápidamente con HCl (6M, 0.5 L, el pH fue medido por ser aproximadamente de 3 hasta aproximadamente -10°C), y se dejó calentar a temperatura ambiente durante la noche. El pH se ajustó a aproximadamente 2.0 por la adición de NaOH (2N, 40 mL) y la solución se observó por ser turbia y algo heterogénea. El análisis de CLAR indicó 6-hidroxibuspirona (92.6 AP) y buspirona (1.27 AP). La mezcla fue transferida a un matraz de 3 cuellos enchaquetado de 22L, equipado con un agitador mecánico, adaptador de gas, condensador de reflujo, y termopar. Se agregó agua (650 mL) y la mezcla se calentó. A aproximadamente 35°C , la mezcla llegó a ser homogénea. (Nota: alternativamente, se pueden agregar 2.5 M de HCl en lugar de 6M de HCl y agua para ajustar el pH a 2.0). La mezcla fue entonces calentada a aproximadamente 58°C para un total de

39 X

aproximadamente 30 horas y mantener a temperatura ambiente por aproximadamente 124 horas. Durante el calentamiento, las muestras fueron periódicamente tomadas para análisis de ^{31}P RMN y CLAR (monitoreando para la extensión de hidrólisis de dietilfosfito a $\text{HP}(\text{O})(\text{OH})(\text{OEt})$ y análisis de CLAR de 6-hidroxibuspirona).

La solución fue entonces neutralizada a pH de 6.84 por la adición lenta (25 min) de una solución de NaOH/salmuera saturada (3.5 N, 1.0 L [700 mL de 10.0 N NaOH y salmuera saturada agregada hasta que el volumen alcanzó 2.0 L). Se agregaron MTBE (650 mL) y salmuera saturada (500 mL) para asistir en la división de fase. La capa acuosa (2900 mL) se removió y reservó para análisis y una muestra de la capa orgánica se reservó para análisis también. A la capa orgánica fue agregada salmuera saturada (650 mL) y MTBE (150 mL) y las fases fueron dejadas separarse. La segunda capa acuosa se removió (800 mL) y se reservó para análisis. Las muestras de las fases fueron analizadas vía ^{31}P RMN (monitoreando para contenido de dietilfosfito) y CLAR (monitoreando la cantidad de 6-hidroxibuspirona dentro de una fase dada).

Un reactor de vidrio, cilíndrico de 4L, equipado con un agitador mecánico, condensador y termopar (para temperaturas tanto del lote como destilado), se cargó con 3800 mL de la solución. La destilación se condujo bajo presión reducida (la presión varió de -19.5 a -20 en Hg),

40.7

hasta que el volumen fue de aproximadamente 500 mL. La fase orgánica rica en producto restante se agregó y la destilación se resumió, reduciendo el volumen a aproximadamente 1000 mL. Se agregó IPA (2000 mL) y la destilación a presión reducida fue resumida hasta que el volumen se redujo a aproximadamente 1000 mL. Se agregó 1000 mL adicionales de IPA llevando el volumen a aproximadamente 2000 mL (no fue detectable THF vía GC y el contenido de agua fue medido por ser 0.13%). La mezcla se calentó a 75°C para disolver todos los sólidos y después se subdividió en dos lotes detallados en A y B abajo.

Lote A. Aproximadamente 1000 mL fueron transferidos a un recipiente equipado con un agitador magnético y se agregó agua (15 mL, titulación Karl Fischer indicó 3.94% de agua). Esta solución fue entonces enfriada lentamente a temperatura ambiente mientras se agitaba, y se impregnó con 6-hidroxibuspirona (aproximadamente 20 mg). La mezcla fue filtrada siete días después en un filtro sinterizado de vidrio de 4-6 micrones y se reservó el licor madre para análisis (740 mL). El sólido blancuzco fue subsecuentemente lavado con IPA (2 x 260 mL). El sólido blanco fue succionado en seco por 1 h y después colocado en un horno a 45°C (27 en Hg con una purga de N₂ por 69 horas). Se obtuvo 6-hidroxibuspirona como un sólido blancuzco (166.0 g, pureza = 99 AP, buspirona AP = 0.35, y un producto colateral trans-diol AP = 0.54).

A13

Lote B. El resto de la solución (contenido de agua 0.13%) se dejó enfriar a temperatura ambiente y se impregnó con 6-hidroxibuspirona (20 mg) a aproximadamente 56°C. La mezcla se filtró siete días después en un filtro sinterizado de vidrio de 4-6 micrones y el reactor se enjuagó (cuatro veces con el licor madre para recuperar todos los sólidos). El licor madre se reservó para análisis (620 mL). El sólido blancuzco fue subsecuentemente lavado con IPA (2 x 260 mL). El sólido blanco fue succionado en seco por 1 hora y después colocado en un horno a 45°C (27 en Hg con una purga de N₂ por 69 horas). Se obtuvo 6-hidroxibuspirona como un sólido blancuzco (156.6, AP = 99, buspirona AP = 0.35, y un producto colateral trans-diol AP = 0.54).

EJEMPLO 5

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3-Hidroxigepirona

Se cargó Gepirona (4,4-dimetil-1-[4-[4-(2-pirimidinil)-1-piperazinil]butil]-2,6-piperidindiona) (10.0 g, 27.8 mmol), a un matraz de 500 mL equipado con un agitador mecánico y una sonda Reac-IR bajo gas inerte. Se cargó tetrahidrofurano (250 mL, 25 mL/g), y la mezcla se agitó a temperatura ambiente hasta ser homogénea. Se agregó trietilfosfito (28.9 g, 174 mol, 29.8 mL, 6.25 equivalentes) y la mezcla se enfrió de -65 hasta -80°C. La mezcla fue agitada a esta temperatura por al menos 10 minutos para dejar estabilizar la señal Reac-IR. Se cargó a la mezcla, 1.0M de

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X
X

bis(trimetilsilil)amida de sodio en THF (27.8 mL, 27.8 mmol, 1.00 equivalentes) a tal relación para mantener la temperatura menos de -60°C . Se cargaron pequeñas cantidades de bis(trimetilsilil)amida de sodio a la mezcla, hasta que la
5 señal IR para buspirona alcanzó un mínimo, indicando la completa desprotonación de gepirona. Se cargó entonces a la mezcla de reacción, gepirona adicional en THF (25 mL/g) en incrementos menores hasta que la señal IR indicó un 3.24% de exceso de gepirona. Se roció aire en la mezcla de reacción,
10 controlando la relación inicial de rociado para mantener la temperatura de la mezcla de reacción menos de -60°C . El rociado se continuó hasta que la reacción fue completa como se indica por CLAR. Se agregó terc-butil éter metílico (40.0 mL), seguido por ácido clorhídrico 1M (45.0 mL), y la
15 solución se calentó a temperatura ambiente. El pH (9.48 a 20.6°C), se ajustó entre 6.5 y 6.9 usando ácido clorhídrico y Na_3PO_4 (pH = 6.95 a 22.7°C). Las fases fueron separadas y la fase orgánica fue lavada dos veces con 25% en peso de salmuera (40.0 mL). El solvente de la capa orgánica rica, fue
20 entonces reemplazado por alcohol isopropílico y la solución fue enfriada a temperatura ambiente para cristalizar el producto de reacción. La suspensión cristaliza fue entonces filtrada y la pasta húmeda fue lavada dos veces con alcohol isopropílico (15.0 mL) y secada para proporcionar 3-
25 hidroxigepirona (9.32 g, 89%), pf 128°C .

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~~X~~

reivindicación 1, caracterizado porque la fuente de oxígeno molecular es aire o gas de oxígeno.

3. Proceso de conformidad con la reivindicación 1, caracterizado porque el agente reductor se selecciona del grupo que consiste triarilfosfitos, triaril y trialquil fosfinas, tiourea, borohidruro de sodio, cloruro de cobre(II) con sulfato de hierro (II), cloruro de hierro (III), isopropóxido de titanio, dimetilsulfuro, dietildisulfuro, sulfito de sodio, tiosulfato de sodio, zinc y ácido acético, y 1-propeno.

4. Proceso de conformidad con la reivindicación 1, caracterizado porque el agente reductor es trialquilfosfito (C_1-8).

5. Proceso de conformidad con la reivindicación 4, caracterizado porque el agente reductor es trietilfosfito.

6. Proceso de conformidad con la reivindicación 1, caracterizado porque R^1 y R^2 se seleccionan independientemente de hidrógeno y alquilo C_1-6 .

7. Proceso de conformidad con la reivindicación 6, caracterizado porque R^1 y R^2 son metilo y n es 4.

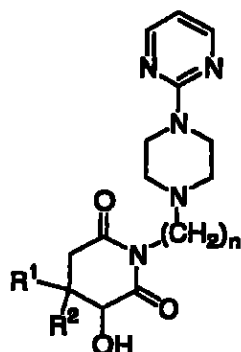
8. Proceso de conformidad con la reivindicación 1, caracterizado porque R^1 y R^2 tomados en conjunto son $-CH_2(CH_2)_{0-5}CH_2-$.

9. Proceso de conformidad con la reivindicación 8, caracterizado porque R^1 y R^2 tomados en conjunto son

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-CH₂CH₂CH₂CH₂- y n es 4.

10. Proceso para preparar hidroxiazapironas de
Fórmula I,



I

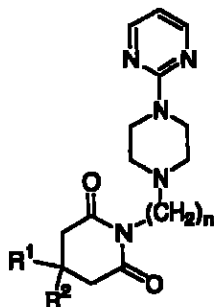
10 caracterizado porque

R¹ y R² son independientemente hidrógeno o alquilo C₁₋₆, o
en donde

R¹ y R² tomados en conjunto son -CH₂(CH₂)₀₋₅CH₂-, y
n es un número entero de 2 a 5,

15 que comprende

(a) hacer reaccionar un compuesto azapirona de
Fórmula II

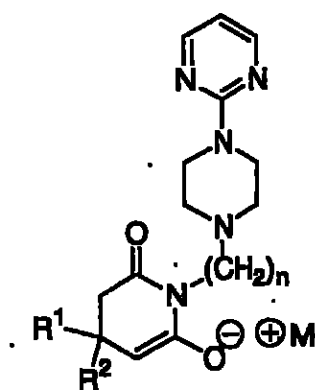


II

con una base fuerte para formar un anión enolato de
25 imida intermediario de Fórmula III

de ~~2~~

5



III

10 (b) hacer reaccionar el enolato de imida III con oxígeno molecular en la presencia de un agente reductor.

11. Proceso de conformidad con la reivindicación 10, caracterizado porque la fuente de oxígeno molecular es aire o gas de oxígeno.

15 12. Proceso de conformidad con la reivindicación 10, caracterizado porque la base fuerte se selecciona del grupo que consiste de bis(trimetilsilil)amida de litio, bis(trimetilsilil)amida de sodio, bis(trimetilsilil)amida de potasio, dialquilamida de litio, dialquilamida de sodio,
20 dialquilamida de potasio, sodamida, alcóxido de litio, alcóxido de sodio, alcóxido de potasio, hidruro de litio, hidruro de sodio e hidruro de potasio.

13. Proceso de conformidad con la reivindicación 12, caracterizado porque la base es bis(trimetilsilil)amida
25 de sodio.

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X
X

14. Proceso de conformidad con la reivindicación 10, caracterizado porque la formación del anión enolato de imida III es maximizada por el uso de espectroscopía para monitorear la conversión de II a III.

5 15. Proceso de conformidad con la reivindicación 14, caracterizado porque la espectroscopía de IR es usada para monitorear la conversión de II a III.

10 16. Proceso de conformidad con la reivindicación 10, caracterizado porque el agente reductor se selecciona del grupo que consiste triarilfosfitos, triaril y trialquil fosfinas, tiourea, borohidruro de sodio, cloruro de cobre(II) con sulfato de hierro (II), cloruro de hierro (III), isopropóxido de titanio, dimetilsulfuro, dietildisulfuro, sulfito de sodio, tiosulfato de sodio, zinc y ácido acético,
15 y 1-propeno.

17. Proceso de conformidad con la reivindicación 10, caracterizado porque el agente reductor es trialquifosfito (C₁₋₈).

20 18. Proceso de conformidad con la reivindicación 17, caracterizado porque el agente reductor es trietilfosfito.

19. Proceso de conformidad con la reivindicación 1, caracterizado porque R¹ y R² son seleccionados independientemente de hidrógeno y alquilo C₁₋₆.

25 20. Proceso de conformidad con la reivindicación

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19, caracterizado porque R^1 y R^2 son metilo y n es 4.

21. Proceso de conformidad con la reivindicación 10, caracterizado porque R^1 y R^2 tomados en conjunto son $-\text{CH}_2(\text{CH}_2)_{0-5}\text{CH}_2-$.

5 22. Proceso de conformidad con la reivindicación 21, caracterizado porque R^1 y R^2 tomados en conjunto son $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$ y n es 4.

RESUMEN DE LA INVENCION

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La presente invención se refiere a un proceso para preparar hidroxiazapironas de Fórmula I, a partir de
5 azapironas de Fórmula II. El proceso comprende tratar
azapironas con una base fuerte, monitorear la formación de enolato de la azapirona por espectroscopía de IR, y hacer reaccionar el enolato con una fuente de oxígeno molecular en la presencia de un agente reductor. El proceso es adecuado
10 para producción a gran escala de hidroxiazapironas.

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

BRISTOL-MYERS SQUIBB COMPANY
P.O. BOX 4000
PRINCETON, NJ 08542-4000
ADD 19 AUG 2004**PCT****NOTIFICATION OF TRANSMITTAL OF
INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

(PCT Rule 71.1)

Docketed Item ND SIPE

Due Date _____

Attorney EmperadoDate of Mailing
(day/month/year)17 AUG 2004

Applicant's or agent's file reference

CT-2748

IMPORTANT NOTIFICATION

International application No.

PCT/US03/24934

International filing date (day/month/year)

07 August 2003 (07.08.2003)

Priority date (day/month/year)

12 August 2002 (12.08.2002)

Applicant

BRISTOL-MYERS SQUIBB COMPANY

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.
4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

REC

SEP 08 2004

BRISTOL-MYERS SQUIBB COMPANY
PATENT DEPARTMENT
WALLINGFORD, CT

Name and mailing address of the IPEA/US

Mail Stop PCT, Attn: IPEA/US
Commissioner for Patents
P.O. Box 1430
Alexandria, Virginia 22313-1430
Facsimile No. (703) 305-3230

Authorized officer

Vickie Kim

Telephone No. 571-272-1600

Form PCT/IPEA/416 (July 1992)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

SLM

Applicant's or agent's file reference CT-2748		FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US03/24934	International filing date (day/month/year) 07 August 2003 (07.08.2003)	Priority date (day/month/year) 12 August 2002 (12.08.2002)	
International Patent Classification (IPC) or national classification and IPC IPC(7): A61K 31/495, 31/30, 31/00 and US Cl.: 514/252.18, 629			
Applicant BRISTOL-MYERS SQUIBB COMPANY			
1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36. 2. This REPORT consists of a total of <u>3</u> sheets, including this cover sheet. ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT). These annexes consist of a total of <u> </u> sheets. 3. This report contains indications relating to the following items: I ☒ Basis of the report II ☐ Priority III ☐ Non-establishment of report with regard to novelty, inventive step and industrial applicability IV ☐ Lack of unity of invention V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement VI ☐ Certain documents cited VII ☐ Certain defects in the international application VIII ☐ Certain observations on the international application			
Date of submission of the demand 20 February 2004 (20.02.2004)		Date of completion of this report 25 July 2004 (25.07.2004)	
Name and mailing address of the IPEA/US Mail Stop PCT, Attn: IPEA/US Commissioner for Patents P.O. Box 1430 Alexandria, Virginia 22313-1430 Facsimile No. (703) 305-3230		Authorized officer <i>Christina Lawrence</i> Vicki Kim Telephone No. 571-272-1600	

Form PCT/IPEA/409 (cover sheet)(July 1998)

52

I. Basis of the report

1. With regard to the elements of the international application:*

- ☒ the international application as originally filed.
- ☒ the description:
pages 1-12 as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.
- ☒ the claims:
pages 13-16 as originally filed
pages NONE, as amended (together with any statement) under Article 19
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.
- ☐ the drawings:
pages NONE, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.
- ☐ the sequence listing part of the description:
pages NONE, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language _____ which is:

- ☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in printed form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

- ☐ the description, pages NONE
- ☐ the claims, Nos. NONE
- ☐ the drawings, sheets/fig NONE

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).

** Any replacement sheet containing such amendments must be referred to under item I and annexed to this report.

V. Reasoned statement under Rule 66.2(a)(II) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**1. STATEMENT**

Novelty (N)	Claims <u>1-22</u>	YES
	Claims <u>NONE</u>	NO
Inventive Step (IS)	Claims <u>NONE</u>	YES
	Claims <u>1-22</u>	NO
Industrial Applicability (IA)	Claims <u>1-22</u>	YES
	Claims <u>NONE</u>	NO

2. CITATIONS AND EXPLANATIONS

Claims 1-22 lack an inventive step under PCT Article 33(3) as being obvious over WO01/45687 A2 (FABRE/KRAMER PHARMACEUTICALS, INC) or WO02/16347 A1 (AKZO NOBEL N.V.).

The claims are drawn to a process of preparing a compound having formula I by utilizing various steps as claimed.

WO'687 or WO'347 relates to a method preparing 3-OH gepirone having the chemical structure embraced by the claimed formula I when both R1 and R2 is substituted with CH3, see WO'687, at page 11 and WO'347 at page 7.

As evidenced by these references, it would have been obvious to one skilled in the art to modify and synthesize 3-OH gepirone or it's derivatives that shares same core structure, absent evidence to the contrary, see US'687, at page 10, lines 25-30.

Thus, the instant claims lack the inventive step.

Claims 1-22 meet the criteria set out in PCT Article 33(4), and thus the claimed invention has industrial applicability because the subject matter claimed can be made or used in industry.

PATENT COOPERATION TREATY

PCT

NOTE OF INFORMAL COMMUNICATION WITH THE APPLICANT

(PCT Rule 66.6)

International application No. PCT/US03/24934	Applicant's or agent's file reference CT-2748	Date of informal communication (day/month/year) 25 July 2004 (25.07.2004)
Applicant BRISTOL-MYERS SQUIBB COMPANY		

Communication ☒ by telephone ☐ personal	Participants ☐ Identity checked ☒ Authorization checked ☐ Personally known ☐ Applicant: BRISTOL-MYERS SQUIBB COMPANY ☒ Agent: Mr. Epperson, James ☒ Examiner(s): Vickie Kim
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Summary of communication:

Preparation of International Preliminary Examination Report (IPER, 409) is authorized by applicant without written opinion (408) to expedite the prosecution. The examiner prepared IPER, accordingly.

☐ An extension of time limit is granted (Form PCT/IPEA/437).

☒ A copy of this note is being sent to the applicant with Form PCT/IPEA/439.

PCT/IPEA/424.

Name and mailing address of the IPEA/US Mail Stop PCT, Attn: IPEA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230 Form PCT/IPEA/428 (July 1992)	Authorized officer <i>Rosetta Lawrence</i> Vickie Kim Telephone No. 571-272-1600
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TRATADO DE COOPERACION EN MATERIA DE PATENTES

P C T

REPORTE DE EXAMEN PRELIMINAR INTERNACIONAL

(Artículo 38 y Regla 70 del PCT)

SS

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✓

Referencia de registro del Solicitante o del Agente CT-2748	PARA TOMAR ACCION ADICIONAL Véase la Notificación de la Transmisión del Reporte de Examen Preliminar Internacional (Forma PCT/IPEA/418)	
Solicitud Internacional No. PCT/US03/24934	Fecha de Presentación Internacional (Día/Mes/Año) 07 Agosto 2003 (07.08.2003)	Fecha de Prioridad (Día/Mes/Año) 12 Agosto 2002 (12.08.2002)
Clasificación de Patente Internacional (IPC) o Clasificación nacional e IPC IPC(7): A61K 31/495, 31/50, 31/00 y US Cl.:514/252.18, 629		
Solicitante BRISTOL-MYERS SQUIBB COMPANY		
1. Este reporte de examen preliminar internacional ha sido preparado por esta Autoridad de Examinación Preliminar Internacional y es transmitido al solicitante de acuerdo con el Artículo 38. 2. Este reporte consiste de <u>3</u> hojas, incluyendo esta hoja de cubierta ☒ Este reporte también está acompañado por ANEXOS, es decir, hojas de la descripción, las reivindicaciones y/o los dibujos, los cuales han sido enmendados y son la base para este reporte y/o las hojas que contienen las rectificaciones hechas antes de esta Autoridad. (Véase la Regla 70.16 y la Sección 607 de las Instrucciones Administrativa bajo el PCT). Estos anexos consisten de un total de <u> </u> Hojas.		
3. Este reporte contiene las indicaciones que están relacionadas con los siguientes puntos: I. ☒ Base del reporte II. ☐ Prioridad III. ☐ Ningún establecimiento del reporte con respecto a la novedad, paso de la invención, o Aplicabilidad industrial IV. ☐ Carencia de unidad de la invención V. ☒ Establecimiento razonado bajo el artículo 35(2) con respecto a la novedad, paso de la invención o aplicabilidad industrial; las citas y explicaciones que soportan tal establecimiento o fundamento. VI. ☐ Ciertos documentos citados VII. ☐ Ciertos defectos en la solicitud internacional VIII. ☐ Ciertas observaciones en la solicitud internacional		
Fecha de presentación de la solicitud 20 Febrero 2004 (20.02.2004)	Fecha en la que se completa este reporte 25 Julio 2004 (25.07.2004)	
Nombre y dirección de envío de la IPEA/EP Mail Stop PCT, Attn: IPEA/US Comisionado de Patentes P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230	Funcionario autorizado Vickie Kim Teléfono No. + 571-272-1600	

Forma PCT/IPEA/408 (hoja de cubierta) (Julio 1998)

I. Bases del Reporte

1. Con respecto a los elementos de la solicitud internacional:*

- ☒ la solicitud internacional como se presentó originalmente.
- ☒ la descripción, páginas 1-12, como se presentó originalmente.
páginas NINGUNA, presentadas con la demanda.
páginas NINGUNA, presentada con la carta de
- ☒ las reivindicaciones,
Nos. 13-16, como se presentó originalmente.
Nos. NINGUNA, como se enmendaron (junto con cualquier declaración) bajo el Artículo 19.
Nos. NINGUNA, presentadas con la demanda.
Nos. NINGUNA, presentada con la carta del _____
- ☐ los dibujos, páginas NINGUNA, como se presentaron originalmente.
páginas NINGUNA, presentadas con la demanda.
páginas NINGUNA, presentadas con la carta de
- ☐ parte del listado de secuencia de la descripción:
páginas NINGUNA, como se presentaron originalmente.
páginas NINGUNA, presentadas con la demanda.
páginas NINGUNA, presentadas con la carta de

2. Con respecto al lenguaje, todos los elementos marcados anteriormente estuvieron disponibles o se proporcionaron a esta Autoridad en el lenguaje en el cual la solicitud internacional se presentó, al menos que se indique de otra manera bajo este punto.

Estos elementos estuvieron disponibles o se proporcionaron a esta Autoridad en el lenguaje siguiente, el cual es:

- ☐ el lenguaje de una traducción proporcionada para el propósito de la búsqueda internacional (bajo la Regla 23.1 (b))
- ☐ el lenguaje de la publicación de la solicitud internacional (bajo la Regla 48.3(b)).
- ☐ el lenguaje de una traducción proporcionada para el propósito del examen preliminar internacional (bajo la Regla 55.2 y/o 55.3).

3. Con respecto a cualquier secuencia de nucleótido y/o aminoácido descrita en la solicitud internacional, el examen preliminar internacional se realizó sobre las bases del listado de secuencia:

- ☐ contenida en la solicitud internacional en forma escrita.
- ☐ presentada junto con la solicitud internacional en forma legible por computadora.
- ☐ proporcionada subsecuentemente a esta Autoridad en forma escrita.
- ☐ proporcionada subsecuentemente a esta Autoridad en forma legible por computadora.
- ☐ se ha proporcionado la declaración de que el listado de secuencia escrito proporcionado subsecuentemente no va más allá de la descripción en la solicitud internacional como se presentó.
- ☐ se ha proporcionado la declaración de que la información registrada en forma legible por computadora es idéntica al listado de secuencia escrito.

4. ☐ Las enmiendas han conducido a la cancelación de:

- ☐ la descripción, páginas. NINGUNA
- ☐ las reivindicaciones, Nos. NINGUNA
- ☐ los dibujos, hoja/fg. NINGUNA

5. ☐ Este reporte ha sido establecido como si (alguna de) las enmiendas no haya sido hecha, puesto que las mismas se han considerado que van más allá de la descripción como se presentó, como está indicado en las observaciones Adicionales posteriores (Regla 70.2(c)). **

* Hojas de reemplazo las cuales han sido proporcionadas a la Oficina receptora en respuesta a una invitación bajo el Artículo 14 se refiere a este reporte como presentadas originalmente y no se anexan a este reporte siempre que no contenga enmiendas (Reglas 70.16 y 70.17)

** Cualquier hoja de reemplazo de contenga dichas enmiendas podrá referirse bajo el punto 1 y ser anexada a este reporte

V. Declaración razonada bajo la Regla 66.2(a)(II) con respecto a la novedad, etapa inventiva o aplicabilidad industrial; citas y explicaciones que soportan dicha declaración

1. Declaración

Novedad (N)	Reivindicaciones	1-22	SI
	Reivindicaciones	NINGUNA	NO
Etapa Inventiva (EI)	Reivindicaciones	NINGUNA	SI
	Reivindicaciones	1-22	NO
Aplicabilidad Industrial (AI)	Reivindicaciones	1-22	SI
	Reivindicaciones	NINGUNA	NO

2. Citas y Explicaciones

Las reivindicaciones 1-22 carecen de una etapa inventiva bajo el Artículo 33(3) del PCT como es obvio sobre el documento WO01/45687 A2 (FABRE/KRAMER PHARMACEUTICALS, INC) o WO02/16347 A1 (AKZO NOBEL N.V.).

Las reivindicaciones se dirigen a un proceso de preparación de un compuesto que tiene fórmula I utilizando varias etapas como se reivindican.

Los documentos WO 687 ó WO 347 se refieren a un método para preparar gepirona 3-OH que tiene la estructura química abarcada por la fórmula I reivindicada, cuando tanto R1 como R2 son substituidos con CH3, véase documento WO687, en la página 11 y WO 347 en la página 7.

Como es evidente por estas referencias, podrá ser obvio para un experto en la técnica, modificar y sintetizar gepirona 3-OH o sus derivados que portan la misma estructura central, evidencia ausente a lo contrario, véase documento US 687, en la página 10, línea 25-30.

Así, las presentes reivindicaciones carecen de etapa inventiva.

Las reivindicaciones 1-22 cubren el criterio mostrado en el Artículo 33(4) del PCT, y así la reivindicación reivindicada tiene aplicabilidad industrial debido a que la materia objeto reivindicada puede ser elaborada y usada en la industria.

TRATADO DE COOPERACIÓN EN MATERIA DE PATENTES

PCT

NOTA DE COMUNICACIÓN INFORMAL CON EL SOLICITANTE

58 0/10

(PCT Regla 66.6)

Solicitud Internacional No. PCT/US03/24934	Archivo de referencia del agente o solicitante CT-2748	Fecha de comunicación informal (día/mes/año) 25 Julio 2004 (25.07.2004)
Solicitante: BRISTOL-MYERS SQUIBB COMPANY		

Comunicación ☒ por teléfono ☐ personal	Participantes ☐ Solicitante: BRISTOL-MYERS SQUIBB COMPANY ☒ Agente: Mr. Epperson, James ☒ Examinadores: Vickie Kim	☐ identidad Verificada ☒ autorización verificada ☐ personalmente conocido
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Sumario de Comunicación

La preparación del Reporte de Examen Preliminar Internacional (IPER 409) se autorizó por el solicitante sin opinión escrita (408) para expedir la persecución. El examinador preparará por consiguiente el IPER.

☐ Una extensión del tiempo límite es otorgada (Forma PCT/IPEA/427).

☒ Una copia de esta notificación está siendo enviada al solicitante con la Forma PCT/IPEA/424.

PCT/IPEA/424.

Nombre y dirección de correspondencia del IPEA/US Mail Stop PCT, Attn: IPEA/US Comisionado para Patentes P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230	Oficial Autorizado Vickie Kim Teléfono No. 571-272-1600
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PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

INVITATION TO CORRECT
DEFECTS IN THE DEMAND

(PCT Rule 60.1)

To:

JAMES EPPERSON
BRISTOL-MYERS SQUIBB COMPANY
P.O. BOX 40
PRINCETON, NEW JERSEY 08543-4000

RECEIVED

BMS PATENT LAW

JUL 12 2004

Docketed Item 0A

Due Date 8/10/04

Date of mailing
(day/month/year)

08 JUL 2004

Applicant's or Agent's reference

CT-2748 PCT

REPLY DUE

within ONE MONTH from
the above date of mailing.
See also below.

International application No.

PCT/US03/24934

International filing date
(day/month/year)

07 Aug 2003

Applicant

BRISTOL-MYERS SQUIBB COMPANY

The applicant is hereby invited within the time limit indicated above to correct the following defects which this International Preliminary Examining Authority has found in the demand for international preliminary examination:

1. ☐ It does not contain the election of at least one Contracting State bound by Chapter II (Rules 53.2(a)(iv) and 53.3).
2. ☐ It does not permit identification of the international application to which it relates (Rule 60.1(b)).
3. ☐ It does not contain the required petition (Rules 53.2(a)(i) and 53.3).
4. ☐ It does not contain the required indications concerning the agent as specified in the Annex (Rules 53.2(a)(ii) and 53.5).
5. ☐ It does not contain the required indications concerning the international application as specified in the Annex (Rules 53.2(a)(iii) and 53.6).
6. ☐ It is not submitted in the required language which is: _____ (Rule 55.1).
7. ☐ It is not made on the printed form (Rule 53.1(a)).
8. ☐ It is presented as a computer print-out the particulars of which do not comply with the Administrative Instructions (Rule 53.1(a)).
9. ☒ It does not contain the required indications concerning the applicant as specified in the Annex (Rules 53.2(a)(ii) and 53.4).
10. ☐ It does not contain the required signature as specified in the Annex (Rules 53.2(b) and 53.8).

Effect of the date of receipt of the corrections on the date of receipt of the demand:

- (i) If the defects noted under items 1 and 2 are corrected within the time limit indicated above, the demand shall be considered as if it had been received on the date when the corrections are received (Rule 60.1(b)). If that date is later than the expiration of 19 months from the priority date, entry into the national phase before the elected Offices will NOT be postponed until the expiration of 30 months from the priority date.
- (ii) If the defects noted under items 3 to 10 are corrected within the time limit indicated above, the demand shall be considered as if it had been received on the actual filing date (Rule 60.1(b)).

Effect of failure to correct the defects within the time limit indicated above:

- (i) In the case of defects noted under items 1 to 8, this Authority will declare that the demand is considered as if it had not been submitted.
- (ii) In the case of defects noted under items 9 and 10, this Authority will declare that the election(s) of the State(s) concerned is(are) considered as if it(they) had not been made.

A copy of this invitation has been sent to the International Bureau.

Name and mailing address of the IPEA/
Mail Stop PCT, Commissioner for Patents
P.O. Box 1450, Alexandria, VA 22313-1450

Facsimile No. 703-305-3230

Form PCT/IPEA/404 (July 1998)

Authorized officer
Nina Gilchrist-Jones

Telephone No. 703-305-6107

CT2748-WO-FC1
EPPERSON
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X

FAXED
7/13/04

3 pages

Continuation of item 4: As to indications concerning the agent (Rule 4.4), the demand:

- a. ☐ does not properly indicate the agent's name (specify):
- b. ☐ does not indicate the agent's address.
- c. ☐ does not properly indicate the agent's address (specify):

Continuation of item 5: As to indications concerning the international application, the demand does not indicate:

- a. ☐ the international filing date.
- b. ☐ the international application number.
- c. ☐ the name of the receiving Office, where the international application number was not known to the applicant at the time the demand was filed.
- d. ☐ the title of the invention.

Continuation of item 9: As to indications concerning the applicant (Rules 4.4 and 4.5), the demand:

- a. ☒ does not indicate all the applicants for the elected States.
- b. ☐ does not properly indicate the applicant's name (specify):
All applicants/inventors that are indicated on the Request must also be indicated on the Demand. (JEFFREY DEPUE, ATUL S. KOTNIS, SIMON LEUNG, ERIC D. DOWDY, DANIEL J. WATSON) Please specify
- c. ☐ does not indicate the applicant's address.
- d. ☐ does not properly indicate the applicant's address (specify):
- e. ☐ does not indicate the applicant's nationality.
- f. ☐ does not indicate the applicant's residence.

Continuation of item 10: As to requirements concerning signature (Rules 4.15 and 90.4), the demand:

- a. ☐ is not signed.
- b. ☐ is not signed by all the applicants for the elected States.
- c. ☐ is not accompanied by the statement referred to in the check list in Box No. VI of the demand explaining the lack of the signature of an applicant for the election of the United States of America.
- d. ☐ is signed by what appears to be an agent/common representative but
☐ the demand is not accompanied by a power of attorney appointing him.
☐ the power of attorney accompanying the demand is not signed by all the applicants for the elected States.

CT2748-WO-PCT M
EPPERSON 61
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PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

NOTIFICATION OF RECEIPT
OF DEMAND BY COMPETENT INTERNATIONAL
PRELIMINARY EXAMINING AUTHORITY

(PCT Rules 59.3(e) and 61.1(b), first sentence
and Administrative Instructions, Section 601(a))

To:
JAMES EPPERSON
BRISTOL-MYERS SQUIBB COMPANY
P.O. BOX 4000
PRINCETON, NEW JERSEY 08543-4000

Date of mailing
(day/month/year) 08 JUL 2004

Applicant's or agent's file reference
CT-2748 PCT

IMPORTANT NOTIFICATION

International application No.
PCT/US03/24934

International filing date (day/month/year)
07 Aug 2003

Priority date (day/month/year)
12 Aug 2002

Applicant
BRISTOL-MYERS SQUIBB COMPANY

1. The applicant is hereby notified that this International Preliminary Examining Authority considers the following date as the date of receipt of the demand for international preliminary examination of the international application:

20 FEB 2004

2. That date of receipt is:

- ☒ the actual date of receipt of the demand by this Authority (Rule 61.1(b)).
☐ the actual date of receipt of the demand on behalf of this Authority (Rule 59.3(e)).
☐ the date on which this Authority has, in response to the invitation to correct defects in the demand (Form PCT/IPEA/404), received the required corrections.

3. ☐ **ATTENTION:** That date of receipt is **AFTER** the expiration of 19 months from the priority date. Consequently, the election(s) made in the demand does (do) not have the effect of postponing the entry into the national phase until 30 months from the priority date (or later in some Offices) (Article 39(1)). Therefore, the acts for entry into the national phase must be performed within 20 months from the priority date (or later in some Offices) (Article 22). For details, see the PCT Applicant's Guide, Volume II.

- ☐ (If applicable) This notification confirms the information given by telephone, facsimile transmission or in person on:

4. Only where paragraph 3 applies, a copy of this notification has been sent to the International Bureau.

Name and mailing address of the IPEA/
Mail Stop PCT, Commissioner for Patents
P.O. Box 1450, Alexandria, VA 22313-1450

Facsimile No. 703-305-3230
Form PCT/IPEA/402 (July 1998)

Authorized officer
Nisa Gilchrist-Jones

Telephone No. 703-305-6000

RECEIVED
BMS PATENT LAW

JUL 12 2004

Docketed Item _____
Due Date _____
Attorney _____

PATENT COOPERATION TREATY

CR2748-WO-PCT

con
62 X

From the INTERNATIONAL SEARCH AUTHORITY

RECEIVED

To:
JAMES EPPERSON
BRISTOL-MYERS SQUIBB COMPANY
P.O. BOX 4000
PRINCETON, NJ 08543-4000

BMS PATENT LAW

MAY 04 2004

PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT
OR THE DECLARATION

MAY 14 2004

Docketed Item

(PCT Rule 44.1)

Due Date

Attorney

EPPERSON

Date of Mailing
(day/month/year)

30 APR 2004

Applicant's or agent's file reference
CT-2748 PCT

FOR FURTHER ACTION See paragraphs 1 and 4 below

International application No.
PCT/US03/24934

International filing date
(day/month/year)

07 August 2003 (07.08.2003)

Applicant
BRISTOL-MYERS SQUIBB COMPANY

1. ☒ The applicant is hereby notified that the international search report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

Where? Directly to the International Bureau of WIPO, 34, chemin des Colombettes
(2111 Geneva 20, Switzerland, Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. Reminders

Shortly after 18 months from the priority date, the International application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90 bis.1 and 90 bis.3, respectively, before the completion of the technical preparations for international publication.

Within 19 months from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later); otherwise the applicant must, within 20 months from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

In respect of other designated Offices, the time limit of 30 months (or later) will apply even if no demand is filed within 19 months.

See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the PCT Applicant's Guide, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the ISA/US
Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
Facsimile No. (703) 305-3230

Authorized officer

Marlene Seidel

Telephone No. 703-308-0196

J. Roberts for

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

63 

Applicant's or agent's file reference CT-2748 PCT	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
International application No. PCT/US03/24934	International filing date (day/month/year) 07 August 2003 (07.08.2003)	(Earliest) Priority Date (day/month/year) 12 August 2002 (12.08.2002)
Applicant BRISTOL-MYERS SQUIBB COMPANY		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 3 sheets.



It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the Report

- a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.



the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing:



contained in the international application in written form.



filed together with the international application in computer readable form.



furnished subsequently to this Authority in written form.



furnished subsequently to this Authority in computer readable form.



the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.



the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

2. ☐ Certain claims were found unsearchable (See Box I).

3. ☐ Unity of invention is lacking (See Box II).

4. With regard to the title,



the text is approved as submitted by the applicant.



the text has been established by this Authority to read as follows:

5. With regard to the abstract,



the text is approved as submitted by the applicant.



the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No. _____



as suggested by the applicant.



None of the figures



because the applicant failed to suggest a figure.



because this figure better characterizes the invention.

INTERNATI NAL SEARCH REPORT

International application No.

PCT/US03/24934

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 31/495, 31/50, 31/00
US CL : 514/252.18, 629

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)
U.S. : 514/252.18, 629

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)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01/45687 A2 (FABRE/KRAMER PHARMACEUTICALS, INC.) 28 June 2001 (28.06.2001), see full text, especially page 11.	1-22
X	WO 02/16347 A1 (AKZO NOBEL N.V.) 28 February 2002 (28.02.2002), see full text, especially pages 6-7.	1-22
X, P	US 6,593,331 B2 (CAMBORDE et al) 15 July 2003 (15.07.2003), see full text, especially column 5-6.	1-22

☐ 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 application or patent 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

"T" 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

"A"

document member of the same patent family

Date of the actual completion of the international search

15 December 2003 (15.12.2003)

Date of mailing of the international search report

30 APR 2004

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
Facsimile No. (703)305-3230

Authorized officer

Marlene Seidel

Telephone No. 703-308-0196

65

✓

Continuation of B. FIELDS SEARCHED Item 3:
CAS ONLINE, CAPLUS, USPATFUL, REGISTRY, TOXCENTER
structure searched and term searched: azapirone, methyl phosphite(reductant), hydroxyazapirone

TRATADO DE COOPERACIÓN DE PATENTES

PCT

REPORTE DE BUSQUEDA INTERNACIONAL

(Artículo 18 y Reglas 43 y 44 del PCT)

66 20

Referencia al expediente del solicitante o del mandatario CT-2748 PCT	PARA ACCION ADICIONAL ver Notificación de la Transmisión del Reporte de Búsqueda Internacional (Forma PCT/ISA/220) así como, en donde aplique el inciso 5 posterior	
No. de solicitud internacional PCT/US 03/24934	Fecha de presentación internacional (día/mes/año) 07 Agosto 2003 (07.08.2003)	(Fecha de Prioridad) (La más cercana) (día/mes/año) 12 Agosto 2002 (12.08.2002)
Solicitante BRISTOL-MYERS SQUIBB COMPANY		

Este reporte de búsqueda internacional ha sido preparado por esta Autoridad de la Búsqueda Internacional y se transmite al solicitante de conformidad con el Artículo 18. Se transmite una copia a la Oficina Internacional.

Este reporte de búsqueda internacional consiste de un total de 3 hojas

☒ También está acompañado de una copia de cada documento de la técnica anterior citado en este reporte.

1. Bases del Reporte

a. Con respecto al lenguaje, la búsqueda internacional se realizó en las bases de la solicitud internacional en el lenguaje en el cual se presentó, a menos que se indique de otra manera bajo este punto.

☐ La búsqueda internacional se realizó en base de una traducción de la solicitud internacional proporcionada a esta Autoridad Regla 23.1(b).

b. Con respecto a cualquier secuencia de nucleótido y/o aminoácido descrita en la solicitud internacional, la búsqueda internacional se realizó en las bases del listado de secuencia:

- ☐ contenida en la solicitud internacional en forma escrita.
- ☐ presentada junto con la solicitud internacional en forma legible por computadora.
- ☐ suministrada subsecuentemente a esta Autoridad en forma escrita.
- ☐ suministrada subsecuentemente a esta Autoridad en forma legible por computadora.
- ☐ la declaración que el listado de secuencia escrito subsecuentemente suministrado no va más allá de la descripción en la solicitud internacional como se presentó, se ha suministrado
- ☐ la declaración que la información registrada en forma legible por computadora es idéntica al listado de secuencia escrito se ha suministrado

2. ☐ Se encontró que ciertas reivindicaciones no son localizables (ver el Cuadro I).

3. ☐ La unidad de la invención es deficiente (ver el Cuadro II).

4. Con respecto al título,

- ☒ el texto se aprueba tal como lo presentó el solicitante.
- ☐ esta Autoridad ha establecido que el texto sea como sigue:

5. Con respecto al resumen,

- ☒ el texto se aprueba tal como lo presentó el solicitante.
- ☐ Esta Autoridad ha establecido el texto, de acuerdo con la Regla 38.2(b), tal como aparece en el Cuadro III. El solicitante puede, dentro de un mes a partir de la fecha de envío por correo de este reporte de búsqueda internacional, proporcionar comentarios a esta autoridad.

6. La figura de los dibujos que se va a publicar con el resumen es la Figura No. _____

- ☐ como lo sugirió el solicitante.
- ☐ porque el solicitante le faltó sugerir una figura.
- ☐ porque esta figura caracteriza mejor la invención.
- ☐ Ninguna de las figuras

REPORTE DE BÚSQUEDA INTERNACIONAL

No. de Solicitud Internacional
PCT/US 03/24934

6X

A. CLASIFICACION DEL ASUNTO RELACIONADO IPC 7 A61K 31/495, 31/50, 31/00 US CL 514/252.18, 629 De acuerdo con la Clasificación Internacional de Patentes (IPC) o tanto la clasificación nacional como la IPC.		
B. CAMPOS BUSCADOS Documentación mínima buscada (sistema de clasificación seguido por los símbolos de clasificación) U.S. : 514/252.18, 629 Documentación buscada diferente de la documentación mínima, al grado que estos documentos se incluyan en los campos buscados. Base de datos, electrónica, consultada durante la búsqueda internacional (nombre de la base de datos, donde se puede practicar, términos de búsqueda usados). Favor de ver hoja de continuación		
C. DOCUMENTOS QUE SE CONSIDERAN PERTINENTES		
Categoría*	Citación del documento, con indicación, donde es apropiado, de los pasajes pertinentes	Pertinente para la reivindicación No.
X	WO 01/45687 A2 (FABRE/KRAMER PHARMACEUTICALS, INC.) 28 Junio 2001 (28.06.2001), véase texto completo, especialmente página 11.	1-22
X	WO 02/16347 A1 (AKZO NOBEL N.V) 28 Febrero 2000 (28.02.2002) véase texto completo, especialmente páginas 6-7.	1-22
X,P	US 6,593,331 B2 (CAMBORDE et al) 15 Julio 2003 (15.07.2003), véase texto completo, especialmente columna 5-6.	1-22
☐ Documentos adicionales se listan en la continuación del cuadro C. ☐ Los miembros de la familia de patentes se listan en el anexo		
* Categorías especiales de los documentos citados: "A" Documento que define el estado general de la técnica, que no se considera que es de pertinencia particular "B" Documento anterior, pero publicado en o después de la fecha de presentación internacional "C" Documento que pueda crear dudas de la reivindicación(es) de prioridad o que se usa para establecer la fecha de publicación de otra situación o otra rama especial (como se especifica) "D" Documento que se refiere a una descripción oral, uso, exhibición u otro medio "E" Documento publicado antes de la fecha de presentación internacional, pero después de la fecha de prioridad reivindicada "F" Documento posterior publicado después de la fecha de presentación internacional o la fecha de prioridad, y que no provoca conflicto con la solicitud, pero se usa para entender el principio o teoría que trata la invención "G" Documento de pertinencia particular; la invención reivindicada no se puede considerar nueva o no se puede considerar que comprende un paso inventivo cuando el documento se toma solo "H" Documento de pertinencia particular; la invención reivindicada no se puede considerar que comprende un paso inventivo cuando el documento se considera con uno o más de estos documentos, estas excepciones son sobre para una persona experta en la técnica "I" Documento miembro de la familia de patentes		
Fecha de la actual terminación de la búsqueda internacional 15 Diciembre 2003 (15.12.2003)		Fecha de envío del reporte de búsqueda internacional 30 ABRIL 2004
Nombre y dirección de envío ISA/ Mail Stop PCT, Attn: ISA/US Comisionado para patentes P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230		Funcionario autorizado Marianne Seidel Teléfono No. 703-308-0196

REPORTE DE BUSQUEDA INTERNACIONAL

Información sobre los miembros de familia de patentes

Solicitud Internacional No.:

PCT/US 03/24934

68

Continuación de B. CAMPOS BUSCADOS Punto 3:

CAS ONLINE, CAPLUS, USPATFUL, REGISTRY, TOXCENTER

Estructura buscada y términos buscados: azapirona, trietil fosfito (agente reductor), hidroxiazapirona

PCT REQUEST

1/8

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69
CT-2748 PCT

D	For receiving Office use only	
D-1	International Application No.	
D-2	International Filing Date	
D-3	Name of receiving Office and "PCT International Application"	
D-4	Form - PCT/RO/101 PCT Request	
D-4-1	Prepared using	PCT-EASY Version 2.92 (updated 01.07.2003)
D-5	Petition The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty	
D-6	Receiving Office (specified by the applicant)	United States Patent and Trademark Office (USPTO) (RO/US)
D-7	Applicant's or agent's file reference	CT-2748 PCT
I	Title of invention	IMPROVED PROCESS FOR HYDROXYAZAPIRONES
II	Applicant	
II-1	This person is:	applicant only
II-2	Applicant for	all designated States except US
II-4	Name	BRISTOL-MYERS SQUIBB COMPANY
II-5	Address:	P. O. Box 4000 Route 206 and Provinceline Road Princeton, NJ 08543-4000 United States of America
II-6	State of nationality	US
II-7	State of residence	US
II-8	Telephone No.	609-252-4000
II-9	Facsimile No.	609-252-4526
III-1	Applicant and/or inventor	
III-1-1	This person is:	applicant and inventor
III-1-2	Applicant for	US only
III-1-4	Name (LAST, First)	DEPUE, Jeffrey
III-1-5	Address:	6 John Hancock Avenue Hillsborough, NJ 08844 United States of America
III-1-6	State of nationality	US
III-1-7	State of residence	US

III-2	Applicant and/or inventor	applicant and inventor US only KOTHIS, Atul, S. 16 Oxford Court Randall Park, NJ 08824 United States of America IN US
III-2-1	This person is:	
III-2-2	Applicant for	
III-2-4	Name (LAST, First)	
III-2-5	Address:	
III-2-6	State of nationality	
III-2-7	State of residence	
III-3	Applicant and/or inventor	applicant and inventor US only LEUNG, Simon 238 Vassar Drive Piscataway, NJ 08854 United States of America CN US
III-3-1	This person is:	
III-3-2	Applicant for	
III-3-4	Name (LAST, First)	
III-3-5	Address:	
III-3-6	State of nationality	
III-3-7	State of residence	
III-4	Applicant and/or inventor	applicant and inventor US only DOWDY, Eric, D. 25-01 Ravens Crest Drive Plainsboro, NJ 08536 United States of America US US
III-4-1	This person is:	
III-4-2	Applicant for	
III-4-4	Name (LAST, First)	
III-4-5	Address:	
III-4-6	State of nationality	
III-4-7	State of residence	
III-5	Applicant and/or inventor	applicant and inventor US only WATSON, Daniel, J. 105 Olympic Court #9 Princeton, NJ 08540 United States of America GB US
III-5-1	This person is:	
III-5-2	Applicant for	
III-5-4	Name (LAST, First)	
III-5-5	Address:	
III-5-6	State of nationality	
III-5-7	State of residence	

PCT REQUEST

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CT-2748 PCT

IV-1	Agent or common representative; or address for correspondence The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:	agent
IV-1-1	Name (LAST, First)	EPPERSON, James
IV-1-2	Address:	Bristol-Myers Squibb Company P.O. Box 4000 Princeton, NJ 08543-4000 United States of America
IV-1-3	Telephone No.	609-252-4000
IV-1-4	Facsimile No.	609-252-4526
IV-1-5	Agent's registration No.	52,867
IV-2	Additional agent(s)	additional agent(s) with same address as first named agent
IV-2-1	Name(s)	BABAJKO, Suzanne(32,880); BAXAM, Deanna(45,266); BELFIELD, Jing(45,914); BUCHHOLZ, Briana(39,123); D'AMICO, Stephen, C.(46,652); DAVIS, Stephen(26,693); DUNCAN, Laurelee(44,096); GIBBONS, Maureen(44,121); GOLIAN, Paul, D.(42,591); KLEIN, Christopher(34,363); LANGE, Keith(44,201); O'BRIEN, Maureen(42,043); PATEL, Rena(41,412); PEIST, Kenneth(45,006); PROVOST, Jonathan(44,292); RODNEY, Burton(22,076); SHKR, Audrey(39,024); ALGIERI, Aldo(31,697); DUBOFF, Samuel(25,969); MAKUJINA, Shah(41,174); RYAN, Richard(30,491); VANATTEN, Mary, K.(39,408); VOLLES, Warren, K.(33,810); BOGIE, Terence(44,544); LAMERDIN, John(44,858); KORSER, Elliott; DUNCAN, JR, Sammy(46,675); WINSLOW, Anastasia(40,875)

PCT REQUEST

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CT-2748 PCT

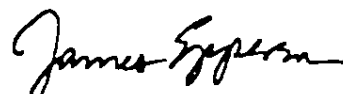
V	Designation of States	
V-1	Regional Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AP: GH GN KE LE MW NZ SD SL SZ TZ UG ZM ZW and any other State which is a Contracting State of the Harare Protocol and of the PCT EA: AM AZ BY KG KZ MD RU TJ TM and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT EP: AT BE BG CH&LI CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC ML PT RO SE SI SK TR and any other State which is a Contracting State of the European Patent Convention and of the PCT OA: BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG and any other State which is a member State of OAPI and a Contracting State of the PCT
V-2	National Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH&LI CN CO CR CU CE DE DK DM DZ EC EE ES FI GB GD GE GH GN HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW
V-3	Precautionary Designation Statement In addition to the designations made under items V-1, V-2 and V-3, the applicant also makes under Rule 4.9(b) all designations which would be permitted under the PCT except any designation(s) of the State(s) indicated under item V-4 below. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit.	
V-4	Exclusion(s) from precautionary designations	NONE
VI-1	Priority claim of earlier national application	
VI-1-1	Filing date	12 August 2002 (12.08.2002)
VI-1-2	Number	60/402,759
VI-1-3	Country	US

PCT REQUEST

5/8

Original (for SUBMISSION) - printed on 07.08.2003 11:00:08 AM

CT-2148 PCT

VI-2	Priority document request The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) identified above as item(s):	VI-1	
VB-1	International Searching Authority Chosen	United States Patent and Trademark Office (USPTO) (ISA/US)	
VII	Declarations	Number of declarations	
VII-1	Declaration as to the identity of the inventor	-	
VII-2	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	-	
VII-3	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	-	
VII-4	Declaration of inventorship (only for the purpose of the designation of the United States of America)	-	
VII-5	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	-	
IX	Check list	number of sheets	electronic file(s) attached
IX-1	Request (including declaration sheets)	6	-
IX-2	Description	12	-
IX-3	Claims	4	-
IX-4	Abstract	1	EZABST00.TXT
IX-5	Drawings	0	-
IX-7	TOTAL	23	
	Accompanying items	paper document(s) attached	electronic file(s) attached
IX-8	Fee calculation sheet	✓	-
IX-9	Original separate power of attorney	✓	-
IX-17	PCT-EASY diskette	-	Diskette
IX-18	Other (specified):	Certification	-
IX-19	Figure of the drawings which should accompany the abstract		
IX-20	Language of filing of the international application	English	
X-1	Signature of applicant, agent or common representative		
X-1-1	Name (LAST, First)	EPPERSON, James	

FOR RECEIVING OFFICE USE ONLY

10-1	Date of actual receipt of the purported international application	
10-2	Drawings:	
10-2-1	Received	
10-2-2	Not received	

PCT REQUEST

CT-2748 PCT

Original (for SUBMISSION) - printed on 07.08.2003 11:00:08 AM

10-3	Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application	
10-4	Date of timely receipt of the required corrections under PCT Article 11(2)	
10-5	International Searching Authority	ISA/US
10-6	Transmittal of search copy delayed until search fee is paid	

FOR INTERNATIONAL BUREAU USE ONLY

11-1	Date of receipt of the record copy by the International Bureau	
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PCT PETITORI

Original (para ADMISION)- Impreso 07.08.2003 11:00:08 AM

0	Para uso de la oficina receptora solamente	
0-1	Solicitud Internacional No.	
0-2	Fecha Internacional de registro	
0-3	Nombre de la oficina receptora y solicitud Internacional ante el PCT	

0-4	Petición ante el PCT forma-PCT/RO/101	
0-4-1	Preparada usando	PCT-EASY Versión 2.92 (actualizada 01.07.2003)
0-5	Petición El abajo firmante requiere que la presente solicitud Internacional sea procesada de acuerdo al Tratado Internacional en Materia de Patentes	
0-6	Oficina receptora (especificada por el solicitante)	Oficina de Patentes y Marcas de Estados Unidos (USPTO) (RO/US)
0-7	Clave de referencia del archivo del agente o solicitante	CT-2748 PCT
I	Título de la invención	PROCESO MEJORADO PARA HIDROXIAZAPIRONAS
II	Solicitante	
II-1	Esta persona es:	Solicitante solamente
II-2	Solicitante para	Todos los estados designados excepto US
II-4	Nombre	BRISTOL-MYERS SQUIBB COMPANY
II-5	Dirección	P.O. Box 4000 Route 206 and Provinceline Road Princeton, NJ 08543-4000 Estados Unidos de América
II-6	Estado de nacionalidad	US
II-7	Estado de residencia	US
II-8	Teléfono No.	609-252-4000
	Fax No.	609-252-4526
III-1	Solicitante y/o inventor	
III-1-1	Esta persona es:	Solicitante e inventor
III-1-2	Solicitante para:	US solamente
III-1-4	Nombre (ULTIMO, Primero)	DEPUE, Jeffrey
III-1-5	Dirección:	6 John Hancock Avenue Hillsborough, NJ 08844 Estados Unidos de América
III-1-6	Estado de nacionalidad	US
III-1-7	Estado de residencia	US

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II-2	Solicitante y/o Inventor	
III-2-1	Esta persona es:	Solicitante e Inventor
III-2-2	Solicitante para	US Solamente
III-2-4	Nombre (ULTIMO, Primero)	KOTNIS, Atul, S.
III-2-5	Dirección:	16 Oxford Court Kendall Park, NJ 08824 Estados Unidos de América
III-2-6	Estado de nacionalidad	IN
III-2-7	Estado de residencia	US
III-3	Solicitante y/o Inventor	
III-3-1	Esta persona es:	Solicitante e Inventor
III-3-2	Solicitante para	US Solamente
III-3-4	Nombre (ULTIMO, Primero)	LEUNG, Simon
III-3-5	Dirección:	238 Vasser Drive Piscataway, NJ 08854 Estados Unidos de América
III-3-6	Estado de nacionalidad	CN
III-3-7	Estado de residencia	US
III-4	Solicitante y/o Inventor	
III-4-1	Esta persona es:	Solicitante e Inventor
III-4-2	Solicitante para	US Solamente
III-4-4	Nombre (ULTIMO, Primero)	DOWDY, Eric, D.
III-4-5	Dirección:	25-01 Ravens Crest Drive Plainsboro, NJ 08536 Estados Unidos de América
III-4-6	Estado de nacionalidad	US
III-4-7	Estado de residencia	US
III-5	Solicitante y/o Inventor	
III-5-1	Esta persona es:	Solicitante e Inventor
III-5-2	Solicitante para	US Solamente
III-5-4	Nombre (ULTIMO, Primero)	WATSON, Daniel, J.
III-5-5	Dirección:	105 Olympic Court #9 Princeton, NJ 08540 Estados Unidos de América
III-5-6	Estado de nacionalidad	GB
III-5-7	Estado de residencia	US

PCT PETITORIO

Original (para ADMISSION)- Impreso 07.08.2003 11:30:08 AM

IV-1	Agente o representante común o dirección para correspondencia La persona identificada posteriormente es por su/ha sido apuntado para actuar en beneficio del(los) solicitante(s) ante las Autoridades Internacionales competentes como:	Agente EPPERSON, James Bristol-Myers Squibb Company P.O. Box 4000 Princeton, NJ 08543-4000 Estados Unidos de América
IV-1-1	Nombre:	609-252-4000
IV-1-2	Dirección:	609-252-4526
IV-1-3	Teléfono No:	
IV-1-4	Facsimil No.:	
IV-2	Agentes adicionales	Agentes adicionales con la misma dirección como el primer agente nombrado BABAJKO, Suzanne (32,880); BAXAM, Deanna (45,266); BELFIELD, Jing (45,914); BUCHHOLZ, Briana (39, 123); D'AMICO, Stephen, C. (46,652); DAVIS, Stephen (26,693); DUNCAN, Laurelee (44,096); GIBBONS, Maureen (44,121); GOLIAN, Paul, D. (42,591); KLEIN, Christopher (34,363); LANGE, Keith (44,201); O'BRIEN, Maureen (42,043); PATEL, Rena (41,412); PEIST, Kenneth (45,006); PROVOOST, Jonathan (44,292); RODNEY, Burton (22,076); SHER, Audrey (39,024); ALGIERI, Aldo (31,697); DUBOFF, Samuel (25,969); MAKUJINA, Shah (41,174); RYAN, Richard (30,491); VANATTEN, Mary, K. (39,408); VOLLES, Warren, K. (33,810); BOGIE, Terence (44,544); LAMERDIN, John (44,858); KORSEN, Elliot; DUNCAN, JR. Sammy (46,675); WINSLOW, Anastasia (40,875)
IV-2-1	Nombre:	

D 78

PCT PETITORIO

Original (para ADMISION)- Impreso 07.08.2003 11:59:08 AM

V	Estados designados	
V-1	Patente regional (otros tipos de protección o tratamiento, si existieran, están especificados entre paréntesis después de la designación(es) concernientes)	AP: GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW y cualquier otro Estado el cual es un Estado Contratante del Protocolo Harare y del PCT EA: AM AZ BY KG KZ MD RU TJ TM y cualquier otro Estado el cual es un Estado Contratante de la Convención de Patentes Euroasiática y del PCT EP: AT BE BG CH&LI CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL PT RO SE SI SK TR y cualquier otro Estado el cual es un Estado Contratante de la Convención de Patentes Europea y del PCT OA: BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG y cualquier otro Estado el cual es un Estado miembro de la OAPI y un Estado Contratante del PCT
V-2	Patente nacional (otros tipos de protección o tratamiento, si existieran, están especificados entre paréntesis después de la designación(es) concernientes)	AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH&LI CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW
V-3	Declaración De Designación Precautoria En adición a las designaciones hechas bajo los términos V-1, V-2 y V-3, el solicitante también hace bajo la regla 4.9(b) todas las designaciones del Estado(s) indicados bajo el artículo V-6 abajo. El solicitante declara que aquellas declaraciones adicionales están sujetas a confirmación y que cualquier designación que no sea confirmada antes de la expiración de 15 meses a partir de la fecha de prioridad se a ser considerada como retirada por el solicitante a la terminación de este tiempo límite.	
V-4	Exclusiones de las designaciones precautorias	NINGUNO
VI-1	Reivindicación prioritaria de la primera aplicación nacional	
VI-1-1	Fecha de presentación	12 Agosto 2002 (12.08.2002)
VI-1-2	Número	60/402,759
VI-1-3	País	US

PCT PETITORIO

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VI-2	Peticion de documento de prioridad La Oficina Receptora requiere para preparar y transmitir a la Oficina Internacional una copia certificada de la primera solicitud identificada anteriormente	VI-1	
VII-1	Autoridad de Búsqueda Internacional Seleccionada	Oficina de Patentes y Marcas de Estados Unidos (USPTO) (ISA/US)	
VIII	Declaraciones	Número de declaraciones	
VIII-1	Declaración como la identidad del inventor	-	
VIII-2	Declaración como el título de la solicitud, como a la fecha de presentación internacional, aplicar para ser otorgada una patente	-	
VIII-3	Declaración como el título de la solicitud, como la fecha de presentación internacional, a la reivindicación de la prioridad de la primera solicitud.	-	
VIII-4	Declaración del inventor (únicamente para la propuesta de la designación de los Estados Unidos de América)	-	
VIII-5	Declaración como descripción no perjudicial o excepciones carentes de novedad	-	
IX	Lista de verificación	Número de hojas	Archivos electrónicos relacionados
IX-1	Solicitud	6	-
IX-2	Descripción	12	-
IX-3	Reivindicaciones	4	-
IX-4	Resumen	1	EZABST00.TXT
IX-5	Dibujos	0	-
IX-7	TOTAL	23	
IX-8	Artículos anexos	Papel o documento(s) unidos	Campos electrónicos unidos
	Hoja de calculo de honorarios	√	-
IX-9	Original del poder separado del abogado	√	-
IX-17	Disco de PCT-EASY disquete	-	disquete
IX-18	Otro (especifique)	Certificación	
IX-19	Figura de dibujos los cuales serán acompañantes del resumen		
IX-20	Idioma de registro de la solicitud internacional	Inglés	
X-1	Firma del solicitante, agente o representante común	(rúbrica)	
X-1-1	Nombre:	EPPERSON, James	

PARA LA OFICINA RECEPTORA SOLAMENTE

10-1	Fecha de la recepción del contenido de la aplicación internacional	
10-2	Dibujos	
10-2-1	Recibidos	
10-2-2	No recibidos	

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10-3	Fecha corregida de la recepción actual debido a recepción última pero a tiempo de papeles o dibujos que completan el contenido de la aplicación internacional	
10-4	Fecha de la recepción a tiempo de las correcciones requeridas bajo el Artículo 11(2) del PCT	
10-5	Autoridad de Búsqueda Internacional	ISA/US
10-6	Transmisión de la copia de búsqueda retrasada hasta que los honorarios estén pagados	

PARA USO DE LA OFICINA INTERNACIONAL SOLAMENTE

11-1	Fecha de la recepción de la copia del documento por la Oficina Internacional	
------	--	--

CERTIFICATE OF MAILING

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being deposited with the United States Postal Service on the date shown below with sufficient postage as first class mail in an envelope addressed to the: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

James Epperson
Type or print name

James Epperson
Signature

August 6, 2004
Date

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

International Application No.: PCT/US03/24934
International Filing Date: August 7, 2003
Priority Date: August 12, 2002
Applicant: Bristol-Myers Squibb Company
For: Improved Process for Hydroxyazapirones
Authorized Officer: Nisa Gilchrist-Jones

MAIL STOP: PCT
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

**RESPONSE TO INVITATION TO CORRECT DEFECTS IN
THE INTERNATIONAL APPLICATION**

Sir:

In response to the Invitation to Correct Defects in the International Application letter of July 8, 2004 having a one month due date for reply, namely August 8, 2004, the following document is enclosed.

The Demand for the PCT International Application, PCT/US03/24934, filed on February 20, 2004 did not indicate all of the applicants/inventors for the elected States. All applicants/inventors indicated on the Request filed August 7, 2003 must also be indicated on the Demand.

This defect has been corrected by submitting the enclosed revised Demand document which indicates all of the names of the applicants/inventors for the elected States and their current home addresses (similar to the names of the applicants/inventors indicated in the Request document).

The home addresses for applicants/inventors Jeffrey Depue, Atul S. Kotnis and Simon Laung are the same addresses as indicated in the Request document of August 7, 2003.

The home addresses for applicants/inventors Eric D. Dowdy and Daniel J. Watson are new addresses from those indicated in the August 7, 2003 Request document.

The Demand Fee Calculation Sheet indicates a corrected Handling Fee (increase in PCT fees from Demand filed on February 20, 2004 from \$148 to \$162).

No fee is believed due for this Response to Invitation to Correct Defects in the International Application. However, in the event a fee is due it is requested that the payment be charged to Deposit Account 19-3880.

Respectfully submitted,

Bristol-Myers Squibb Company
Patent Department
P.O. Box 4000
Princeton, NJ 08543-4000
203-677-6974

Date: 8/6/2004

James Epperson
James Epperson
Agent for Applicants
Reg. No. 52,867

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The demand must be filed directly with the competent International Preliminary Examining Authority or, if two or more Authorities are competent, with the one chosen by the applicant. The full name or two-letter code of that Authority may be indicated by the applicant on the line below:

IPEA/ US

PCT

CHAPTER II

DEMAND

under Article 31 of the Patent Cooperation Treaty:

The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty.

For International Preliminary Examining Authority use only			
Identification of IPEA		Date of receipt of DEMAND	
Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION		Applicant's or agent's file reference CT-2748	
International application No. PCT/US03/24934	International filing date (day/month/year) 07 August 2003 (07-08-03)	(Earliest) Priority date (day/month/year) 12 August 2002 (12-08-02)	
Title of invention IMPROVED PROCESS FOR HYDROXYAZAPIRONES			
Box No. II APPLICANT(S)			
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of BRISTOL-MYERS SQUIBB COMPANY P.O. Box 4000 Princeton, New Jersey 08543-4000 United States of America		Telephone No. 609-252-3414	
		Facsimile No. 609-252-4528	
		Teleprinter No.	
		Applicant's registration No. with the Office	
State (that is, country) of nationality: US		State (that is, country) of residence: US	
Name and (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) DEPUE, Jeffrey 8 John Hancock Avenue Hillaborough, New Jersey 08844 United States of America			
State (that is, country) of nationality: US		State (that is, country) of residence: US	
Name and (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) KOTNIS, Atul S. 18 Oxford Court Kendall Park, New Jersey 08824 United States of America			
State (that is, country) of nationality: India		State (that is, country) of residence: US	
☒ Further applicants are indicated on a continuation sheet.			

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Sheet No. 2.

International application No.

PCT/US03/24834

Continuation of Box No. II APPLICANT(S)

If none of the following sub-boxes is used, this sheet should not be included in the demand.

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

LEUNG, Simon
238 Vasser Drive
Piscataway, New Jersey 08854
United States of America

State (that is, country) of nationality:

China

State (that is, country) of residence:

US

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

DOWDY, Eric D.
1151 Compass Lane #203
Foster City, California 94404
United States of America

State (that is, country) of nationality:

US

State (that is, country) of residence:

US

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

WATSON, Daniel J.
1205 Deer Creek Drive
Plainsboro, New Jersey 08538
United States of America

State (that is, country) of nationality:

Great Britain

State (that is, country) of residence:

US

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

State (that is, country) of nationality:

State (that is, country) of residence:

☐

Further applicants are indicated on another continuation sheet.

Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The following person is ☒ agent ☐ common representative
and ☒ has been appointed earlier and represents the applicant(s) also for international preliminary examination.
☐ is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.
☐ is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

EPPEPERSON, James
Bristol-Myers Squibb Company
P.O. Box 4000
Princeton, New Jersey 08543-4000
United States of America

Telephone No.
203-677-6974

Facsimile No.
203-677-6900

Teleprinter No.

Agent's registration No. with the Office
52,867

☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION

Statement concerning amendments:*

1. The applicant wishes the international preliminary examination to start on the basis of:

- ☒ the international application as originally filed
the description ☐ as originally filed
☐ as amended under Article 34
the claims ☐ as originally filed
☐ as amended under Article 19 (together with any accompanying statement)
☐ as amended under Article 34
the drawings ☐ as originally filed
☐ as amended under Article 34

2. ☐ The applicant wishes any amendment to the claims under Article 19 to be considered as reversed.
3. ☐ The applicant wishes the start of the international preliminary examination to be postponed until the expiration of the applicable time limit under Rule 69.1(d).
4. ☐ The applicant expressly wishes the international preliminary examination to start earlier than at the expiration of the applicable time limit under Rule 54bis.1(a).

* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Language for the purposes of international preliminary examination: English

- ☒ which is the language in which the international application was filed.
☒ which is the language of a translation furnished for the purposes of international search.
☒ which is the language of publication of the international application.
☒ which is the language of the translation (to be) furnished for the purposes of international preliminary examination.

Box No. V ELECTION OF STATES

The filing of this demand constitutes the election of all Contracting States which are designated and are bound by Chapter II of the PCT.

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Sheet No. 4.

International application No.
PCT/US03/24934

Box No. VI CHECK LIST

The demand is accompanied by the following elements, in the language referred to in Box No. IV, for the purposes of international preliminary examination:

- | | | |
|--|---|--------|
| 1. translation of international application | : | sheets |
| 2. amendments under Article 34 | : | sheets |
| 3. copy (or, where required, translation) of amendments under Article 19 | : | sheets |
| 4. copy (or, where required, translation) of statement under Article 19 | : | sheets |
| 5. letter | : | sheets |
| 6. other (specify) | : | sheets |

For International Preliminary Examining Authority use only
received not received

☐	☐
☐	☐
☐	☐
☐	☐
☐	☐
☐	☐

The demand is also accompanied by the item(s) marked below:

- | | |
|--|--|
| 1. ☒ fee calculation sheet | 5. ☐ statement explaining lack of signature |
| 2. ☐ original separate power of attorney | 6. ☐ sequence listing in computer readable form |
| 3. ☐ original general power of attorney | 7. ☐ tables in computer readable form related to sequence listing |
| 4. ☐ copy of general power of attorney; reference number, if any. | 8. ☐ other (specify): |

Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).

 Agent
James Epperson

For International Preliminary Examining Authority use only

1. Date of actual receipt of DEMAND:

2. Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b):

3. ☐ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply.
☐ The applicant has been informed accordingly.
4. ☐ The date of receipt of the demand is WITHIN the time limit of 19 months from the priority date as extended by virtue of Rule 80.5.
5. ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82.

6. ☐ The date of receipt of the demand is AFTER the expiration of the time limit under Rule 54bis.1(a) and item 7 or 8, below, does not apply.
7. ☐ The date of receipt of the demand is WITHIN the time limit under Rule 54bis.1(a) as extended by virtue of Rule 80.5.
8. ☐ Although the date of receipt of the demand is after the expiration of the time limit under Rule 54bis.1(a), the delay in arrival is EXCUSED pursuant to Rule 82.

For International Bureau use only

Demand received from IPEA on:

87 9 28

CHAPTER II

PCT

FEE CALCULATION SHEET

Annex to the Demand

International application No. PCT/US03/24934		For International Preliminary Examining Authority use only	
Applicant's or agent's file reference CT-2748		Date stamp of the IPEA	
Applicant BRISTOL-MYERS SQUIBB COMPANY			
CALCULATION OF PRESCRIBED FEES			
1. Preliminary examination fee		600.00	P
2. Handling fee (<i>Applicants from certain States are entitled to a reduction of 75% of the handling fee. Where the applicant is (or all applicants are) so entitled, the amount to be entered at H is 25% of the handling fee.</i>)		162.00	H
3. Total of prescribed fees Add the amounts entered at P and H and enter total in the TOTAL box		762.00	
		TOTAL	
MODE OF PAYMENT			
☒ authorization to charge deposit account with the IPEA (see below)	☐ cash		
☐ cheque	☐ revenue stamps		
☐ postal money order	☐ coupons		
☐ bank draft	☐ other (specify):		
AUTHORIZATION TO CHARGE (OR CREDIT) DEPOSIT ACCOUNT (This mode of payment may not be available at all IPEAs)			
		IPEA/ US	
☒ Authorization to charge the total fees indicated above.	Deposit Account No.: 19-3880		
☒ (This check-box may be marked only if the conditions for deposit accounts of the IPEA so permit) Authorization to charge any deficiency or credit any overpayment in the total fees indicated above.	Date: August 8, 2004		
		Name: James Epperson	
		Signature: James Epperson	

TRANSMITTAL LETTER TO THE UNITED STATES RECEIVING OFFICE

PTO-1382 (Rev. 04-2003) (Modified)

PCTUS2.FRP /REV03

Date	20-02-04
International Application No.	PCT/US03/24934
Attorney Docket No.	CT-2748

I. Certification under 37 CFR 1.10 (If applicable)

EV 404518685 US
Express Mail mailing number

20-02-04
Date of Deposit

I hereby certify that the application/correspondence attached hereto 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 Mail Stop PCT, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.


Signature of person mailing correspondence

James Epperson
Typed or printed name of person mailing correspondence

II. ☐ New International Application

TITLE	
-------	--

Earliest priority date (Day/Month/Year)

SCREENING DISCLOSURE INFORMATION: In order to assist in screening the accompanying international application for purposes of determining whether a license for foreign transmittal should and could be granted and for other purposes, the following information is supplied. (Note: check as many boxes as apply):

- A. ☐ The invention disclosed was not made in the United States.
- B. ☐ There is no prior U.S. application relating to this invention.
- C. ☐ The following prior U.S. application(s) contain subject matter which is related to the invention disclosed in the attached international application. (NOTE: priority to these applications may or may not be claimed on form PCT/RO/101 (Request) and this listing does not constitute a claim for priority).

application no.		filed on	
application no.		filed on	

- D. ☐ The present international application contains additional subject matter not found in the prior U.S. application(s) identified in paragraph C. above. The additional subject matter is found on pages and ☐ DOES NOT ALTER ☐ MIGHT BE CONSIDERED TO ALTER the general nature of the invention in a manner which would require the U.S. application to have been made available for inspection by the appropriate defense agencies under 35 U.S.C. 181 and 37 CFR 5.1. See 37 CFR 5.15.

III. ☐ A Response to an Invitation from the RO/US. The following document(s) is (are) enclosed:

- A. ☐ A Request for An Extension of Time to File a Response
- B. ☐ A Power of Attorney (General or Regular)
- C. ☐ Replacement pages:

pages		of the request (PCT/RO/101)	pages		of the figures
pages		of the description	pages		of the abstract
pages		of the claims			

- D. ☐ Submission of Priority Documents

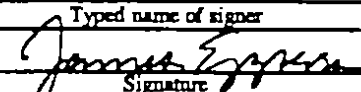
Priority document		Priority document	
-------------------	--	-------------------	--

- E. ☐ Fees as specified on attached Fee Calculation sheet form PCT/RO/101 annex

IV. ☐ A Request for Rectification under PCT 91 ☐ A Petition ☐ A Sequence Listing Diskette

- V. ☒ Other (please specify): PCT Demand for International Preliminary Examination;
PCT Demand Fee Calculation Sheet

The person
signing this
form is the:

☐ Applicant	James Epperson
☒ Attorney/Agent (Reg. No.) 52,887	Typed name of signer
☐ Common Representative	 Signature

U.S. Department of Commerce: Patent and Trademark Office

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The demand must be filed directly with the competent International Preliminary Examining Authority or, if two or more Authorities are competent, with the one chosen by the applicant. The full name or two-letter code of that Authority may be indicated by the applicant on the line below.

IPEA/ US

PCT

CHAPTER II

DEMAND

under Article 31 of the Patent Cooperation Treaty:

The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty.

For International Preliminary Examining Authority use only			
Identification of IPEA		Date of receipt of DEMAND	
Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION		Applicant's or agent's file reference CT-2748	
International application No. PCT/US03/24834	International filing date (day/month/year) 07 August 2003 (07-08-03)	(Earliest) Priority date (day/month/year) 12 August 2002 (12-08-02)	
Title of invention IMPROVED PROCESS FOR HYDROXYAZAPIRONES			
Box No. II APPLICANT(S)			
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of BRISTOL-MYERS SQUIBB COMPANY P.O. Box 4000 Princeton, New Jersey 08543-4000 United States of America		Telephone No. 609-252-3414	
		Facsimile No. 609-252-4528	
		Teleprinter No.	
		Applicant's registration No. with the Office	
State (that is, country) of nationality: US		State (that is, country) of residence: US	
Name and (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)			
State (that is, country) of nationality:		State (that is, country) of residence:	
Name and (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)			
State (that is, country) of nationality:		State (that is, country) of residence:	
☐ Further applicants are indicated on a continuation sheet.			

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2**Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE**The following person is ☒ agent ☐ common representativeand ☒ has been appointed earlier and represents the applicant(s) also for international preliminary examination.☐ is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.☐ is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

EPPERSON, James
Bristol-Myers Squibb Company
P.O. Box 4000
Princeton, New Jersey 08543-4000
United States of America

Telephone No.

203-677-6874

Facsimile No.

203-677-6900

Teleprinter No.

Agent's registration No. with the Office

52,867

☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.**Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION****Statement concerning amendments:***

1. The applicant wishes the international preliminary examination to start on the basis of:

☒ the international application as originally filedthe description ☐ as originally filed☐ as amended under Article 34the claims ☐ as originally filed☐ as amended under Article 19 (together with any accompanying statement)☐ as amended under Article 34the drawings ☐ as originally filed☐ as amended under Article 342. ☐ The applicant wishes any amendment to the claims under Article 19 to be considered as reversed.3. ☐ The applicant wishes the start of the international preliminary examination to be postponed until the expiration of the applicable time limit under Rule 69.1(d)).4. ☐ The applicant expressly wishes the international preliminary examination to start earlier than at the expiration of the applicable time limit under Rule 54bis.1(a).

* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Language for the purposes of international preliminary examination: English☒ which is the language in which the international application was filed.☒ which is the language of a translation furnished for the purposes of international search.☒ which is the language of publication of the international application.☒ which is the language of the translation (to be) furnished for the purposes of international preliminary examination.**Box No. V ELECTION OF STATES**

The filing of this demand constitutes the election of all Contracting States which are designated and are bound by Chapter II of the PCT.

Box No. VI CHECK LIST

The demand is accompanied by the following elements, in the language referred to in Box No. IV, for the purposes of international preliminary examination:

- | | | |
|--|---|--------|
| 1. translation of international application | : | sheets |
| 2. amendments under Article 34 | : | sheets |
| 3. copy (or, where required, translation) of amendments under Article 19 | : | sheets |
| 4. copy (or, where required, translation) of statement under Article 19 | : | sheets |
| 5. letter | : | sheets |
| 6. other (specify) | : | sheets |

For International Preliminary Examining Authority use only

received not received

☐	☐
☐	☐
☐	☐
☐	☐
☐	☐
☐	☐

The demand is also accompanied by the item(s) marked below:

- | | |
|--|--|
| 1. ☒ fee calculation sheet | 5. ☐ statement explaining lack of signature |
| 2. ☐ original separate power of attorney | 6. ☐ sequence listing in computer readable form |
| 3. ☐ original general power of attorney | 7. ☐ tables in computer readable form related to sequence listing |
| 4. ☐ copy of general power of attorney, reference number, if any. | 8. ☐ other (specify): |

Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).

 Agent
James Epperson

For International Preliminary Examining Authority use only

1. Date of actual receipt of DEMAND:

2. Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b):

3. ☐ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply.

☐ The applicant has been informed accordingly.

4. ☐ The date of receipt of the demand is WITHIN the time limit of 19 months from the priority date as extended by virtue of Rule 80.5.

5. ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82.

6. ☐ The date of receipt of the demand is AFTER the expiration of the time limit under Rule 54bis.1(a) and item 7 or 8, below, does not apply.

7. ☐ The date of receipt of the demand is WITHIN the time limit under Rule 54bis.1(a) as extended by virtue of Rule 80.5.

8. ☐ Although the date of receipt of the demand is after the expiration of the time limit under Rule 54bis.1(a), the delay in arrival is EXCUSED pursuant to Rule 82.

For International Bureau use only

Demand received from IPEA on:

PCT

FEE CALCULATION SHEET

Annex to the Demand

CHAPTER H

International application No. PCT/US03/24934 Applicant's or agent's file reference CT-2748	For International Preliminary Examining Authority use only Date stamp of the IPEA								
Applicant BRISTOL-MYERS SQUIBB COMPANY									
CALCULATION OF PRESCRIBED FEES 1. Preliminary examination fee 600.00 P 2. Handling fee (Applicants from certain States are entitled to a reduction of 75% of the handling fee. Where the applicant is (or all applicants are) so entitled, the amount to be entered at H is 25% of the handling fee.) 148.00 H 3. Total of prescribed fees Add the amounts entered at P and H and enter total in the TOTAL box <table border="1" style="margin-left: auto; margin-right: auto;"> <tr> <td style="text-align: center;">748.00</td> </tr> <tr> <td style="text-align: center;">TOTAL</td> </tr> </table>		748.00	TOTAL						
748.00									
TOTAL									
MODE OF PAYMENT <table style="width: 100%;"> <tr> <td>☒ authorization to charge deposit account with the IPEA (see below)</td> <td>☐ cash</td> </tr> <tr> <td>☐ cheque</td> <td>☐ revenue stamps</td> </tr> <tr> <td>☐ postal money order</td> <td>☐ coupons</td> </tr> <tr> <td>☐ bank draft</td> <td>☐ other (specify):</td> </tr> </table>		☒ authorization to charge deposit account with the IPEA (see below)	☐ cash	☐ cheque	☐ revenue stamps	☐ postal money order	☐ coupons	☐ bank draft	☐ other (specify):
☒ authorization to charge deposit account with the IPEA (see below)	☐ cash								
☐ cheque	☐ revenue stamps								
☐ postal money order	☐ coupons								
☐ bank draft	☐ other (specify):								
AUTHORIZATION TO CHARGE (OR CREDIT) DEPOSIT ACCOUNT (This mode of payment may not be available at all IPEAs) ☒ Authorization to charge the total fees indicated above. ☒ (This check-box may be marked only if the conditions for deposit accounts of the IPEA so permit) Authorization to charge any deficiency or credit any overpayment in the total fees indicated above. IPEA/ <u>US</u> Deposit Account No.: <u>19-3880</u> Date: <u>February 20, 2004</u> Name: <u>James Epperson</u> Signature: <u>James Epperson</u>									

PATENT COOPERATION TREATY

From the RECEIVING OFFICE

To:

JAMES EPPERSON
BRISTOL-MYERS SQUIBB COMPANY
P.O. BOX 4000
PRINCETON, NEW JERSEY 08543-4000

FAXED
9/30/03

Date of mailing

PCT

Invitation

INVITATION TO CORRECT DEFECTS IN
THE INTERNATIONAL APPLICATION

(PCT Articles 3(4)(I) and 14(1) and Rule 26)

Date of mailing (day/month/year)	19 Sep 2003
Applicant's or agent's file reference	CT-2748 PCT
REPLY DUE	within 1 month/days from the above date of mailing
International application No.	PCT/US03/24834
International filing date (day/month/year)	07 Aug 2003
Applicant BRISTOL-MYERS SQUIBB COMPANY	

1. ☐ The applicant is hereby invited, within the time limit indicated above, to correct, in the international application as filed, the defects specified on the attached:
- ☒ Annex A
- ☐ Annex B1 (text matter of the international application as filed)
- ☐ Annex C1 (drawings of the international application as filed)
2. ☐ The applicant is hereby invited, within the time limit indicated above, to correct, in the translation of the international application furnished under Rule 12.3 or 12.4, the defects specified on the attached:
- ☐ Annex A
- ☐ Annex B2 (text matter of the translation of the international application)
- ☐ Annex C2 (drawings of the translation of the international application)

Additional observations (if necessary):

HOW TO CORRECT THE DEFECTS?

Correction must be submitted by filing a replacement sheet embodying the correction and a letter accompanying the replacement sheet, which shall draw attention to the difference between the replaced sheet and the replacement sheet. A correction may be stated in a letter only if it is of such a nature that it can be transferred from the letter to the record copy without adversely affecting the clarity and direct reproducibility of the sheet onto which the correction is to be transferred (Rule 26.4).

ATTENTION

Failure to correct the defects will result in the international application being considered withdrawn by this receiving Office (see Rule 26.5 for further details).

A copy of this invitation and any attachments has been sent to the International Bureau

☒ and the International Searching Authority

Name and mailing address of the receiving Office	Authorized officer
Mail Stop PCT, Consulate-General for Patents P.O. Box 1450, Alexandria, VA 22313-1450	Mark Hogarth
Facsimile No. 703-305-1250	Telephone No. 703-305-3749

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ANNEX A TO FORM PCT/RO/106

International application No.

PCT/US03/24834

The receiving Office has found the following defects in the international application as filed:

1. As to signature* of the international application (Rules 4.15 and 90.4), the request:
 - a. ☐ is not signed
 - b. ☐ is not signed by all the applicants
 - c. ☐ is not accompanied by the statement referred to in the check list in Box No. VIII of the request explaining the lack of the signatures of an applicant for the designation of the United States of America
 - d. ☒ is signed by what appears to be an agent/consular representative but
 - ☐ the international application is not accompanied by a power of attorney appointing him
 - ☒ the power of attorney accompanying the international application was not signed by all the applicants
 - e. ☐ other (specify):

* All applicants must sign, including inventors if they are also applicants (e.g., where the United States of America is designated).

2. As to indications concerning the applicant, the request (Rules 4.4 and 4.5):

- a. ☐ does not properly indicate the applicant's name (specify):
- b. ☐ does not indicate the applicant's address
- c. ☐ does not properly indicate the applicant's address (specify):
- d. ☐ does not indicate the applicant's nationality
- e. ☐ does not indicate the applicant's residence
- f. ☐ other (specify):

3. As to the language of certain elements of the international application, other than the description and claims (Rules 12.1(e) and 26.3(a)(i) and (c)):

- a. ☐ the request is not in a language of publication accepted by this receiving Office; (the) language(s) accepted by this receiving Office is/are:
- b. ☐ the text matter of the drawings is not in the language in which the international application is to be published, which is:
- c. ☐ the abstract is not in the language in which the international application is to be published, which is:

4. The title of the invention:

- a. ☐ is not indicated in Box No. I of the request (Rule 4.1(n))
- b. ☐ is not indicated at the top of the first sheet of the description (Rule 5.1(n))
- c. ☐ as appearing in Box No. I of the request is not identical with the title heading the description (Rule 5.1(n))

5. As to the abstract (Rule 8):

- ☐ the international application does not contain an abstract

JMS PATENT FLOW

9/10 SEP 25 2003

PATENT COOPERATION TREATY

From the RECEIVING OFFICE

Docketed Item

Due Date

PCT Attorney

To:

JAMES EPPERSON
BRISTOL-MYERS SQUIBB COMPANY
P.O. BOX 4000
PRINCETON, NEW JERSEY 08543-4000

NOTIFICATION CONCERNING PAYMENT
OF PRESCRIBED FEES

(PCT Rules 14, 15 and 16 and Administrative
Instructions, Sections 102bis(c), 304(a) and (b),
323(b), 707(b) and 803)

Date of mailing (day/month/year) 19 Sep 2003

Applicant's or agent's file reference

CT-3748 PCT

PAYMENT DUE

see item 3 for time limits

International application No.

PCT/US03/24834

International filing date/Data of receipt (day/month/year)

07 Aug 2003

Priority date (day/month/year)

12 Aug 2002

Applicant

BRISTOL-MYERS SQUIBB COMPANY

1. The applicant is hereby notified that this receiving Office has received:

- ☒ the payment of all the prescribed fees, and ☐ an overpayment, which will be refunded in due course.
☐ no or insufficient payment of the prescribed fees and the applicant is hereby invited to pay the balance due, as summarized under item 2, within the time limit(s) indicated under item 3.

2. Fee and payment calculations:

1,808.00	-	1,808.00	=	0.00
Total fees payable		Amount paid		Balance

- ☐ The details of the calculation are given in the Annex.

3. Time limit(s) for payment and amount(s) payable (Rules 14.1, 15.4 and 16.1(III)):

- ☐ within ONE MONTH from the date of receipt of the international application (for the transmittal fee (if any), the search fee, the basic fee and the designation fee). The amount payable for each fee is the amount applicable on the date of receipt of the international application.
- ☐ within ONE YEAR from the priority date (only for the designation fee and only if this time limit expires later than the above time limit).
- If the designation fee is paid within one month from the date of receipt of the international application, the amount payable is the amount applicable on that date of receipt.
- If the designation fee is paid within one year from the priority date but later than one month from the date of receipt of the international application, the amount payable is the amount applicable on the date of payment. The receiving Office should be consulted for the applicable amount.
- ☐ within 16 MONTHS from the priority date (only for the fee for priority documents). The applicant's attention is drawn to the fact that the request made by the applicant under Rule 17.1(b) will be considered not to have been made unless the fee is paid within that time limit.

4. Additional observations (if necessary):

- ☐ The search copy will not be transmitted to the International Searching Authority until the search fee is paid (therefore the start of the international search will be delayed) (Rule 23.1(a) and (b)).

Name and mailing address of the receiving Office

Mail Stop PCT, Commissioner for Patents
P.O. Box 1450, Alexandria, VA 22313-1450

Facsimile No. 703-305-3230

Authorized officer

Mark Hogarth

Telephone No. 703-305-3749

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XANNEX TO FORM PCT/RO/102
CALCULATION OF THE PRESCRIBED FEESInternational application No.
PCT/US03/24934

T Transmittal Fee			
Prescribed amount:	240.00	☒ T	
Amount paid:	240.00		☐ correct amount
Balance:	0.00		☐ overpayment
			☐ balance due
S Search Fee			
Prescribed amount:	700.00	☒ S	
Amount paid:	700.00		☐ correct amount
Balance:	0.00		☐ overpayment
			☐ balance due
I International Fee			
B Basic Fee			
Fixed amount for first 30 sheets	328.00	☒ b1	
$\frac{0}{\text{Number of sheets in excess of 30}} \times \frac{12.00}{\text{Fee per sheet}} =$	0.00	☒ b2	
Additional component: $400 \times \frac{0.00}{\text{Fee per sheet}} =$	0.00	☒ b3	
Prescribed amount (b1 + b2 + b3) =	328.00	☒ B	
D Designation Fee			
Amount of designation fee:	104.00		
Number of designation fees payable (maximum 5):	5		
Prescribed amount =	520.00	☒ D	
R Reduction where PCT-EASY software is used or where the international application is filed in electronic form (See the PCT Applicant's Guide, Volume I, General Part, for details on the availability of this reduction):			
	0.00	☒ R	
Sub-total (B+D-R):	848.00	☒ B+D-R	
Prescribed total amount (The amount to be entered at I is the sub-total entered at (B+D-R), except where the applicant is for all applicants are entitled to a reduction of 75%, in which case the amount to be entered at I is 25% of the sub-total (B+D-R); certain applicants from certain States are entitled to a reduction of 75% of the international fee; see Notes to the Fee Calculation Sheet as annexed to the Request Form, PCT/RO/101, for details):		848.00	☒ I
Amount paid:	848.00		☐ correct amount
Balance:	0.00		☐ overpayment
			☐ balance due
P Fee for priority document			
Prescribed amount:	20.00	☒ P	
Amount paid:	20.00		☐ correct amount
Balance:	0.00		☐ overpayment
			☐ balance due
Additional observations (if necessary):			
☐ The amount paid for the designation fee covers the following designations: _____			
☐ Other (specify): _____			

SEP 25 2003

PATENT COOPERATION TREATY **Noted Item**

From the RECEIVING OFFICE

Due Date**Agency**

To:

JAMES EPPERSON
BRISTOL-MYERS SQUIBB COMPANY
P.O. BOX 4000
PRINCETON, NEW JERSEY 08543-4000NOTIFICATION OF THE INTERNATIONAL
APPLICATION NUMBER AND OF THE
INTERNATIONAL FILING DATE

(PCT Rule 20.5(c))

Date of mailing
(day/month/year)

18 Sep 2003

Applicant's or agent's file reference

CT-2741 PCT

IMPORTANT NOTIFICATION

International application No.

PCT/US03/24934

International filing date (day/month/year)

07 Aug 2003

Priority date (day/month/year)

12 Aug 2002

Applicant

BRISTOL-MYERS SQUIBB COMPANY

Title of the invention

IMPROVED PROCESS FOR HYDROXYAZAPRONES

1. The applicant is hereby notified that the international application has been accepted the international application number and the international filing date indicated above.

2. The applicant is further notified that the record copy of the international application:



was transmitted to the International Bureau on

18 Sep 2003



has not yet been transmitted to the International Bureau for the reason indicated below and a copy of this notification has been sent to the International Bureau:



because the necessary national security clearance has not yet been obtained.



because of reasons in respect of:

* The International Bureau monitors the transmission of the record copy by the receiving Office and will notify the applicant (with Form PCT/IB/301) of the receipt. Should the record copy not have been received by the expiration of 14 months from the priority date, the International Bureau will notify the applicant (Rule 22.1(c)).

3. FOREIGN TRANSMITTAL LICENSE INFORMATION

Completed by: MH



Additional license for foreign transmittal not required. This subject matter is covered by a license already granted or the equivalent U.S. national application. Refer to that license for information concerning its scope.



License for foreign transmittal not required. 37 CFR 5.11(e)(1) or 37 CFR 5.11(e)(2). However, a license may be required for additional subject matter. See 37 CFR 5.15(b).



Foreign transmittal license granted. 35 U.S.C. 184; 37 CFR 5.11 on

08 Sep 2003

(date)



37 CFR 5.15(a)



37 CFR 5.15(b)

Name and mailing address of the receiving Office

Mail Stop PCT, Commissioner for Patents
P.O. Box 1450, Alexandria, VA 22313-1450

Facsimile No. 703-305-3230

Authorized officer

Mark Hogarth

Telephone No. 703-305-3748

BRIEFS PATENT OFFICE

SEP 25 2003

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

Docketed Item _____

PCT
Attorney _____NOTIFICATION OF RECEIPT
OF SEARCH COPY

(PCT Rule 25.1)

To: JAMES EPPERSON BRISTOL-MYERS SQUIBB COMPANY P.O. BOX 4000 PRINCETON, NEW JERSEY 08543-4000
--

Date of mailing
(day/month/year)

19 Sep 2003

Applicant's or agent's file reference

CT-8748 PCT

IMPORTANT NOTIFICATION

International application No.

PCT/US03/24834

International filing date (day/month/year)

07 Aug. 2003

Priority date (day/month/year)

12 Aug 2002

Applicant

BRISTOL-MYERS SQUIBB COMPANY

1. Where the International Searching Authority and the receiving Office are not the same Office:

The applicant is hereby notified that the search copy of the international application was received by this International Searching Authority on the date indicated below.

Where the International Searching Authority and the receiving Office are the same Office:

The applicant is hereby notified that the search copy of the international application was received on the date indicated below.

19 Sep 2003

(Date of receipt)

2. ☐ The search copy was accompanied by a nucleotide and/or amino acid sequence listing in computer-readable form.

3. Time limit for establishment of international search report

The applicant is informed that the time limit for establishing the international search report is 3 months from the date of receipt indicated above or 9 months from the priority date, whichever time limit expires later.

4. A copy of this notification has been sent to the International Bureau and, where the first sentence of paragraph 1 applies, to the receiving Office.

Name and mailing address of the ISA/
Mail Stop PCT, Commissioner for Patents
P.O. Box 1450, Alexandria, VA 22313-1450
Facsimile No. 703-305-3220

Authorized officer
Mark Hogarth
Telephone No. 703-385-3749

TO: JAMES EPPERSON BRISTOL-MYERS SQUIBB COMPANY P.O. BOX 4000 PRINCETON, NEW JERSEY 08543-4000		UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) NOTIFICATION OF STATUS OF REQUIREMENTS UNDER 35 U.S.C. 371	
		DATE OF MAILING (day/month/year) 19 Sep 2003	
		FILE REFERENCE CT-2748 PCT	
IDENTIFICATION OF INTERNATIONAL APPLICATION			
International application No. PCT/US03/24934		International filing date (day/month/year) 07 Aug 2003	
		Priority Date Claimed 12 Aug 2002	
Applicant for DO/EO/US DEPUE, JEFFREY			
NOTIFICATION			
The applicant is hereby advised that the U.S. Patent and Trademark Office in its capacity as ☒ Designated Office ☐ Elected Office has received following items as of the date of mailing indicated above.			
1. ☐ U.S. Nation fee [35 U.S.C 371 (c) (1)] 2. ☐ Oath of declaration [35 U.S.C 371 (c) (4)] 3. ☒ Copy of International application as [35 U.S.C 371 (c) (2)] 4. ☐ Translation of Application [35 U.S.C 371 (c) (2)] 5. ☐ Amendments under PCT Article 19 [35 U.S.C 371 (c) (3)] 6. ☐ Translation of PCT Article 19 Amendments [35 U.S.C 371 (c) (3)] 7. ☐ Search Report or Declaration under PCT Article 17(2) [35 U.S.C 371 (a)] 8. ☐ International Preliminary Examination Report and its Annexes, if any, under PCT Article 36(3)(b) [35 U.S.C 371 (a)] 9. ☐ Translation of Annex to the International Preliminary Examination Report under PCT Article 36(3)(b) [35 U.S.C 371 (c) (5)] 10. ☐ Other items received: ☐ Assignment Document ☐ Prior Art Statement ☐ Preliminary Amendment			
A. ☐ Requirements for U.S. National processing have been met. Processing will commence ☐ at the expiration of the applicable time limit under either ☐ PCT Article 22 [35 U.S.C 371 (b)] or ☐ PCT Article 39 [35 U.S.C 371 (b)] ☐ on the date indicated below under the provisions of 35 U.S.C 371 (d)			
U.S. NATIONAL SERIAL#		DATE UNDER 35 U.S.C. 102(a)	
		DATE OF COMMENCEMENT OF NATIONAL PROCESSING	
All correspondence submitted after the date of commencement of U.S. National processing indicated above should refer to the U.S. National Serial Number and the appropriate U.S. National processing organization of Officer.			
B. ☐ As the above identified application has been accepted for U.S. National processing under the provision of 35 U.S.C. 371 (f) before expiration of the applicable time limit under ☐ PCT Article 22 ☐ PCT Article 39, applicant is reminded that ☐ Amendments under PCT Article 19 and/or ☐ the International Preliminary Examination Report and its Annexes, if any, under PCT Article 36(3) (a), and (b) and any translation thereof, if applicable, must be submitted to the Patent and Trademark Office as soon as they are available.			

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International application No. PCT/US03/24934	International filing date 07 Aug 2003	Priority Date Claimed 12 Aug 2002
---	--	--------------------------------------

- C. ☒ In order that U.S. National processing may begin, certain items must be received by the DO/EO/US by the expiration of applicable time limit under
- ☒ PCT Article 22 or
 - ☒ PCT Article 39.
- Specifically:
- ☒ 1. U.S. National Fee
 - ☒ 2. Oath or Declaration
 - ☐ 3. Copy of Application
 - ☐ 4. Translation of application
 - ☒ 5. Amendments under PCT Article 19, if any
 - ☐ 6. Translation of PCT Article 19 Amendments, if applicable
 - ☐ 7. Search Report or PCT Article 17(2) declaration
 - ☐ 8. International Preliminary Examination Report and its Annexes, if any, under PCT Article 36(3)(a), if applicable
 - ☐ 9. Translation of Annexes to the International Preliminary Examination Report under PCT Article 36(3)(b), if applicable

THE ABOVE CHECK ITEMS MUST BE TIMELY RECEIVED TO AVOID ABANDONMENT OF THE APPLICATION.
[35 U.S.C. 371(4)]

D. Further information for the applicant:

This is only a reminder.

UNITED STATES DESIGNATED/ELECTED OFFICE	
Address Only: Mail Stop PCT, Commissioner for Patents P.O. Box 1450, Alexandria, VA 22313-1450	Authorized Officer Mark Hogarth 703-305-3749

P. 18
10/0
934

PCT/US03/24934

UNITED STATES RECEIVING OFFICE (PO USE) CODING AND RECORDING SHEET												☐ USA-INTL			
IDENTIFICATION OF THE INTERNATIONAL APPLICATION															
INTERNATIONAL APPLICATION NUMBER						INTERNATIONAL FILING DATE									
APPLICANT NAME:															
PAYMENTS								REFUNDS							
Payment as Filed				Request Amount		Request Amount		To Request Amount		To Request Amount					
				DOLLARS	CENTS	DOLLARS	CENTS	DOLLARS	CENTS	DOLLARS	CENTS				
Request Amount				DATE		DATE		DATE		DATE					
☐ CASH/CHECK				☐ CASH/CHECK		☐ CASH/CHECK		☐ BY CHECK		☐ BY CHECK					
USD															
EUR															
GBP															
JPY															
INR															
AUD															
CAD															
CHF															
SEK															
NOK															
DKK															
PLN															
CZK															
HUF															
RON															
BGN															
MDL															
LEU															
Total Paid:				Total Paid:		Total Paid:		Total Refunded:		Total Refunded:					
Amount included for fee:				fee:		fee:									
Amount included for cost:				cost:		cost:									
000100 193880 PCT:US03/E4324 00 DA 00 DA 00 DA 00 DA 00 DA 00 DA															
FOUR Authorization				FOUR Authorization (FOUR Authorization)				FOUR Authorization				FOUR Authorization			

701.00	243.00	DR
701.002	700.00	DR
701.70	328.00	DR
701.707	520.00	DR
701.8007	20.00	DR

PATENT COOPERATION TREATY

OCT 23 2003

Docketed Item

Due Date PCT

Attorney

NOTIFICATION CONCERNING
SUBMISSION OR TRANSMITTAL
OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

From the INTERNATIONAL BUREAU

To:

EPPERSON, James
Bristol-Myers Squibb Company
P.O. Box 4000
Princeton, NJ 08543-4000
United States of America

Date of mailing (day/month/year) 03 October 2003 (03.10.03)	
Applicant's or agent's file reference CT-2748 PCT	IMPORTANT NOTIFICATION
International application No. PCT/US03/24934	International filing date (day/month/year) 07 August 2003 (07.08.03)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 12 August 2002 (12.08.02)
Applicant BRISTOL-MYERS SQUIBB COMPANY et al	

1. The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).
2. This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.
3. An asterisk(*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, the attention of the applicant is directed to Rule 17.1(d) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.
4. The letters "NR" appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
12 Augu 2002 (12.08.02)	60/402,759	US	02 Octo 2003 (02.10.03)

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Sam, Rejl
Facsimile No. (41-22) 338.89.85	Telephone No. (41-22) 338 8201

PATENT COOPERATION TREATY
OCT 23 2003

Docketed Item

Due Date PCT

Attorney

NOTIFICATION OF RECEIPT OF
RECORD COPY

(PCT Rule 24.2(a))

From the INTERNATIONAL BUREAU

To:

EPPERSON, James
Bristol-Myers Squibb Company
P.O. Box 4000
Princeton, NJ 08543-4000
United States of America

Date of mailing (day/month/year)

30 September 2003 (30.09.03)

IMPORTANT NOTIFICATION

Applicant's or agent's file reference

CT-2748 PCT

International application No.

PCT/US03/24934

The applicant is hereby notified that the International Bureau has received the record copy of the international application as detailed below.

Name(s) of the applicant(s) and State(s) for which they are applicants:

BRISTOL-MYERS SQUIBB COMPANY (for all designated States except US)
DEPUE, Jeffrey et al (for US)

International filing date

07 August 2003 (07.08.03)

Priority date(s) claimed

12 August 2002 (12.08.02)

Date of receipt of the record copy
by the International Bureau

26 September 2003 (26.09.03)

List of designated Offices

AP : GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW
EA : AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
EP : AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR
OA : BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
National : AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ,
EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU,
LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ,
TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

ATTENTION

The applicant should carefully check the data appearing in this Notification. In case of any discrepancy between these data and the indications in the international application, the applicant should immediately inform the International Bureau.

In addition, the applicant's attention is drawn to the information contained in the Annex, relating to:

- ☒ time limits for entry into the national phase - see updated important information (as of April 2002)
- ☐ confirmation of precautionary designations (if applicable)
- ☒ requirements regarding priority documents (if applicable)

A copy of this Notification is being sent to the receiving Office and to the International Searching Authority.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 338.89.85

Authorized officer:

Evelyne HUCHON

Telephone No. (41-22) 338 9010

CERTIFICATE OF MAILING

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being deposited with the United States Postal Service on the date shown below with sufficient postage as first class mail in an envelope addressed to the Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

James Epperson
Type or print name

James Epperson
Signature

October 17, 2003
Date

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

International Application No.: PCT/US03/24934
International Filing Date: August 7, 2003
Priority Date: August 12, 2002
Applicant: Bristol-Myers Squibb Company
For: Improved Process for Hydroxyazapirones

MAIL STOP: PCT
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

RESPONSE TO INVITATION TO CORRECT DEFECTS IN
THE INTERNATIONAL APPLICATION

Sir:

In response to the Invitation to Correct Defects in the International Application letter of September 19, 2003 having a one month due date for reply, namely October 19, 2003, the following document is enclosed.

The PCT international application, PCT/US03/24934, was filed August 7, 2003 and contained a PCT Power of Attorney document unsigned by applicants/inventors (where the United States of America was designated).

This defect has been corrected by submitting the enclosed PCT Power of Attorney document which has now been signed by all of the applicants/inventors.

No fee is believed due. However, in the event a fee is due it is requested that the payment be charged to Deposit Account 19-3880.

Respectfully submitted,

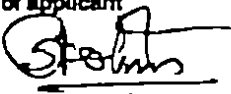
Bristol-Myers Squibb Company
Patent Department
P.O. Box 4000
Princeton, NJ 08543-4000
203-677-8974
Date: 10/17/2003

James Epperson
James Epperson
Agent for Applicants
Reg. No. 52,867

PCT POWER OF ATTORNEY

0-1	PCT Power of Attorney (for an international application filed under the Patent Cooperation Treaty) (PCT Rule 90.4)	
0-1-1	Prepared using	PCT-EASY Version 2.92 (updated 01.07.2003)
1	The undersigned applicant(s)	DEPUE, Jeffrey
1-1-1	hereby appoints (appoint) the following person	KPPERSON, James; BABAJKO, Suzanne; BAXAM, Deanna; BELFIELD, Jing; BUCHHOLZ, Briana; D'AMICO, Stephan, C.; DAVIS, Stephen; DUNCAN, Laurelee; GIBBONS, Maureen; GOLIAN, Paul, D.; KLEIN, Christopher; LANGE, Keith; O'BRIEN, Maureen; PATEL, Rana; PEIST, Kenneth; PROVOOST, Jonathan; RODNEY, Burton; SHER, Audrey; ALGIERI, Aldo; DUBOFF, Samuel; MAKUJINA, Shah; RYAN, Richard; VANATTEN, Mary, K.; VOLLES, Warren, K.; BOGIE, Terence; LAMERDIN, John; KORSEN, Elliott; DUNCAN, JR, Sammy; WINSLOW, Anastasia Bristol-Myers Squibb Company P.O. Box 4000 Princeton, NJ 08543-4000 United States of America
1-2	as	agent
1-3	to represent the undersigned before	all the competent International Authorities
1-4	In connection with the international application identified below:	
1-4-1	Title of the invention	IMPROVED PROCESS FOR HYDROXYAZAPIRONES
1-4-2	Applicant's or agent's file reference	CT-2748 PCT
1-4-3	International application number (if already available)	
1-4-4	filed with the following Office as receiving Office	United States Patent and Trademark Office (USPTO) (RO/US)
1-5	and to make or receive payments on behalf of the undersigned.	
2-2	Signature of applicant	
2-2-1	Name	DEPUE, Jeffrey
3	Date 10/16/03	

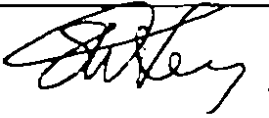
PCT POWER OF ATTORNEY

0-1	PCT Power of Attorney (for an International application filed under the Patent Cooperation Treaty) (PCT Rule 90.4)	
0-1-1	Prepared using	PCT-EASY Version 2.92 (updated 01.07.2003)
1	The undersigned applicant(s)	KOTNIS, Atul, S.
1-1-1	hereby appoints (appoint) the following person	EPPERSON, James; BABAJKO, Suzanne; BAXAM, Deanna; BELFIELD, Jing; BUCHHOLZ, Briana; D'AMICO, Stephen, C.; DAVIS, Stephen; DUNCAN, Laurelee; GIBBONS, Maureen; GOLIAN, Paul, D.; KLEIN, Christopher; LANGE, Keith; O'BRIEN, Maureen; PATEL, Rena; PEIST, Kenneth; PROVOOST, Jonathan; RODNEY, Burton; SHER, Audrey; ALGIERI, Aldo; DUBOFF, Samuel; MAKUJINA, Shah; RYAN, Richard; VANATTEN, Mary, K.; VOLLES, Warren, K.; BOGIE, Terence; LAMERDIN, John; KORSSEN, Elliott; DUNCAN, JR, Sammy; WINSLOW, Anastasia Bristol-Myers Squibb Company P.O. Box 4000 Princeton, NJ 08543-4000 United States of America
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1-4-3	International application number (if already available)	
1-4-4	filed with the following Office as receiving Office	United States Patent and Trademark Office (USPTO) (RO/US)
1-5	and to make or receive payments on behalf of the undersigned.	
2-3	Signature of applicant 	
2-3-1	Name 10/6/05	KOTNIS, Atul, S.
3	Date	

PCT POWER OF ATTORNEY

1/1

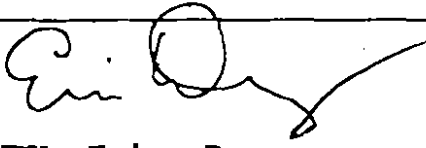
CT-2748 PCT

0-1	PCT Power of Attorney (for an international application filed under the Patent Cooperation Treaty) (PCT Rule 90.4)	
0-1-1	Prepared using	PCT-EASY Version 2.92 (updated 01.07.2003)
1	The undersigned applicant(s)	LEUNG, Simon
1-1-1	hereby appoints (appoint) the following person	EPPERSON, James; BABAJKO, Suzanne; BAXAM, Deanna; BELFIELD, Jing; BUCHHOLZ, Briana; D'AMICO, Stephen, C.; DAVIS, Stephen; DUNCAN, Laurelee; GIBBONS, Maureen; GOLIAN, Paul, D.; KLEIN, Christopher; LANGE, Keith; O'BRIEN, Maureen; PATEL, Rena; PEIST, Kenneth; PROVOOST, Jonathan; RODNEY, Burton; SHER, Audrey; ALGIERI, Aldo; DUBOFF, Samuel; MAKUJINA, Shah; RYAN, Richard; VANATKEN, Mary, K.; VOLLES, Warren, K.; BOGIE, Terence; LAMERDIN, John; KORSEN, Elliott; DUNCAN, JR, Sammy; WINSLOW, Anastasia Bristol-Myers Squibb Company P.O. Box 4000 Princeton, NJ 08543-4000 United States of America
1-2	as	agent
1-3	to represent the undersigned before	all the competent International Authorities
1-4	In connection with the international application identified below:	
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1-4-2	Applicant's or agent's file reference	CT-2748 PCT
1-4-3	International application number (if already available)	
1-4-4	filed with the following Office as receiving Office	United States Patent and Trademark Office (USPTO) (RO/US)
1-5	and to make or receive payments on behalf of the undersigned.	
2-4	Signature of applicant	
2-4-1	Name	LEUNG, Simon
3	Date	10/14/03

PCT POWER OF ATTORNEY

1/1

CT-2748 PCT

0-1	PCT Power of Attorney (for an International application filed under the Patent Cooperation Treaty) (PCT Rule 90.4)	
0-1-1	Prepared using	PCT-EASY Version 2.92 (updated 01.07.2003)
1	The undersigned applicant(s)	DOWDY, Eric, D.
1-1-1	hereby appoints (appoint) the following person	EPPERSON, James; BABAJKO, Suzanne; BAXAM, Deanna; BELFIELD, Jing; BUCHHOLZ, Briana; D'AMICO, Stephen, C.; DAVIS, Stephen; DUNCAN, Laurelee; GIBBONS, Maureen; GOLIAN, Paul, D.; KLEIN, Christopher; LANGE, Keith; O'BRIEN, Maureen; PATEL, Rana; PEIST, Kenneth; PROVOOST, Jonathan; RODNEY, Burton; SHER, Audrey; ALGIERI, Aldo; DUBOFF, Samuel; MAKUJIRA, Shah; RYAN, Richard; VANATTEN, Mary, K.; VOLLES, Warren, K.; BOGIE, Terence; LAMERDIN, John; KORSEN, Elliott; DUNCAN, JR, Sammy; WINSLOW, Anastasia Bristol-Myers Squibb Company P.O. Box 4000 Princeton, NJ 08543-4000 United States of America
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1-4-2	Applicant's or agent's file reference	CT-2748 PCT
1-4-3	International application number (if already available)	
1-4-4	filed with the following Office as receiving Office	United States Patent and Trademark Office (USPTO) (RO/US)
1-5	and to make or receive payments on behalf of the undersigned.	
2-3	Signature of applicant	
2-5-1	Name	DOWDY, Eric, D.
3	Date	10/3/03

PCT POWER OF ATTORNEY

1/1

CT-2748 PCT

0-1	PCT Power of Attorney (for an International application filed under the Patent Cooperation Treaty) (PCT Rule 90.4)	
0-1-1	Prepared using	PCT-EASY Version 2.92 (updated 01.07.2003)
1	The undersigned applicant(s)	WATSON, Daniel, J.
1-1-1	hereby appoints (appoint) the following person	KPPERSON, James; BABAJKO, Suzanne; BAXAM, Deanna; BELFIELD, Jing; BUCHHOLZ, Briana; D'AMICO, Stephen, C.; DAVIS, Stephen; DUNCAN, Laurelee; GIBBONS, Maureen; GOLIAN, Paul, D.; KLEIN, Christopher; LANGE, Keith; O'BRIEN, Maureen; PATEL, Rana; PEIST, Kenneth; PROVOOST, Jonathan; RODNEY, Burton; SHER, Audrey; ALGIERI, Aldo; DUBOFF, Samuel; MAKUJIMA, Shah; RYAN, Richard; VANATTEN, Mary, K.; VOLLES, Warren, K.; BOGIE, Terence; LAMERDIN, John; KORSEN, Elliott; DUNCAN, JR, Sammy; WINSLOW, Anastasia Bristol-Myers Squibb Company P.O. Box 4000 Princeton, NJ 08543-4000 United States of America
1-2	as	agent
1-3	to represent the undersigned before	all the competent International Authorities
1-4	In connection with the International application identified below:	
1-4-1	Title of the invention	IMPROVED PROCESS FOR HYDROXYAZAPIRONES
1-4-2	Applicant's or agent's file reference	CT-2748 PCT
1-4-3	International application number (if already available)	
1-4-4	filed with the following Office as receiving Office	United States Patent and Trademark Office (USPTO) (RO/US)
1-5	and to make or receive payments on behalf of the undersigned.	
2-6	Signature of applicant	
2-6-1	Name <i>10/6/03</i>	WATSON, Daniel, J.
3	Date	

PCT (ANNEX - FEE CALCULATION SHEET)

Original (for SUBMISSION) - printed on 07.08.2003 11:00:08 AM

CT-2748 PCT

(This sheet is not part of and does not count as a sheet of the international application)

0	For receiving Office use only	
0-1	International Application No.	
0-2	Date stamp of the receiving Office	
0-4	Form - PCT/RO/101 (Annex) PCT Fee Calculation Sheet Prepared using	PCT-EASY Version 2.92 (updated 01.07.2003)
0-9	Applicant's or agent's file reference	CT-2748 PCT
2	Applicant	BRISTOL-MYERS SQUIBB COMPANY, et al.
12	Calculation of prescribed fees	fee amount/multiplier Total amounts (USD)
12-1	Transmittal fee T	⇒ 240
12-2-1	Search fee S	⇒ 700
12-2-2	International search to be carried out by	US
12-3	International fee	
	Basic fee	
	(first 30 sheets) b1	407
12-4	Remaining sheets	0
12-5	Additional amount (X)	9
12-6	Total additional amount b2	0
12-7	b1 + b2 = B	407
12-8	Designation fees	
	Number of designations contained in international application	97
12-9	Number of designation fees payable (maximum 5)	5
12-10	Amount of designation fee (X)	88
12-11	Total designation fees D	440
12-12	PCT-EASY fee reduction R	-125
12-13	Total international fee (B+D-R) I	⇒ 722
12-14	Fee for priority document	
	Number of priority documents requested	1
12-15	Fee per document (X)	20
12-16	Total priority document fee P	⇒ 20
12-17	TOTAL FEES PAYABLE (T+S+I+P)	⇒ 1,682
12-18	Mode of payment	authorization to charge deposit account
12-20	Deposit account instructions	
	The receiving Office:	United States Patent and Trademark Office (USPTO) (RO/US)
12-20-1	Authorization to charge the total fees indicated above.	✓

PCT (ANNEX - FEE CALCULATION SHEET)

Original (for SUBMISSION) - printed on 07.08.2003 11:00:08 AM

CT-2748 PCT

12-20-2	Authorization to charge any deficiency or credit any overpayment in the total fees indicated above.	✓
12-20-3	Authorization to charge the fee for priority document.	✓
12-21	Deposit account No.	19-3880
12-22	Date	07 August 2003 (07.08.2003)
12-23	Name and signature	EPPERSON, James <i>James Epperson</i>

VALIDATION LOG AND REMARKS

13-2-7	Validation messages Contents	Green? The international application contains no drawings. Please verify.
13-2-8	Validation messages Payment	Green? Please ensure that you have a valid deposit account with the receiving Office selected.

PCT POWER OF ATTORNEY

1/2

Printed on 07.08.2003 10:38:34 AM

CT-2748 PCT

0-1	PCT Power of Attorney (for an International application filed under the Patent Cooperation Treaty) (PCT Rule 80.4)	
0-1-1	Prepared using	PCT-EASY Version 2.92 (updated 01.07.2003)
1	The undersigned applicant(s)	BRISTOL-MYERS SQUIBB COMPANY
1-1-1	hereby appoints (appoint) the following person	EPPERSON, James; BABAJKO, Suzanne; BAXAM, Deanna; BELFIELD, Jing; BUCHHOLZ, Briana; D'AMICO, Stephen, C.; DAVIS, Stephen; DUNCAN, Laurelee; GIBBONS, Maureen; GOLIAN, Paul, D.; KLEIN, Christopher; LANGE, Keith; O'BRIEN, Maureen; PATEL, Rena; PRIST, Kenneth; PROVOOST, Jonathan; RODNEY, Burton; SHER, Audrey; ALGIERI, Aldo; DUBOFF, Samuel; MAKUJIMA, Shah; RYAN, Richard; VANATTEN, Mary, K.; VOLLES, Warren, K.; BOGIE, Terence; LAMERDIN, John; KORSEW, Elliott; DUNCAN, JR, Sammy; WINSLOW, Anastasia Bristol-Myers Squibb Company P.O. Box 4000 Princeton, NJ 08543-4000 United States of America
1-2	as	agent
1-3	to represent the undersigned before	all the competent International Authorities
1-4	In connection with the international application identified below:	
1-4-1	Title of the invention	IMPROVED PROCESS FOR HYDROXYAZAPIRONES
1-4-2	Applicant's or agent's file reference	CT-2748 PCT
1-4-3	International application number (if already available)	
1-4-4	filed with the following Office as receiving Office	United States Patent and Trademark Office (USPTO) (RO/US)
1-5	and to make or receive payments on behalf of the undersigned.	
2-5	Signature of applicant	<i>Richard P. Ryan</i>
2-5-1	Name	BRISTOL-MYERS SQUIBB COMPANY
2-5-2	Name of signatory	Richard P. Ryan
2-5-3	Capacity	Sr. Patent Counsel

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PCT POWER OF ATTORNEY

CT-2748 ROT

Printed on 07.08.2003 10:38:34 AM

3	Date	07 August 2003 (07.08.2003)
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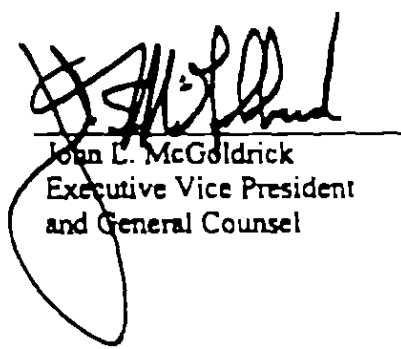
CERTIFICATION

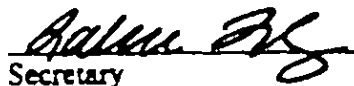
The undersigned, being the Executive Vice President and General Counsel of Bristol-Myers Squibb Company, hereby designates:

Suzanne Babajko
Stephen B. Davis
Blair Q. Ferguson
John M. Kilcoyne
Christopher Klein
David Morse
Richard Ryan

(a) to present to the Patent, Trademark, Copyright and similar Government Offices of all countries or to any competent authority, all original, divisional, continuation and reissue applications, petitions and request in the name of Bristol-Myers Squibb Company and its subsidiary companies, for letters patent for inventions, utility models, industrial models and designs and improvements or additions thereof, trademarks and copyrights; (b) to initial and prosecute oppositions and appeals; (c) to appear before all officers duly authorized, all Ministers, Bureaus, Clerk's Offices and Commissions or Commissioners that may be necessary; (d) to sign and approve on behalf of this corporation all documents and powers of attorney which judgment of the authorized individuals may be necessary or desirable to carry out the powers hereby conferred; (e) to request all proceedings; (f) to pay over or withdraw all taxes, obtain receipts therefor and give discharge; (g) to withdraw applications and all documents relating thereto; (h) to commence proceedings against infringers and assure the defense in infringement actions; and (i) generally to do all that in the judgment of the authorized individual may be necessary to secure granting of the privileges above-mentioned.

IN WITNESS WHEREOF, I have placed my hand and caused the seal of the Company to be affixed hereto on this 22nd day of May 2002.


John L. McGoldrick
Executive Vice President
and General Counsel


Secretary

PCT POWER OF ATTORNEY

1/2

CT-2748 PCT

Printed on 07.08.2003 10:21:21 AM

0-1	PCT Power of Attorney (for an International application filed under the Patent Cooperation Treaty) (PCT Rule 90.4)	
0-1-1	Prepared using	PCT-EASY Version 2.92 (updated 01.07.2003)
1	The undersigned applicant(s)	DEPUE, Jeffrey; KOTNIS, Atul, S.; LEUNG, Simon; DOWDY, Eric, D.; WATSON, Daniel, J.
1-1-1	hereby appoints (appoint) the following person	EPPERSON, James; BABAJKO, Suzanne; BAXAM, Deanna; BELFIELD, Jing; BUCHHOLZ, Briana; D'AMICO, Stephen, C.; DAVIS, Stephen; DUNCAN, Laurelee; GIBBONS, Maureen; GOLIAN, Paul, D.; KLEIN, Christopher; LANGE, Keith; O'BRIEN, Maureen; PATEL, Rena; PEIST, Kenneth; PROVOOST, Jonathan; RODNEY, Burton; SHER, Audrey; ALGIERI, Aldo; DUBOFF, Samuel; MAKUJINA, Shah; RYAN, Richard; VANATTEN, Mary, K.; VOLLES, Warren, K.; BOGIE, Terence; LAMERDIN, John; KORSEN, Elliott; DUNCAN, JR, Sammy; WINSLOW, Anastasia Bristol-Myers Squibb Company P.O. Box 4000 Princeton, NJ 08543-4000 United States of America
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1-4-4	filed with the following Office as receiving Office	United States Patent and Trademark Office (USPTO) (RO/US)
1-5	and to make or receive payments on behalf of the undersigned.	
2-1	Signature of applicant	
2-1-1	Name	DEPUE, Jeffrey

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PCT POWER OF ATTORNEY

Printed on 07.08.2003 10:21:21 AM

CT-2748 PCT

2-2	Signature of applicant	
2-2-1	Name	KOTHIS, Atul, S.
2-3	Signature of applicant	
2-3-1	Name	LEUNG, Simon
2-4	Signature of applicant	
2-4-1	Name	DOWDY, Eric, D.
2-5	Signature of applicant	
2-5-1	Name	WATSON, Daniel, J.
3	Date	07 August 2003 (07.08.2003)

This invention describes a process for preparing hydroxyazapirones of Formula I from azapirones of Formula II. The process comprises treating azapirones with a strong base, monitoring enolate formation of the azapirone by IR spectroscopy, and reacting the enolate with a source of molecular oxygen in the presence of a reductant. The process is suitable for large scale production of hydroxyazapirones.

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117

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CT 2748-US- (118)
EPPERSON



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1400
Alexandria, Virginia 22313-1400
www.uspto.gov

APPL NO.	FILING OR 371 (c) DATE	ART UNIT	FILE FEE REC'D	ATTY. DOCKET NO	DRAWINGS	TOT CLMS	IND CLMS
10/838,070	08/07/2003	1814	916	CT-2748 NP		22	2

23914
STEPHEN B. DAVIS
BRISTOL-MYERS SQUIBB COMPANY
PATENT DEPARTMENT
P O BOX 4000
PRINCETON, NJ 08543-4000

CONFIRMATION NO. 9854

UPDATED FILING RECEIPT



0C000000011585811

JAN 13 2004

BRISTOL-MYERS SQUIBB COMPANY
PATENT DEPARTMENT
PRINCETON, NJ

Date Mailed: 12/30/2003

Receipt is acknowledged of this regular Patent Application. It will be considered in its order and you will be notified as to the results of the examination. Be sure to provide the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION when inquiring about this application. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. If an error is noted on this Filing Receipt, please write to the Office of Initial Patent Examination's Filing Receipt Corrections, facsimile number 703-746-9195. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections (if appropriate).

Applicant(s)

Jeffrey Depue, Hillsborough, NJ; ✓
Atul S. Kotnis, Kendall Park, NJ; ✓
Simon Laung, Piscataway, NJ; ✓
Eric D. Dowdy, San Mateo, CA; ✓
Daniel J. Watson, Princeton, NJ; ✓

RECEIVED
BMS PATENT LAW

1/6 JAN 05 2004

Docketed Item UFR
Due Date RPO-4/8/04
Attorney JE

Domestic Priority data as claimed by applicant

This appln claims benefit of 80/402,759 08/12/2002 ✓

Foreign Applications

If Required, Foreign Filing License Granted: 11/04/2003 ✓

Projected Publication Date: 04/08/2004 ✓

Non-Publication Request: No

Early Publication Request: No

Title

Process for hydroxyazaprones ✓

119
✓
21

Preliminary Class

514

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Title 35, United States Code, Section 184
Title 37, Code of Federal Regulations, 5.11 & 5.15**

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Commissioner for Patents
Washington, DC 20231
www.uspto.gov

APPLICATION NUMBER	FILING DATE	GRP ART UNIT	FILE REC'D	ATTY DOCKET NO	DRAWINGS	TOT CLAIMS	IND CLAIMS
60/402,759	08/12/2002		210	CT2748PSP			

23914
STEPHEN B. DAVIS
BRISTOL-MYERS SQUIBB COMPANY
PATENT DEPARTMENT
P O BOX 4000
PRINCETON, NJ 08543-4000

CONFIRMATION NO. 8686
UPDATED FILING RECEIPT

OC000000009028905

Date Mailed: 10/30/2002

Receipt is acknowledged of this provisional Patent Application. It will not be examined for patentability and will become abandoned not later than twelve months after its filing date. Be sure to provide the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION when inquiring about this application. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. If an error is noted on this Filing Receipt, please write to the Office of Initial Patent Examination's Filing Receipt Corrections, facsimile number 703-746-8195. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections (if appropriate).

Applicant(s)

Jeffrey DePue, Hillsborough, NJ;
Atul S. Kotnis, Kendall Park, NJ;
Simon Leung, Piscataway, NJ;
Eric D. Dowdy, Plainsboro, NJ;
Daniel J. Watson, Princeton, NJ;

RECEIVED
BMS PATENT LAB

NOV 04 2002

Docketed Item _____
Due Date _____
Attorney D. Ryan

If Required, Foreign Filing License Granted 08/30/2002

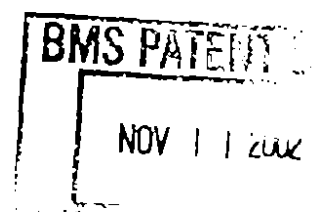
Projected Publication Date: None, application is not eligible for pre-grant publication

Non-Publication Request: No

Early Publication Request: No

Title

Process for hydroxyazapirones



LICENSE FOR FOREIGN FILING UNDER
Title 35, United States Code, Section 184

APOSTILLE

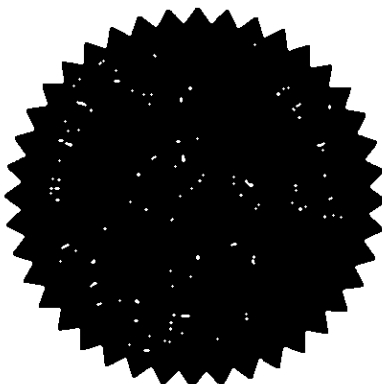
121

(CONVENTION DE LA HAYE DU 5 OCTOBRE 1961)

1. COUNTRY: UNITED STATES OF AMERICA
2. THIS PUBLIC DOCUMENT HAS BEEN SIGNED BY:
MARIA CASTALDO
3. ACTING IN THE CAPACITY OF:
NOTARY PUBLIC OF NEW JERSEY
4. BEARS THE SEAL/STAMP OF:
MARIA CASTALDO, NOTARY

CERTIFIED

5. AT TRENTON, NEW JERSEY
6. THE 20TH DAY OF JANUARY 2005
7. BY: John E McCormac, CPA, NEW JERSEY TREASURER
8. NO. A217602
9. SEAL/STAMP:
10. SIGNATURE



122 ~~4~~
~~12~~
✓

CT2748 COLOMBOIA

AFFIDAVIT

I, **Stephen B. Davis**, Senior Patent Counsel, Patent Department,
BRISTOL-MYERS SQUIBB COMPANY, do hereby certify that this is
a notarized true and accurate assignment signed by the inventors.

Stephen B. Davis
Stephen B. Davis
Senior Patent Counsel

STATE OF NEW JERSEY)
)
COUNTY OF MERCER)

Subscribed and sworn to before me this
19th day of Jan., 2005

Maria Castaldo
Maria Castaldo
Notary Public of New Jersey
My commission expires October 6, 2008

SEAL

123



UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
ASSISTANT SECRETARY AND COMMISSIONER
OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

AUGUST 08, 2003

PTAS

BRISTOL-MYERS SQUIBB COMPANY
STEPHEN B. DAVIS
PATENT DEPARTMENT
P.O. BOX 4000
PRINCETON, NJ 08543-4000



700038247

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NOTICE OF RECORDATION OF ASSIGNMENT DOCUMENT

THE ENCLOSED DOCUMENT HAS BEEN RECORDED BY THE ASSIGNMENT DIVISION OF THE U.S. PATENT AND TRADEMARK OFFICE. A COMPLETE MICROFILM COPY IS AVAILABLE AT THE ASSIGNMENT SEARCH ROOM ON THE REEL AND FRAME NUMBER REFERENCED BELOW.

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RECORDATION DATE: 08/06/2003

REEL/FRAME: 013856/0713
NUMBER OF PAGES: 8

BRIEF: ASSIGNMENT OF ASSIGNOR'S INTEREST (SEE DOCUMENT FOR DETAILS).

ASSIGNOR:

DEPUE, JEFFREY

DOC DATE: 10/03/2002

ASSIGNOR:

KOTNIS, ATUL S.

DOC DATE: 10/07/2002

ASSIGNOR:

LEUNG, SIMON SHUN WANG

DOC DATE: 10/03/2002

ASSIGNOR:

DOWDY, ERIC D.

DOC DATE: 10/03/2002

ASSIGNOR:

WATSON, DANIEL J.

DOC DATE: 10/07/2002

ASSIGNEE:

BRISTOL-MYERS SQUIBB COMPANY
LAWRENCEVILLE-PRINCETON ROAD
PRINCETON, NEW JERSEY 08543-4000

OPR/ASSIGNMENTS

8/8/03 8:05 PAGE 3/4 RightFAX

124 

013856/0713 PAGE 2

SERIAL NUMBER: 60402759
PATENT NUMBER:

FILING DATE: 08/12/2002
ISSUE DATE:

MARY BENTON, EXAMINER
ASSIGNMENT DIVISION
OFFICE OF PUBLIC RECORDS

FORM PTO-1585
(Rev. 8-03)

RECORDATION FORM COVER SHEET

U.S. DEPARTMENT OF COMMERCE
Patent and Trademark Office

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PATENTS ONLY

To the Honorable Commissioner of Patents and Trademarks: Please record the attached original documents or copy thereof.

1. Name of conveying party(ies):

Jeffrey Depue, Atul S. Kotnile, Simon Shun
Wang Laung, Eric D. Dowdy, Daniel J. WatsonAdditional name(s) of conveying party(ies) attached? ☐ Yes ☒ No

3. Nature of conveyance:

- ☒ Assignment ☐ Merger
☐ Security Agreement ☐ Change of Name
☐ Other _____

Execution Date: 10/3/02 & 10/7/02

2. Name and address of receiving party(ies)

Name: Bristol-Myers Squibb Company

Internal Address: _____

Street Address: Lawrenceville-Princeton Road

City: Princeton State: NJ ZIP: 08543-4000

Additional name(s) & address(es) attached? ☐ Yes ☒ No

4. Application number(s) or patent number(s):

If this document is being filed together with a new application, the execution date of the application is: _____

A. Patent Application No.(s)

60/402,768 filed August 12, 2002

B. Patent No.(s)

Additional numbers attached? ☐ Yes ☒ No

5. Name and address of party to whom correspondence concerning document should be mailed:

Name: Stephen B. Davis

Internal Address: Bristol-Myers Squibb Company

Patent Department

Street Address: P.O. Box 4000

City: Princeton State: NJ ZIP: 08543-4000

6. Total number of applications and patents involved: 1

7. Total fee (37 CFR 3.41) \$ 40

☐ Enclosed☒ Authorized to be charged to deposit account and any other additional fees required.

8. Deposit account number:

19-3880 (In the name of Bristol-Myers Squibb Company)

(Attach duplicate copy of this page if paying by deposit account)

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9. Statement and signature.

To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.

James Edgerton

Name of Person Signing
Reg. No. 58,867

Signature

Date

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Total number of pages including cover sheet, attachments, and documents 8

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Alexandria, VA 22303-1480

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1. Name of conveying party(ies):

Jeffrey Depue, Atul S. Kotnis, Simon Shun
Wang Laung, Eric D. Dowdy, Daniel J. Watson

Additional name(s) of conveying party(ies) attached? ☐ Yes ☒ No

3. Nature of conveyance:

- ☒ Assignment ☐ Merger
☐ Security Agreement ☐ Change of Name
☐ Other _____

Execution Date: 10/3/02 & 10/7/02

2. Name and address of receiving party(ies)

Name: Bristol-Myers Squibb Company

Internal Address: _____

Street Address: Lawrenceville-Princeton Road

City: Princeton State: NJ ZIP: 08543-4000

Additional name(s) & address(es) attached? ☐ Yes ☒ No

4. Application number(s) or patent number(s):

If this document is being filed together with a new application, the execution date of the application is: _____

A. Patent Application No.(s)

60/402,759 filed August 12, 2002

B. Patent No.(s)

Additional numbers attached? ☐ Yes ☒ No

5. Name and address of party to whom correspondence concerning document should be mailed:

Name: Stephen B. Davis

Internal Address: Bristol-Myers Squibb Company

Patent Department

Street Address: P.O. Box 4000

City: Princeton State: NJ ZIP: 08543-4000

6. Total number of applications and patents involved: 1

7. Total fee (37 CFR 3.41) \$ 40

☐ Enclosed

☒ Authorized to be charged to deposit account and any other additional fees required.

8. Deposit account number:

19-3880 (In the name of Bristol-Myers Squibb Company)

(Attach duplicate copy of this page if paying by deposit account)

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9. Statement and signature.

To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.

James Epperson

Name of Person Signing
Reg. No. 52,867

James Epperson
Signature

8/6/2003
Date

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Total number of pages including cover sheet, attachments, and document: 8

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Commissioner for Patents, P.O. Box 1450
Alexandria, VA 22313-1450

ASSIGNMENT

We,

Jeffrey Depue	residing at	6 John Hancock Avenue Hillsborough, New Jersey 08844 United States of America
Atul S. Kotnis	residing at	16 Oxford Court Kendall Park, New Jersey 08824 United States of America
Simon Shun Wang Leung	residing at	238 Vasser Drive Piscataway, New Jersey 08854 United States of America
Eric D. Dowdy	residing at	39-14 Ravens Crest Drive Plainsboro, New Jersey 08536 United States of America
Daniel J. Watson	residing at	105 Olympic Court, #9 Princeton, New Jersey 08540 United States of America,

pursuant to contractual obligations heretofore assumed by us and/or for good and valuable consideration, the receipt and adequacy of which is hereby acknowledged, do hereby sell and assign to **Bristol-Myers Squibb Company**, a Delaware corporation, having a place of business at Lawrenceville-Princeton Road, Princeton, NJ 08543-4000, its successors, assigns and legal representatives, all our right, title and interest, which includes the right to and full benefit of such priorities as may now or hereafter be granted to us by local laws or by treaty, including any international convention for the protection of industrial property, in and for all countries of the world, including the United States and its territories and possessions, in and to the invention entitled:

Improved Process for Hydroxyazapirones

invented by us and described in the provisional United States patent application

Application No. 60/402,759, filed August 12, 2002,

including said provisional United States patent application and any application claiming priority from said provisional application, filed in any country, and any patents which may be issued and/or granted thereon, and all divisions, continuations, reissues, reexamination certificates and extensions thereof in all countries, the said interest being the entire ownership of said invention and

all of said applications, patents (including reissue patents), extensions and reexamination certificates to be held and enjoyed by the said Bristol-Myers Squibb Company and its successors and assigns to the full end of the terms to which said patents (including reissue patents), extensions and reexamination certificates may be granted and/or issued, as fully and entirely as the same would have been held and enjoyed by us if this sale, assignment and transfer had not been made;

And we hereby agree to communicate to said assignee or its representatives any facts known to us respecting said invention, to testify in any legal proceedings, to sign and/or execute any further documents and/or instruments which may be necessary, lawful and proper in and/or for the filing and/or prosecution of all applications, including divisional, continuation and reissue applications, extensions and reexamination certificates and/or the granting and/or issuance thereof and/or to otherwise secure title to said invention and all of said applications, patents (including reissue patents, extensions and reexamination certificates in said assignee, and in general to do everything possible to aid said assignee, its successors and assigns to obtain and enforce proper protection for said invention in all countries.

129

Worldwide
Case CT2748PSP

Signed this 3rd day of October, 2002 by Jeffrey Depue
Jeffrey Depue

STATE OF New Jersey,
COUNTY OF Middlesex ss.

On the 3rd day of October, 2002, before me came

Jeffrey Depue

to me known to be the person of that name mentioned in, and who executed the foregoing Assignment document and acknowledged that he executed it.

Laura H. Derbin
Notary Public

[SEAL]

My commission expires _____

LAURA H. DERBIN
NOTARY PUBLIC, STATE OF NEW JERSEY
ID # 2278973
Commission Expires Sept. 7, 2006

130
Worldwide
Case CT2748PSP

Signed this 7th day of October, 2002 by

Atul S. Kotnis
Atul S. Kotnis

STATE OF New Jersey)
COUNTY OF Middlesex) ss.

On the 7th day of October, 2002, before me came

Atul S. Kotnis

to me known to be the person of that name mentioned in, and who executed the foregoing Assignment document and acknowledged that he executed it.

Laura H. Derbin
Notary Public

[SEAL]

My commission expires _____

LAURA H. DERBIN
NOTARY PUBLIC, STATE OF NEW JERSEY
ID # 2278973
Commission Expires Sept. 7, 2006

13h
Workfile
Case CT2748PSP

Signed this 3 day of October, 2002 by Simon Shun Wang Leung
Simon Shun Wang Leung

STATE OF New Jersey,
COUNTY OF Middlesex ss.

On the 3rd day of October, 2002, before me came

Simon Shun Wang Leung

to me known to be the person of that name mentioned in, and who executed the foregoing Assignment document and acknowledged that he executed it.

Laura H. Derbin
Notary Public

[SEAL]

My commission expires _____

LAURA H. DERBIN
NOTARY PUBLIC, STATE OF NEW JERSEY
ID # 2278973
Commission Expires Sept. 7, 2006

Eric D. Dowdy

Worldwide

\$5.

On the 3rd day of October, 2002, before me came

to me known to be the person of that name mentioned in, and who executed the foregoing Assignment document and acknowledged that he executed it.

Sandra H. Neelands
Notary Public

My commission expires _____

LAURA H. DERBIN
NOTARY PUBLIC, STATE OF NEW JERSEY
ID # 2278973
Commission Expires Sept. 7, 2006

133

Worldwide
Case CT2748RSP

Signed this 7th day of October, 2002 by D. J. Watson
Daniel J. Watson

STATE OF New Jersey,
COUNTY OF Middlesex ss.

On the 7th day of October, 2002, before me came

Daniel J. Watson

to me known to be the person of that name mentioned in, and who executed the foregoing Assignment document and acknowledged that he executed it.

Laura H. Derbin
Notary Public

[SEAL]

My commission expires _____

LAURA H. DERBIN
NOTARY PUBLIC, STATE OF NEW JERSEY
ID # 2278973
Commission Expires Sept. 7, 2006

139



TRADUCCIÓN AL ESPAÑOL del documento de cesión de la solicitud de patente a Bristol-Myers Squibb Company, firmado por los cedentes y el cesionario.

APOSTILLE

(CONVENCIÓN DE LA HAYA DEL 5 DE OCTUBRE DE 1961)

1. **PAÍS: ESTADOS UNIDOS DE AMÉRICA**
2. **ESTE DOCUMENTO PÚBLICO HA SIDO FIRMADO POR MARIA CASTALDO**
3. **ACTUANDO EN CAPACIDAD DE NOTARIO PÚBLICO DE NEW JERSEY**
4. **LLEVA EL SELLO/TIMBRE DE: MARIA CASTALDO, NOTARIO**

CERTIFICADO

5. **EN TRENTON, NEW JERSEY**
6. **EL 20 DE ENERO DE 2005**
7. **POR: John E. McCormac, CPA, TESORERO DE NEW JERSEY**
8. **NO. A217602**
9. **SELLO/TIMBRE**
10. **FIRMA**

Jonh E. McCormac (firma)

135



Declaración Juramentada por escrito

Yo, Stephen B. Davis, Asesor Principal de Patentes, Departamento de Patentes -
BRISTOL-MYERS SQUIBB COMPANY certifico que esta una cesión notariada,
verdadera y precisa firmada por los inventores.

(Firma)

Stephen B. Davis

ESTADO DE NEW JERSEY

)

CONDADO DE MERCER

)

ss.

)

Firmado ante mi este 19 de Enero de 2005

(Firma)

Maria Castaldo

Notario Público de New Jersey

Mi comisión expira el 6 de octubre de 2008

[Sello]

8 de Agosto de 2003
BISTOL-MYERS SQUIBB COMPANY
STEPHEN B. DAVIS
DEPARTAMENTO DE PATENTES
CASILLA POSTAL 4000
PRINCETON, NJ 08543-4000

136

OFICINA DE MARCAS Y PATENTES DE LOS ESTADOS UNIDOS
INFORME DE GRABACIÓN DE DOCUMENTO DE CESION

EL DOCUMENTO ADJUNTO HA SIDO GRABADO POR LA DIVISIÓN DE CESIONES DE LA OFICINA DE MARCAS Y PATENTES DE LOS ESTADOS UNIDOS. HAY DISPONIBLE UNA COPIA COMPLETA EN MICROFILME EN EL CUARTE DE BÚSQUEDA DE CESIONES EN EL NÚMERO DE ROLLO Y CUADRO REFERENCIADOS ABAJO.

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FECHA DE GRABACIÓN: 08/06/2003

ROLLO/CUADRO: 013856/0713
NÚMERO DE PÁGINAS: 8

RESUMEN: CESIÓN DE INTERÉS DEL CEDENTE (VER DOCUMENTO PARA DETALLES).

CEDENTE:

DEPUE, JEFFREY

FECHA DE DOC: 10/03/2002

CEDENTE:

KOTNIS, ATUL S.

FECHA DE DOC: 10/07/2002

CEDENTE:

LEUNG, SIMON SHUN WANG

FECHA DE DOC: 10/03/2002

CEDENTE:

DOWDY, ERIC D.

FECHA DE DOC: 10/03/2002

CEDENTE:

WATSON, DANIEL J.

FECHA DE DOC: 10/07/2002

CESIONARIO:

BRISTOL-MYERS SQUIBB COMPANY
LAWRENCEVILLE-PRINCETON ROAD
PRINCETON, NEW JERSEY 08543-4000

013858/0713 PAGINA 2

NÚMERO DE SERIE: 60402759
NÚMERO DE PATENTE:

FECHA DE PRESENTACIÓN: 08/12/2002
FECHA DE EMISIÓN:

MARY BENTON, EXAMINADOR
DIVISIÓN DE CESIONES
OFICINA DE REGISTROS PÚBLICOS

137
~~137~~
137

138 0

FORMULARIO PTO-1585 (Rev. 8-93) OMB No. 0851-0011 (exp. 4/94) TU0059 (PSP)	PORTADA DEL FORMULARIO DE REGISTRO 700026737 SOLO PATENTES	Departamento de Comercio de los Estados Unidos Oficina de Marcas y Patentes			
Al Honorable Comisionado de Marcas y Patentes: por favor registre los documentos originales adjuntos o copias de los mismos.					
1. Nombre de la(s) parte(s) cedente(s): Jeffrey Depue, Atul S. Kotnis, Simon Shun, Wang Leung, Eric D. Dowdy, Daniel J. Watson Se adjunta(n) nombre(s) adicional(es) de la(s) parte(s) cedente(s) ☐ SI ☒ No	2. Nombre y dirección de la(s) parte(s) que recibe(n) Nombre: <u>Bristol-Myers Squibb Company</u> Dirección Interna: _____ Dirección: <u>Lawrenceville-Princeton Road</u> Ciudad: <u>Princeton</u> Estado: <u>NJ</u> ZIP: <u>08543-4000</u> ¿Se adjunta(n) nombre(s) y dirección(es) adicional(es)? ☐ SI ☒ No				
3. Naturaleza del traspaso: ☒ Cesión ☐ Fusión ☐ Acuerdo de Seguridad ☐ Cambio de Nombre ☐ Otro: _____ Fecha de Ejecución: <u>10/3/02 & 10/7/02</u>					
4. Número(s) de Solicitud o número(s) de Patente: Si este documento está siendo entregado junto con una nueva solicitud, la fecha de ejecución de la solicitud es: _____ <table style="width: 100%;"><tr><td style="width: 50%; vertical-align: top;">A. Solicitud(es) de Patente No(s). 60/402,759 presentada el 5 de Agosto de 2002</td><td style="width: 50%; vertical-align: top;">B. No(s). de Patente ¿Se adjuntan números adicionales? ☐ SI ☒ No</td></tr></table>			A. Solicitud(es) de Patente No(s). 60/402,759 presentada el 5 de Agosto de 2002	B. No(s). de Patente ¿Se adjuntan números adicionales? ☐ SI ☒ No	
A. Solicitud(es) de Patente No(s). 60/402,759 presentada el 5 de Agosto de 2002	B. No(s). de Patente ¿Se adjuntan números adicionales? ☐ SI ☒ No				
5. Nombre y dirección de la parte a quien se le debe enviar la correspondencia de los documentos concernientes: Nombre: <u>Stephen B. Davis</u> Dirección Interna: <u>Bristol-Myers Squibb Company</u> <u>Departamento de Patentantes</u> Dirección: <u>Apartado Postal 4000</u> Ciudad: <u>Princeton</u> Estado: <u>NJ</u> ZIP: <u>08542-4000</u>	6. Número total de solicitudes y patentes involucradas: <u>1</u> 7. Tarifa Total (37 CFR \$ 40 3.41) ☐ Adjunta ☒ Autorización para ser cargada a una cuenta de depósito y cualquier otra tarifa adicional requerida. 8. Número de cuenta depósito: <u>19-3880 (a nombre de Bristol-Myers Squibb Company)</u> (Anexar copia por duplicado de esta página si se paga por cuenta de depósito)				
NO USAR ESTE ESPACIO					
9. Declaración y firma: Hasta donde se y creo, la información anterior es veraz y correcta y cualquier copia adjunta es una copia veraz del documento original. <table style="width: 100%;"><tr><td style="width: 33%;"><u>James Epperson</u> Nombre del suscrito Reg. No. 52,867</td><td style="width: 33%; text-align: center;"><u>(Firma)</u> Firma</td><td style="width: 33%; text-align: right;"><u>8/5/2003</u> Fecha</td></tr></table> ☐ Certificado de envío por el reverso Número total de páginas incluyendo la portada, anexos, y documentos: <u>8</u>			<u>James Epperson</u> Nombre del suscrito Reg. No. 52,867	<u>(Firma)</u> Firma	<u>8/5/2003</u> Fecha
<u>James Epperson</u> Nombre del suscrito Reg. No. 52,867	<u>(Firma)</u> Firma	<u>8/5/2003</u> Fecha			

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FORMULARIO PTO-1585 (Rev. 8-93) OMB No. 0851-0011 (exp. 4/94) TU0059 (PSP)	PORTADA DEL FORMULARIO DE REGISTRO 700026737 SOLO PATENTES	Departamento de Comercio de los Estados Unidos Oficina de Marcas y Patentes			
Al Honorable Comisionado de Marcas y Patentes: por favor registre los documentos originales adjuntos o copias de los mismos.					
10. Nombre de la(s) parte(s) cedente(s): Jeffrey Depue, Atul S. Kotnis, Simon Shun, Wang Leung, Eric D. Dowdy, Daniel J. Watson Se adjunta(n) nombre(s) adicional(es) de la(s) parte(s) cedente(s) ☐ SI ☒ No	11. Nombre y dirección de la(s) parte(s) que recibe(n) Nombre: <u>Bristol-Myers Squibb Company</u> Dirección Interna: _____ Dirección: <u>Lawrenceville-Princeton Road</u> Ciudad: <u>Princeton</u> Estado: <u>NJ</u> ZIP: <u>08543-4000</u> ¿Se adjunta(n) nombre(s) y dirección(es) adicional(es)? ☐ SI ☒ No				
12. Naturaleza del traspaso: ☒ Cesión ☐ Fusión ☐ Acuerdo de Seguridad ☐ Cambio de Nombre ☐ Otro: _____ Fecha de Ejecución: <u>10/3/02 & 10/7/02</u>	13. Número(s) de Solicitud o número(s) de Patente: Si este documento está siendo entregado junto con una nueva solicitud, la fecha de ejecución de la solicitud es: _____ <table style="width: 100%;"> <tr> <td style="width: 50%; vertical-align: top;"> C. Solicitud(es) de Patente No(s). 80/402,759 presentada el 5 de Agosto de 2002 </td> <td style="width: 50%; vertical-align: top;"> D. No(s). de Patente ¿Se adjuntan números adicionales? ☐ SI ☒ No </td> </tr> </table>		C. Solicitud(es) de Patente No(s). 80/402,759 presentada el 5 de Agosto de 2002	D. No(s). de Patente ¿Se adjuntan números adicionales? ☐ SI ☒ No	
C. Solicitud(es) de Patente No(s). 80/402,759 presentada el 5 de Agosto de 2002	D. No(s). de Patente ¿Se adjuntan números adicionales? ☐ SI ☒ No				
14. Nombre y dirección de la parte a quien se le debe enviar la correspondencia de los documentos concernientes: Nombre: <u>Stephen B. Davis</u> Dirección Interna: <u>Bristol-Myers Squibb Company</u> <u>Departamento de Patentes</u> Dirección: <u>Apartado Postal 4000</u> Ciudad: <u>Princeton</u> Estado: <u>NJ</u> ZIP: <u>08542-4000</u>	15. Número total de solicitudes y patentes involucradas: 1 16. Tarifa Total (37 CFR \$ 40 3.41) ☐ Adjunta ☒ Autorización para ser cargada a una cuenta de depósito y cualquier otra tarifa adicional requerida. 17. Número de cuenta depósito: <u>19-3880 (a nombre de Bristol-Myers Squibb Company)</u> (Anexar copia por duplicado de esta página si se paga por cuenta de depósito)				
NO USAR ESTE ESPACIO					
18. Declaración y firma: Hasta donde se y creo, la información anterior es veraz y correcta y cualquier copia adjunta es una copia veraz del documento original. <table style="width: 100%;"> <tr> <td style="width: 33%; vertical-align: bottom;"> <u>James Epperson</u> Nombre del suscrito Reg. No. 52,867 </td> <td style="width: 33%; text-align: center; vertical-align: bottom;"> (Firma) _____ Firma </td> <td style="width: 33%; text-align: right; vertical-align: bottom;"> <u>8/8/2003</u> Fecha </td> </tr> </table> ☐ Certificado de envío por el reverso Número total de páginas incluyendo la portada, anexos, y documentos: 8			<u>James Epperson</u> Nombre del suscrito Reg. No. 52,867	(Firma) _____ Firma	<u>8/8/2003</u> Fecha
<u>James Epperson</u> Nombre del suscrito Reg. No. 52,867	(Firma) _____ Firma	<u>8/8/2003</u> Fecha			

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CESIÓN

Nosotros,

Jeffrey Depue

residente en

6 John Kancock Avenue
Hillsborough, New Jersey 08844
Estados Unidos de América

Atul S. Kotnis

residente en

16 Oxford Court
Kendall Park, New Jersey 08824
Estados Unidos de América

Simon Shun Wang Leun

residente en

238 Vasser Drive
Piscataway, New Jersey 08854
Estados Unidos de América

Eric D. Dowdy

residente en

39-14 Ravens Crest Drive
Plainsboro, New Jersey 08536
Estados Unidos de América

Daniel J. Watson

residente en

105 Olympic Court, #9
Princeton, New Jersey 08540
Estados Unidos de América

en virtud de obligaciones contractuales hasta ahora asumidas por nosotros y/o en buena y valiosa consideración, el recibo y suficiencia del mismo se reconoce aquí, por medio de la presente vendemos y cedemos a Bristol-Myers Squibb Company, una corporación de Delaware, que funciona en Lawrenceville-Princeton Road, Princeton, NJ 08534-4000, sus sucesores, cedentes y representantes legales, todo nuestro derecho, título e interés, el cual incluye el beneficio correcto y completo de tales prioridades que puedan ser concedidas ahora o en adelante a nosotros por leyes locales o tratados, incluyendo cualquier convenio internacional para la protección de propiedad industrial, en y para todos los países del mundo, incluyendo a los Estados Unidos y sus territorios y posesiones, en y a la invención titulada:

Proceso mejorado para Hidroxiazapironas

inventado por nosotros y descrito en la solicitud de patente provisional de los Estados Unidos

Solicitud No. 60/402,759, presentada el 12 de Agosto de 2002.

incluyendo dicha solicitud de patente no provisional de los Estados Unidos y cualquier solicitud que reivindique prioridad de dicha solicitud provisional, presentada en cualquier

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país, y cualquier patente que pueda ser emitida y/o otorgada a la misma, y todas las divisiones, continuaciones, reemisiones, certificado de reexaminación y extensiones de la misma en todos los países, dicho interés siendo la propiedad total de dicha invención y de todas dichas solicitudes, patentes (incluyendo patentes reemitidas), extensiones y certificados de reexaminación a ser tenido y disfrutados por Bristol-Myers Squibb Company y sus sucesores y cedentes por la totalidad de los términos que sean concedidos y/o emitidos a dicha patente (incluyendo patentes reemitidas), extensiones, y certificados de reexaminación, tan completa y totalmente como los mismos habrían sido tenidos y disfrutados por nosotros si esta venta, cesión y transferencia no hubiera sido hecha;

Y por la presente acordamos comunicar a dicho cesionario o sus representantes cualquier hecho que conozcamos respecto a esta invención, atestiguar en cualquier proceso legal, firmar y/o ejecutar cualquier documento adicional y/o instrumentos que puedan ser necesarios, legales y apropiados en y/o para la presentación y/o procesamiento de todas las solicitudes, incluyendo solicitudes de división, continuación y reemisión, certificados de extensión y reexaminación y/o concesión y/o emisión de la misma y/o de otro modo asegurar el título de dicha invención y de todas dichas solicitudes, patentes (incluyendo reemisión de patentes, certificados de extensión y reexaminación a dicho cesionario, y en general hacer todo lo posible para ayudar a dicho cesionario, sus sucesores y cesionarios a obtener y hacer cumplir la protección apropiada para dicha invención en todos los países.

Firmado este 3 de Octubre de 2002 por

Jeffrey Depue (Firma)
Jeffrey Depue

142 

Reconocimiento

Estado de New Jersey)
)
Condado de Middlesex)

ss:

En este 3 de Octubre de 2002 ante mi, vino

Jeffrey Depue

a quien conozco como la misma persona de ese nombre mencionada en y quien
ejecutó el instrumento anterior, y reconoció que lo hizo.

[Sello]

Laura H. Derbin (Firma)
Notario Público

Mi comisión expira: _____

Hay un sello que dice:
LAURA H. DERBIN
NOTARIO PUBLICO, ESTADO DE NEW JERSEY
ID # 2278973
La comisión expira el 7 de Septiembre de 2006

Firmado este 7 de Octubre de 2002 por

Atul S. Kotnis (Firma)
Atul S. Kotnis

143

Reconocimiento

Estado de New Jersey)

)

ss:

Condado de Middlesex)

En este 7 de Octubre de 2002 ante mi, vino

Atul S. Kotnis

a quien conozco como la misma persona de ese nombre mencionada en y quien
ejecutó el instrumento anterior, y reconoció que lo hizo.

[Sello]

Laura H. Derbin (Firma)
Notario Público

Mi comisión expira: _____

Hay un sello que dice:

LAURA H. DERBIN

NOTARIO PUBLICO, ESTADO DE NEW JERSEY

ID # 2278973

La comisión expira el 7 de Septiembre de 2006

Firmado este 3 de Octubre de 2002 por

Simon Shun Wang Leung (Firma)
Simon Shun Wang Leung

144

Reconocimiento

Estado de New Jersey)
)
Condado de Middlesex)

ss:

En este 3 de Octubre de 2002 ante mi, vino

Simon Shun Wang Leung

a quien conozco como la misma persona de ese nombre mencionada en y quien
ejecutó el instrumento anterior, y reconoció que lo hizo.

[Sello]

Laura H. Derbin (Firma)
Notario Público

Mi comisión expira: _____

Hay un sello que dice:
LAURA H. DERBIN
NOTARIO PUBLICO, ESTADO DE NEW JERSEY
ID # 2278973
La comisión expira el 7 de Septiembre de 2006

Firmado este 7 de Octubre de 2002 por

Daniel J. Watson (Firma)
Daniel J. Watson

146



Reconocimiento

Estado de New Jersey)
)
Condado de Middlesex)

ss:

En este 7 de Octubre de 2002 ante mi, vino

Daniel J. Watson

a quien conozco como la misma persona de ese nombre mencionada en y quien
ejecutó el instrumento anterior, y reconoció que lo hizo.

[Sello]

Laura H. Derbin (Firma)
Notario Público

Mi comisión expira: _____

Hay un sello que dice:
LAURA H. DERBIN
NOTARIO PUBLICO, ESTADO DE NEW JERSEY
ID # 2278973
La comisión expira el 7 de Septiembre de 2006



Brigard & Castro

SANTA FE DE BOGOTA - COLOMBIA

PODER

Yo (nosotros)

domiciliado(s) en

Nombre(amos) a: RAMIRO CASTRO DUQUE y/o HECTOR GOMEZ MEJIA, de Santafé de Bogotá, Colombia, apoderados verdaderos y legales con poder especial, amplio y suficiente, para recabar de las oficinas y autoridades colombianas administrativas, judiciales y de policía, en cualquier instancia o recurso, la obtención de patentes de invención, registros de marcas, diseños industriales, modelos de utilidad, depósitos de nombres comerciales y enseñanzas, registros de derechos de autor y contratos sobre los mismos, obtención de certificados de obtentor de variedades vegetales, así como sus prórrogas, renovaciones, anotaciones de traspaso, cambios de nombre y/o domicilio; elaborar, tramitar y registrar contratos de licencia y licencias de cualesquiera clases; intervenir como demandante o como demandado en cualquier instancia y recurso ante cualquier juez, corporación, funcionario público o autoridad en acciones judiciales, administrativas y de policía tales como: oposiciones al registro de marcas; acciones de caducidad, cancelación y nulidad; acciones reivindicatorias, acciones derivadas de la obtención o explotación de licencias; acciones de competencia desleal; demandas penales; acciones de indemnización de perjuicios, reclamos y observaciones a solicitudes de patentes, diseños industriales, modelos de utilidad, en el ejercicio de medidas cautelares y en otras acciones o medidas similares.

A este efecto, lo(s) faculto(amos) para: elevar solicitudes, formular descripciones, enmiendas, protestas, declaraciones, oposiciones, cancelaciones, nulidades, apelaciones y reclamos; pagar impuestos, cuotas y gravámenes prescritos por la ley; renunciar o desistír a derechos concedidos o en curso de concesión; recibir toda clase de documentos y valores, dando el recibo respectivo, y, en general, para dar ante dichas autoridades todos los pasos necesarios al efecto indicado y tomar todas las medidas que creyeren conducentes al resguardo de mis (nuestros) intereses, con todas las demás facultades legales necesarias.

Este poder comprende la facultad de ratificar o confirmar en mi (nuestro) nombre lo actuado así como la facultad de desistír, transigir, comprometer, y la de sustituirlo en todo o en parte y revocar sustituciones. Asimismo nombre(amos) a: RAMIRO CASTRO DUQUE y/o HECTOR GOMEZ MEJIA, domiciliado(s) en la Carrera 7 No. 16-56 Piso 9, mis (nuestros) apoderados en Colombia, con facultades para recibir notificaciones y designar apoderados judiciales o extrajudiciales.

Otorgado y firmado en

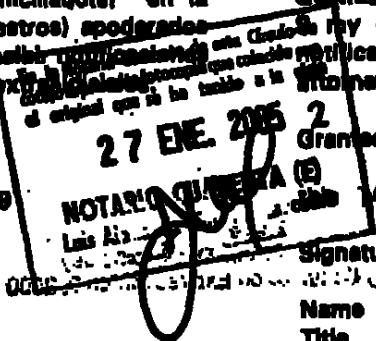
de

de 19

Firma

Nombre

Cargo



POWER OF ATTORNEY

I (We) BRISTOL-MYERS SQUIBB COMPANY

domiciled in

Princeton, New Jersey, USA

Hereby appoint RAMIRO CASTRO DUQUE and/or HECTOR GOMEZ MEJIA, of Santafé de Bogotá, Colombia, my (our) true and lawful attorneys with special, ample and sufficient power to obtain from the Colombian administrative, judicial and police offices and authorities, in any instance, privileges of patents of invention, registration of trademarks, industrial designs and utility models; registration of commercial names and emblems, registration of copyright and contracts related thereto, certificates of obtainers of vegetable varieties, as well as extensions, renewals and recordal of assignments and changes of name and domicile related to the above; to prepare, prosecute and register licenses of any kind; to act as plaintiff or defendant in any instance or recourse, and before any judge, corporation, public official or authority in judicial, administrative and police actions, such as: oppositions to the registration of trademarks; caducity, cancellation and nullity actions; claim actions derived from the obtaining or exploitation of licenses, action of unfair competition; penal demands, actions of indemnities for damages; claims or observations on patent applications, models, industrial designs and utility models; in the exercise of preventive measures; and in other actions or similar proceedings.

To that effect they hereby empowered to file applications, formulate descriptions, amendments, protests, declarations, oppositions, cancellations, nullities, appeals and claims; to pay taxes, quotas and assessments prescribed by law, renounce or waive the rights granted or in the process of granting; to receive all kinds of documents and valuables, giving the respective release of receipt, and, in general, to take before said authorities the necessary steps to such effect, and any measures that they may deem pertinent to the safeguard of my (our) interest(s) with all the other necessary legal powers.

This power includes the faculty to ratify or confirm desist, settle and compromise on my (our) behalf, and to substitute this power in whole or in part and to revoke substitutions. At the same time I (We) hereby appoint RAMIRO CASTRO DUQUE and/or HECTOR GOMEZ MEJIA, domiciled in Carrera 7 No. 16-56, Piso 9, my (our) attorney(s) in fact, with powers to receive notifications and to designate judicial and extrajudicial attorneys.

Granted and signed in Princeton, New Jersey, USA

day of April 1999

BRISTOL-MYERS SQUIBB COMPANY

Stephen B. Davis
Stephen B. Davis
Associate Counsel Patents

CERTIFICADO NOTARIAL (SOCIEDAD)

NOTARIAL CERTIFICATE (CORPORATION)

Yo, _____ de _____
personalmente compareció ante mí

a quien conozco, y de quien me consta que firmó el
anterior documento, debidamente juramentado declaró
y dijo que él es

Sociedad legalmente constituida para un período de
duración que aún no ha terminado; que el declarante
está autorizado por dicha compañía para conferir este
poder; que el sello estampado por él al pie de tal poder,
en nombre y representación de la expresada compañía,
es el sello oficial de ella; y que el objeto para el cual se
confiere este instrumento está comprendido dentro del
de esta sociedad.

El suscrito Notario hace constar que tuvo a la vista las
pruebas de la existencia de la sociedad.

Estado de _____
Fecha _____

y que quien confiere el presente poder es su
representante.

On this 14th day of April of 1998

personally appeared before me
Stephen B. Davis
to me known, and known to me to be the person who
signed the foregoing instrument who being by me duly
sworn did depose and say that he (she) is the

Associate Counsel Patents
of BRISTOL-MYERS SQUIBB COMPANY

Which is legally constituted for a term not yet expired,
that deponent is authorized by said Company to confer
this Power of Attorney; that the seal affixed hereunto
by the deponent in the name and on behalf of said
Corporation is the corporate seal thereof; and that the
purpose for which this instrument is granted is included
within the corporate purpose of company.

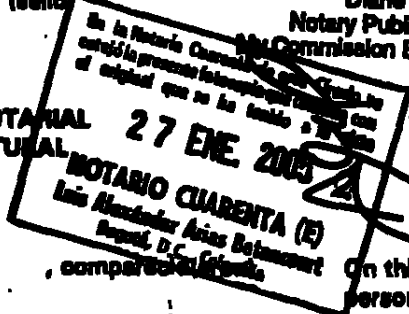
The undersigned Notary Public attests that he has seen
the documents that prove the existence of the
company.

State of Delaware
under date of November 13, 1989

and that he (she) who grants the present power of
attorney is its Representative.

Notario Público (sello)

CERTIFICADO NOTARIAL
PERSONA NATURAL



Diane C. Bartram Public Notary (Seal)
Notary Public of New Jersey
My Commission Expires March 8, 2000

NOTARIAL CERTIFICATE
NATURAL PERSON

Yo, _____ de _____
compareció ante mí

a quien (as) conozco y me consta que es(son) la(s)
persona(s) firmante(s) del documento que precede y
quien(es) declara(n) que otorgan el mismo para los
fines y propósitos que en él se expresan.

On this 14th day of April of 1999

personally appeared before me
Stephen B. Davis

who is(are) known to me and who I attest executed the
foregoing document and he (they) declared he (they)
grant(s) the document for the uses and purposes therein
expressed.

Notario Público (sello)

Diane C. Bartram
Notary Public of New Jersey
My Commission Expires March 8, 2000

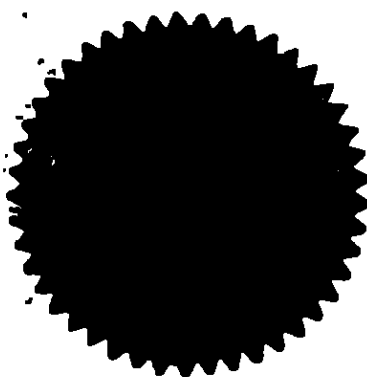
Notary Public (Seal)

LEGALIZATION ANTE CONSUL COLOMBIANO ES
REQUERIDA.

LEGALIZATION BEFORE COLOMBIAN CONSUL IS REQUIRED.

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STATE OF NEW JERSEY. } ss.
County of Mercer

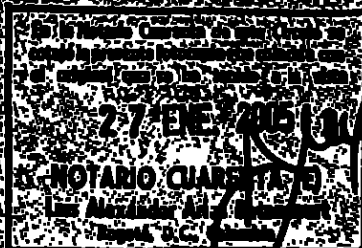


I, CATHERINE DICOSTANZO, Clerk of the County of Mercer,

Do Hereby Certify that *Luane C. Bortone*
Esq., whose name is subscribed to the acknowledgment, proof or affidavit of
the annexed instrument, and thereon written, is and was at the time of
taking the same, a Notary Public in and for said State,
dwelling in said County, commissioned and sworn and duly authorized by
the laws thereof to take the proofs and acknowledgments of deeds or other
instruments of writing, and affidavits to be recorded in said State, and that I
am well acquainted with the handwriting of said official, and verily believe
that the signature is genuine.
Further Certify that impression of Seal of Notaries Public not required by
law be filed in my office.

In Testimony Whereof, I have hereunto set my hand and affixed the seal of
said County and Courts, at Trenton this *15th* day of
April A.D. nineteen hundred and *twenty one*

Catherine DiCostanzo Mercer County Clerk.



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F

EL SUSCRITO CONSUL DE COLOMBIA

VISTOS LOS DOCUMENTOS PRESENTADOS POR LOS INTERESADOS

CERTIFICA

Que el Señor (a), **CATHERINE Dicostanzo**, Clerck del condado de Mercer estado de New Jersey, autenticó la firma de la notario(a) publico(a) sr (a). **DIANE C. BARTRAN** del estado de New Jersey, Estados Unidos de América y quien ejercia las funciones antes expresadas, y que la firma y sello que en el documento aparecen como suyos, son los que usa y acostumbra en sus actos oficiales;

Que la notario(a) antes citada autenticó la firma del señor **STEPHEN B. DAVIS** quien actua en calidad de Asesor de Patentes de la Compañia **BRISTOL-MEYERS SQUIBB COMPANY** sociedad que existe y esta legalmente organizada bajo las leyes del estado de Delaware U.S.A



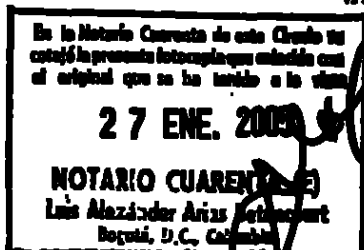
Que ha tenido a la vista los documentos probatorios de los hechos citados y constatados por el notario público y el County Clerck del estado de New Jersey, los cuales forman parte integral del presente documento.

Se expide la presente certificación en cumplimiento de los artículos 259 del Código de Procedimiento Civil y 480 del Código de Comercio y a solicitud del interesado el 20 de Abril de 1999.

NO SE ASUME RESPONSABILIDAD POR EL CONTENIDO DEL DOCUMENTO ADJUNTO.

PAGADO IMPUESTO DE TIMBRE Y DERECHOS CONSULARES.

VALOR CINCUENTA Y SIETE DOLARES US\$57.00 RECIBO No. 200283



Federico Mejía Mejía
Cónsul de Colombia

MINISTERIO DE RELACIONES
EXTERIORES

044498

CUYA FIRMA APLICA EN EL
DOCUMENTO DESEMPAÑADO
LAS FUNCIONES INDICADAS

NO SE ASUME
RESPONSABILIDAD DEL TEXTO

99 APR 29 AM 9:43

JEFE DE LEGALIZACIONES
SANTAFE DE BOGOTA D.C.

En la Notaría Cuarenta de esta Ciudad se
coteó y presento fotocopia que concuerda con
el original que se le envió a la Notaría

27 ENE. 2005

NOTARIO CUARENTA (S)
Luis Alexander Arias Betancourt
Bogotá, D.C., Colombia



150 7

TRADUCCION OFICIAL No. 260/99 de las Legalizaciones que se encuentran a continuación de un Poder otorgado por BRISTOL-MYERS SQUIBB COMPANY, una sociedad domiciliada en Princenton, New Jersey, Estados Unidos de América al doctor RAMIRO CASTRO DÚQUE y/o HECTOR GOMEZ MEJIA, de Santafé de Bogotá, D.C., Colombia, del inglés al español, las cuales para su identificación se sellan con el Sello del Traductor al mismo tiempo que la presente.-

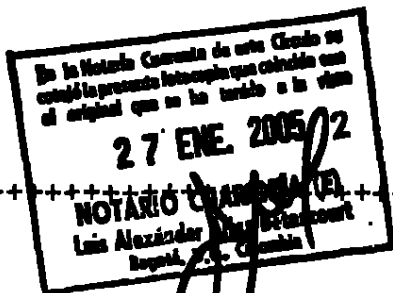
ANEXOS: El Poder arriba mencionado, Certificaciones Notariales, Certificación de las Firmas Notariales, Certificación del Consulado General de Colombia en New York, Estado de New York, Estados Unidos de América, Autenticación por el Ministerio de Relaciones Exteriores de Colombia.-

Diane C. Bartram (firmado)
Notario Público
HAY UN SELLO QUE DICE:

Diane C. Bartram
Notario Público de New Jersey
Mi Comisión Expira el 9 de Marzo del
año 2000

Diane C. Bartram (firmado)
Notario Público
HAY UN SELLO QUE DICE:

Diane C. Bartram
Notario Público de New Jersey
Mi Comisión Expira el 9 de Marzo del
año 2000



Diane C. Bartram (firmado)
Notario Público
HAY UN SELLO QUE DICE:

Diane C. Bartram
Notario Público de New Jersey
Mi Comisión Expira el 9 de Marzo del
año 2000

HUGO NAVARRO ALVAREZ
TRADUCTOR E. INTERPRETE OFICIAL
Rep. 14-77-2000-10-1997

151 7

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Diane C. Bartram (firmado)
Notario Público

HAY UN SELLO QUE DICE:

Diane C. Bartram
Notario Público de New Jersey
Mi Comisión Expira el 9 de Marzo del
año 2000

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Diane C. Bartram (firmado)
Notario Público

HAY UN SELLO QUE DICE:

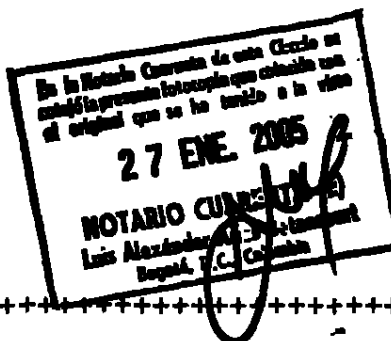
Diane C. Bartram
Notario Público de New Jersey
Mi Comisión Expira el 9 de Marzo del
año 2000

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Diane C. Bartram (firmado)
Notario Público

HAY UN SELLO QUE DICE:

Diane C. Bartram
Notario Público de New Jersey
Mi Comisión Expira el 9 de Marzo del
año 2000



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ESTADO DE NEW JERSEY
Condado de Mercer

Yo, CATHERINE DICOSTANZO, Escribano del Condado de Mercer,

Por Medio del Presente Certifico que Diane C. Bartram, cuyo nombre está suscrito al reconocimiento, prueba o declaración jurada del instrumento anexo, y en éste escrito, es y era en el momento de tomar el mismo, un Notario Público en y para dicho Estado, residente en dicho Condado, comisionado y juramentado y debidamente autorizado por las leyes de éste para tomar las pruebas y recono-

HUGO NAVARRO ALVAREZ
INTERPRETE E INTERPRETE OFICIAL
P.O. BOX 10000, NEW YORK, N.Y. 10001

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cimientos de escrituras u otros instrumentos escritos, y declaraciones juradas para ser registrados en dicho Estado, y que estoy familiarizado con la caligrafía de dicho funcionario, y de veras creo que la firma es genuina.

Además Certifico que la impresión del Sello de Notarios Públicos no está requerida por la ley para ser presentada en mi oficina.

En Testimonio de lo Cual, he firmado el presente de mi puño y letra y fijado el sello de dichos Condado y Tribunales, en Tranton este día 15 de Abril del A.D. de mil novecientos noventa y nueve.

Catherine DiConstanzo (fdo.) Escribano del Condado de Mercer.

SELLO EN RELIEVE.

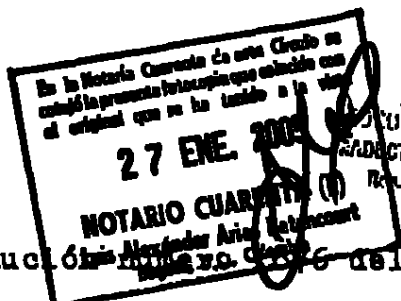
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EN ESPAÑOL: La Certificación del Consulado General de Colombia en New York, Estado de New York, Estados Unidos de América bajo el número 200283 de fecha 20 de Abril de 1999; Autenticación hasta por el Ministerio de Relaciones Exteriores de Colombia bajo el número 044498 de fecha 29 de Abril de 1999.

(Pagado Impuesto de Timbre y Derechos Consulares por valor de \$57.00 Dólares).

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ES TRADUCCION FIEL Y COMPLETA DE LOS DOCUMENTOS ADJUNTOS.



ALVARO ALVAREZ
TRADUCTOR E INTERPRETE OFICIAL
Rev. 1978 Modificado 1997

Resolución No. 0000000000 del Ministerio de Justicia.

Fecha: Mayo 3 de 1999.

JEFE DE LA SECCION DE
SANTAFE DE BOGOTA D.C.
60 MAY - 99 AM 11:09
RESPONSABILIDAD DEL TEXTO
NO SE ASUME

MINISTERIO DE RELACIONES
EXTERIORES
044498
DOCUMENTO DESEMPLEADO
LAS FUNCIONES INDICADAS
CUYA FIRMATA APARECE EN EL



GAVIRIA

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ORGANIZACION ELECTORAL
REGISTRADURIA NACIONAL DEL ESTADO CIVIL

REGISTRO CIVIL DE DEFUNCION

Indicativo
Serial

5562241

Datos de la oficina de registro							
Clase de oficina	Registraduria	Notaria	☒	Consulado	Corregimiento	Insp. de Policia	Código
País - Departamento - Municipio - Corregimiento o Inspección de Policía							
COLOMBIA CUNDINAMARCA BOGOTA D.C.						NOTARIA 32.	

Datos del Inscrito	
Apellido y nombres completos	
CASTRO DUQUE RAMIRO	
Documento de identificación (Clase y número)	Sexo (en Letras)
C.C. No. 170322 DE BOGOTA	MASCULINO

Fecha de la defunción				Hora		Número de certificado de defunción	
Año	2	0	0	4	Mañana	1	0
Día	3	0	04:10 PM		A= 2094375.		
Lugar que profiere la sentencia				Fecha de la sentencia			
-----				Año Mes Día			
Documento presentado				Nombre y cargo del funcionario			
Autorización judicial ☐ Certificado Médico ☒				ANDRES DIAZ CAMPOS.- R. M. No. 79982662			

Datos del denunciante	
Apellido y nombres completos	
EDGAR DAVID REGINO II.	
Documento de identificación (Clase y número)	Firma
C.C. No. 15.030.154 DE LORICA/ CORDOBA	

Primer testigo	
Apellido y nombres completos	
Documento de identificación (Clase y número)	Firma
-----	-----

Segundo testigo	
Apellido y nombres completos	
Documento de identificación (Clase y número)	Firma
-----	-----

Fecha de inscripción				Notario y funcionario que autoriza	
Año	2	0	0	4	Mañana
Día	1	0	2	BLANCA RESTREPO	

PADRES		ESPACIO PARA NOTAS	
ALFONSO CASTRO			
MERCEDES DUQUE			

ORIGINAL PARA LA OFICINA DE REGISTRO

NOTARIA 32

DEL CÍRCULO DE SANTO PE DE BOGOTÁ, D.C.

Germán Blázquez Moreno L.
Notario

COMO SECRETARIO DELEGADO DE LA NOTARIA TREINTA Y DOS (32) DEL
CÍRCULO DE BOGOTÁ

CERTIFICO QUE:

La presente acta es fiel copia del original tomada del registro
civil de defunciones serial indicativa número: 5562201
que expide en la ciudad de Bogotá D.C. hoy: 03 NOV. 2004



156
154

SUPERINTENDENCIA I LINTERALTO
Radicacion : 85812425 00000000
Fecha (AND): 2005-02-11 10:49:01
Tramite : 011 PCT-PATENT 379 FASE INCI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

	USUARIO	RADICADOR
PATENTE DE INVENCION ✓	()	()
- Indicación de que se solicita la concesión de una patente.	()	()
- Datos de identificación del solicitante o de la persona que se presenta la solicitud.	()	()
- Descripción de la invención.	()	()
- Dibujos de ser estos pertinentes. X	()	()
- Comprobante de Pago de las tasas establecidas.	()	()

COMPLETA () INCOMPLETA ()

DISEÑO INDUSTRIAL ()

- Indicación de que se solicita el registro de Diseño Industrial	()	()
- Datos de identificación del solicitante o de la persona que presenta la solicitud.	()	()
- Representación gráfica o fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño.	()	()
- Comprobante de pago de las tasas establecidas	()	()

COMPLETA () INCOMPLETA ()

ESQUEMA DE TRAZADO ()

- Indicación de que solicita el registro de un Esquema de trazado.	()	()
- Datos de identificación del solicitante o de la persona que presenta La solicitud.	()	()
- Representación gráfica del esquema de trazado	()	()
- Comprobante de pago de las tasas establecidas.	()	()

COMPLETA () INCOMPLETA ()

Firma Responsable:

Gaudia M Nova

Fecha:



Industria y Comercio
SUPERINTENDENCIA

Folio 157

155

2020
Bogotá DC

Doctor
HECTOR GOMEZ MEJIA
Apoderado
BRISTOL – MYERS SQUIBB COMPANY

REFERENCIA:	Radicación No.	05-12425
	Solicitud Internacional	PCT/US2003/024934
	Fecha inicio fase nacional	12-03-2005
	Trámite	011
	Evento	379
	Actuación	416
	Oficio No.	196
	Folios	001

Teniendo en cuenta que la solicitud de privilegio de patente que se tramita bajo el expediente indicado en la referencia, reúne los requisitos de forma establecidos en la Decisión 486 de la Comisión de la Comunidad Andina, el Tratado de Cooperación en Materia de Patentes (PCT), el Reglamento y la Circular Única de la Superintendencia de Industria y Comercio, se envía el extracto de la solicitud a la Oficina de Comunicaciones para efecto de su publicación en la Gaceta de Propiedad Industrial.

Cúmplase
Dado en Bogotá DC

22 MAR. 2005'


ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones

202027

Carrera 13 No. 27-00 Pisos 5, 7 y 10
Conmutador: 382 0840
Fax: 350 5220
E-mail: Info slc.gov.co
www.slc.gov.co
Bogotá, D.C., Colombia

DIVISION DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 05-012425

EL EXTRACTO DE LA PRESENTE SOLICITUD DE PATENTE DE INVENCION

PCT FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No 551

DE FECHA 29 DE ABRIL DEL 2005, EL TERMINO HABIL SEÑALADO POR LA

LEY EXPIRA EL 29 DE JULIO DEL 2005

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI ☐ ☐

NO ☐ ☒ ☐

Bogotá D.C., Octubre de 2006

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

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RADICACIÓN: 6-12425

EDICTO No. 18014

LA SECRETARÍA GENERAL AD-HOC
HACE SABER:

Que esta Superintendencia profirió Resolución No. 29243 de 30-OCT-2006. Que el contenido de la parte resolutive es como sigue: El Superintendente de Industria y Comercio.

RESUELVE

ARTICULO PRIMERO: Declarar abandonada la solicitud de privilegio de patente de invención que entró en fase nacional en virtud del Tratado de Cooperación en Materia de Patentes (PCT), de acuerdo con las razones expuestas en la parte considerativa de la presente resolución.

ARTICULO SEGUNDO: Notificar personalmente el contenido de la presente resolución al doctor Héctor Gómez Mejía, o a quien haga sus veces, en su calidad de apoderado de Bristol - Myers Squibb Company., entregándole copia de la misma, advirtiéndole que contra ella proceda el recurso de reposición interpuesto ante el Superintendente de Industria y Comercio, al momento de la notificación o dentro de los 5 días hábiles siguientes a ella.

NOTIFÍQUESE Y CÚMPLASE

Dada en Bogotá, D.C., a los 30 OCT. 2006

EL SUPERINTENDENTE DE INDUSTRIA Y COMERCIO,


JAIME RODRÍGUEZ COBAR

Para notificar a los interesados, se fija el presente EDICTO en lugar visible al público en la SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO, por el término de (10) diez días hábiles contados a partir de las 8:30 a.m. de hoy.

Secretaría General Ad-Hoc 17-NOV-2006 Este edicto se desliza hoy 30-NOV-2006 a las cinco (5:00 p.m.)
Secretaría General Ad-Hoc
EDICTO No. 18014