

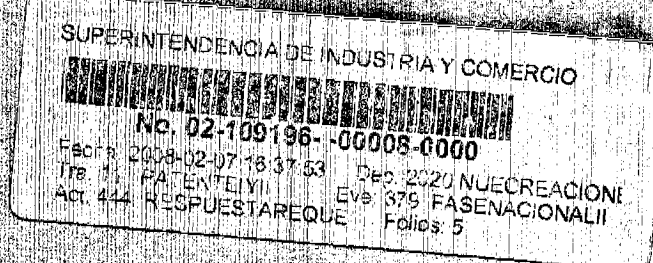
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Señores

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

DIVISIÓN DE NUEVAS CREACIONES

E. S. D.



Ref: Expediente No. 02-109.196

Solicitud de patente de invención titulada: "S-METIL-DIHIDRO-ZIPRASIDONA PARA EL TRATAMIENTO LOS TRASTORNOS PSIQUIÁTRICOS Y OCULARES"

Solicitante: PFIZER PRODUCTS INC.

RESPUESTA AL OFICIO No. 12057, NOTIFICADO POR FIJACIÓN EN LISTA No. 359,
DE FECHA 28 DE SEPTIEMBRE DE 2007,
(EXAMEN DE FONDO)

CARLOS R. OLARTE, mayor de edad y vecino de Bogotá, identificado tal como aparece al pie de mi firma, en mi carácter de apoderado de la sociedad solicitante, me permito manifestar lo siguiente ante el auto emanado por ese Despacho, dentro del plazo legal de prórroga previsto en el artículo 45 de la Decisión 486:

1. Con el ánimo de superar la única objeción del Examinador, me permito presentar un Capítulo Reivindicatorio Modificado, que reemplaza en su totalidad al Capítulo Reivindicatorio presentado al momento de radicar la presente solicitud el 10 de octubre de 2003. Para tal efecto, adjunto un recibo de pago que cubre la tasa de modificación correspondiente.

Valga anotar que el Capítulo Reivindicatorio Modificado presentado cumple a cabalidad con lo estipulado en el Artículo 34 de la Decisión 486 de la CAN, ya que éste de ninguna manera implica una ampliación de la protección correspondiente a la divulgación contenida en la solicitud inicial; por el contrario, corresponde a una franca limitación de la materia reivindicada inicialmente.

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2. a- El Examinador argumenta las reivindicaciones 1 a 13 se encuentran caracterizadas por un tratamiento terapéutico y no por los elementos constitutivos de la composición farmacéutica.

b- En respuesta a lo anterior, me permito anotar que en el Capítulo Reivindicatorio Modificado, las composiciones se encuentran correctamente definidas mediante sus constituyentes y la proporción de los mismos en la mezcla.

3. a- En su análisis de nivel inventivo el Examinador argumenta que los documentos CA2252898 (D1) y Prakash et al. (D2) afectan el nivel inventivo de la presente invención. El objeto reivindicado, que es una composición para tratar un trastorno psiquiátrico, que comprende una cantidad de S-metil-dihidroziprasidona o una de sus sales y un vehículo farmacéuticamente aceptable, se derivaría de los documentos mencionados anteriormente, por cuanto D1 ya había divulgado composiciones para uso parenteral de la sal de mesilato de Ziprasidona junto con un vehículo, y D2 había revelado la existencia del metabolito de Ziprasidona, denominado S-metil-dihidroziprasidona.

b- Llamo respetuosamente la atención del Examinador al hecho que D1 no contempla formulaciones de S-metil-dihidroziprasidona, en las que el principio activo se encuentra en las proporciones de las composiciones reivindicadas en el Capítulo Reivindicatorio Modificado. Una persona versada en la materia no podría, a partir de las enseñanzas de D1 o D2, establecer que las composiciones, con activos en las proporciones específicamente reivindicadas, presentarían efectos satisfactorios.

Ahora bien, toda persona medianamente versada en la materia sabe que cambios en la formulación pueden conducir a efectos mejorados, por ejemplo en su farmacocinética. Por lo tanto, a partir de los conocimientos proporcionados por D1 y D1, tanto individualmente como en combinación, es imposible que una persona medianamente versada en la materia hubiera podido llegar exactamente a las composiciones aquí reivindicadas.

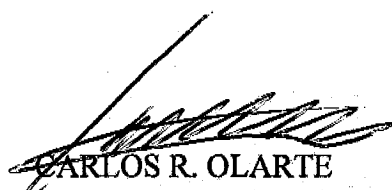
Por lo tanto, la presente invención resulta inventiva frente al arte previo citado por el Examinador, dado su carácter imprevisible e inesperado. Bien explica el Manual Andino de Patentes que el nivel inventivo se debe considerar como el proceso creativo que conlleva a resultados que no pueden deducirse del estado de la técnica en forma evidente.¹

¹ Manual Andino de Patentes. Secretaría General de la CAN, OMPI, EPO. 2004. ISBN:9978-43-855-6. Sección 10.1.

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por aclarar, ruego se emita un segundo examen de fondo con el fin de brindar la oportunidad al solicitante de proporcionar las explicaciones pertinentes.

Atentamente,


CARLOS R. OLARTE
C.C. No. 79.782.747 de Bogotá
T.P. 74.295

Anexos:

- Capítulo Reivindicatorio Modificado.
- Recibo de pago correspondiente a la tasa de modificación.

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CAPITULO REIVINDICATORIO MODIFICADO

1. Una composición farmacéutica para el tratamiento de trastornos psiquiátricos y/o oculares caracterizada por que comprende 6-cloro-5-(2-{4-[imino-(2-metilsulfanilfenil)-metil]piperazin-1-il}-etil)-1,3-dihidro-indol-2-ona o una de sus sales farmacéuticamente aceptables, junto con un vehículo farmacéuticamente aceptable, donde la relación en peso de ingrediente activo:vehículo varía en el intervalo de 1:6 a 2:1.
2. La composición según la Reivindicación 1, donde el compuesto activo 6-cloro-5-(2-{4-[imino-(2-metilsulfanilfenil)-metil]piperazin-1-il}-etil)-1,3-dihidro-indol-2-ona, se encuentra en una proporción en entre 5%-70% en peso.
3. La composición según la Reivindicación 1 donde la relación en peso de ingrediente activo:vehículo se encuentra de 1:4 a 1:1.
4. La composición según la Reivindicación 1 que se administra por vía oral, parenteral, rectal, intranasal o tópica en dosis diarias entre 0,5 a 500 mg por día; más específicamente en cantidades de 10mg a 80 mg por Kg de peso corporal/día.
5. La composición según la Reivindicación 1 donde los vehículos se escogen entre el grupo constituido por diluyentes o cargas solidas, medios acuosos estériles y diversos disolventes orgánicos no tóxicos y similares.
6. La composición según la Reivindicación 1 donde los trastornos a tratar se seleccionan entre esquizofrenia, trastorno de ansiedad generalizada, fobia, trastorno bipolar, trastorno de estrés post-traumático, demencia, manifestación en el comportamiento de retraso mental, manifestación en el comportamiento de un trastorno de la conducta, autismo, glaucoma y retinopatía isquémica.

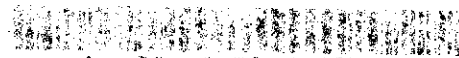
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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 80017607

RECIBO OFICIAL DE CAJA : 08 - 10,536
FECHA : FEBRERO 7 DE 2008

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 07- 00100-00000-0000

LA PRESENTE CERTIFICA QUE EL/LOS ASISTENTE(S) DEL DEPARTAMENTO DE INDUSTRIA Y COMERCIO, PRESENTE(S) EN LA OFICINA DE ASISTENCIA TECNICA, PARA RESPONDER A LAS CONSULTAS DE LOS ASISTENTES.

***** CONSIGNACION *****

ASISTENTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBEK	CONSIGNACION	BANCO DE BOGOTA	062754387	2661942	07/02/2008	4,673,000.00

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

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-03	CAMBIO DE MODALIDAD Y MODIFICA	
12		MARCAS Y LENAS COMERCIALES	103,000.00
		TOTAL :	\$ 103,000.00

CIENTO TRES MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

Short Communication

Characterization of the Novel Benzisothiazole Ring-Cleaved Products of the Antipsychotic Drug Ziprasidone

ABSTRACT:

Characterization of two novel benzisothiazole ring cleaved metabolites of the antipsychotic drug, ziprasidone (ZIP), in rat has been described. Metabolites designated M6 and M9 were isolated from urine and bile of the rat dosed with radiolabeled ZIP and purified by reversed-phase HPLC. The chemical structures of these metabolites were assigned based on tandem mass spectrometry in combination with chemical derivatization techniques. M6 and M9 were unaffected upon treatment with *N*-(tert-butyltrimethylsilyl)-*N*-methyltrifluoroacetamide. Reaction of M9 with aqueous TiCl_3 also did not change the HPLC retention time or the CID spectrum of

metabolite M9. These data excluded the possibility that these metabolites were owing to *N*-oxidation and/or aromatic hydroxylation. M6 and M9 were generated only when *in vitro* incubations of ZIP were conducted with human liver S-9 fraction in the presence of S-adenosyl-L-methionine. Based on these data, metabolites M6 and M9 were identified as *S*-methyl-dihydro-ZIP and *S*-methyl-dihydro-ZIP-sulfoxide, respectively. The structure of M9 was unambiguously confirmed by comparing the LC/MS retention time and mass spectral data with synthetic standard. A mechanism for the formation of these metabolites from ZIP is proposed.

ZIP¹ (fig. 1) is a substituted benzisothiazolylpiperazine that exhibits potent and highly selective dopamine D₂ and serotonin 5-HT₂ receptor antagonistic activities (1, 2). It is undergoing clinical trials for the treatment of schizophrenia. Its preclinical and clinical pharmacological profiles suggested that ZIP should be an efficacious antipsychotic with little or no liability for motor side effects (3). Previous studies have shown that ZIP is extensively metabolized in rats (4) and dogs, and in humans² after oral administration of radiolabeled ZIP. Only a very small amount of administered radioactivity (<1%) was excreted in urine as unchanged drug. Approximately 41% of the administered radioactivity was excreted in the urine and bile of rats (4). The major metabolites were due to oxidation on the benzisothiazole ring and *N*-dealkylation of the ethyl side chain attached to the piperazinyl nitrogen atom. Metabolism of benzisothiazoles typically involves oxidation at the sulfur, resulting in formation of sulfoxides and sulfones (5, 6). But, in addition to ZIP-SO and ZIP-SO₂, two additional metabolites of ZIP were detected in the urine and bile of rats that seem to be modified on the benzisothiazole ring at sites other than sulfur oxidation (4). These metabolites accounted for 31 and 34% of the total radioactivity excreted in rat urine and bile, respectively. This short communication describes the characterization of these two novel metabolites of ZIP, resulting from the reductive cleavage of the

benzisothiazole ring. Metabolites were isolated from rat urine and bile, and purified by HPLC, and characterized by: 1) LC/MS and LC/MS/MS; 2) derivatization with MTBSTFA or diazomethane; 3) treatment with aqueous TiCl_3 ; and 4) comparison of chromatographic and spectral behaviors with the metabolites obtained from an *in vitro* incubation of ¹⁴C-ZIP with human liver homogenate (S-9) in the presence of SAM. The structure of one metabolite was unambiguously confirmed by coelution on HPLC with synthetic standard.

Materials and Methods. ¹⁴C-ZIP, ZIP-SO, ZIP-SO₂, dihydro-ZIP, and *S*-methyl-dihydro-ZIP were synthesized at Pfizer Central Research (Groton, CT). ¹⁴C-ZIP showed a specific activity of 9.0 mCi/mmol (21.8 $\mu\text{Ci}/\text{mg}$) and a radiochemical purity of $\geq 98\%$, as determined by radio-HPLC. MTBSTFA and TiCl_3 were purchased from Aldrich Chemical Co. (St. Louis, MO) and Fisher Scientific (Springfield, NJ), respectively. SAM and ³H-SAM were purchased from Sigma Chemical Co. (St. Louis, MO) and NEN-Research Products (Boston, MA), respectively. Diazomethane was generated just before use from *N*-methyl-*N*-nitroso-*p*-toluene sulfonamide obtained from Aldrich (Milwaukee, WI).

Urine and bile (0–24 hr) from a previous study (4) were used for the isolation and purification of metabolites. The mixture of metabolites was subjected to chromatography on an HPLC system. Chromatography was conducted on a YMC basic HPLC column (4.6 mm $\times$ 250 mm, 5 μm) with a binary mixture of 20 mM ammonium acetate (pH 5.0, solvent A) and methanol (solvent B), as described previously (4). Several injections were made, and the radioactive fractions corresponding to metabolites M6 and M9 (with retention times of ~ 32.2 and ~ 40.1 min, respectively) were collected and concentrated on a

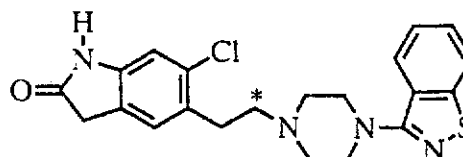


FIG. 1. Structure of ZIP.

Asterisk indicates position of the ¹⁴C-label.

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¹ Abbreviations used are: ZIP, ziprasidone (5-[2-{4-[(1,2-benzisothiazol-3-yl)piperazin-1-yl]ethyl}-6-chloro-1,3-dihydro-indol-2-one) hydrochloride hydrate; 5-HT, 5-hydroxytryptamine; ZIP-SO, ziprasidone sulfoxide; ZIP-SO₂, ziprasidone sulfone; MTBSTFA, *N*-(tert-butyltrimethylsilyl)-*N*-methyltrifluoroacetamide; SAM, S-adenosyl-methionine; dihydro-ZIP, 6-chloro-5-[2-{4-[[imino-(2-mercapto-phenyl)-methyl]-piperazin-1-yl]-ethyl}-1,3-dihydro-indol-2-one; *S*-methyl-dihydro-ZIP, 6-chloro-5-[2-{4-[[imino-(2-methylsulfanyl-phenyl)-methyl]-piperazin-1-yl]-ethyl}-1,3-dihydro-indol-2-one; CID, collision-induced dissociation; TMT, thiol methyltransferase; TPMT, thiopurine methyltransferase.

² C. Prakash et al., manuscript in preparation.

Send reprint requests to: Dr. Chandra Prakash, Department of Drug Metabolism, Central Research Division, Pfizer, Inc., Groton, CT 06340.

nitrogen evaporator. Derivatization of the purified metabolites **M6** and **M9** (each ~5000 dpm and 100 ng) was conducted by reaction with MTBSTFA or diazomethane using standard procedures (4, 7). The reaction with TiCl_3 was performed as described (8).

In vitro incubations of ZIP with human liver microsomes or S-9 were conducted using standard procedures. The typical incubation mixture (1 ml total volume) contained 100 mM potassium phosphate buffer (pH 7.4), 0.5 μM cytochrome P450 (microsomes) or protein equivalent to 32 mg/ml of liver (S-9), ^{14}C -ZIP (50 μM , 0.2% dimethylsulfoxide), SAM or ^3H -SAM (50 μM), and an NADPH-generating system (9 mM MgCl_2 , 0.54 mM NADP^+ , 6.2 mM DL-isocitric acid, and 0.5 units/ml isocitric dehydrogenase). The reactions were initiated by addition of an NADPH regenerating system after a 5-min preincubation period. Reactions were incubated at 37°C for 30 min and were stopped by addition of methanol (2 ml).

Analysis of metabolites was performed on a SCIEX API III HPLC/MS/MS system using ion spray. The ion spray interface was operated at 6000 V, and the mass spectrometer was operated in the positive ion mode. CID studies were performed using argon gas at a collision energy of 25–30 eV and a collision gas thickness of 3.5×10^{14} molecules/ cm^2 .

Results and Discussion. Representative reversed-phase HPLC tracings showing the metabolite profiles from rat urine and bile are shown in fig. 2, *a* and *b*, respectively. The presence of two metabolites designated **M6** and **M9**, along with several additional metabolites of ZIP, was established in both urine and bile (4). Metabolite **M9** showed a protonated molecular ion at m/z 429, 16 mass units higher than the parent drug. Its CID spectrum (m/z 429) showed fragment ions at m/z 280, 263, 219, 194, 150, and 123 (fig. 3*a*). The ion at m/z 280 corresponds to a charge initiated fragmentation of the piperazinyl nitrogen—benzisothiazole carbon bond with the expulsion of the benzisothiazole + 16 amu moiety as a neutral molecule. The ion at m/z 150 resulted from the cleavage of the same nitrogen—carbon bond with charge retention on the benzisothiazole + 16 amu moiety and suggested the addition of one oxygen atom to the benzisothiazole ring. The presence of other characteristic fragment ions at m/z 194 and 263 further suggested that the addition of an oxygen atom had occurred remote from the oxindole part of the molecule. The assignment of these ions was confirmed by a parallel CID spectrum of m/z 431 (MH^+ , ^{37}Cl), which gave fragment ions at m/z 282, 265, 196, 150, and 123. These results strongly suggested that the oxidation had occurred at the benzisothiazole moiety. However, the retention time of **M9** was different from that of the synthetic ZIP-SO standard, suggesting a modification of the benzisothiazole other than sulfur oxidation.

Based on addition of 16 mass units to the benzisothiazole moiety, three structures were originally considered for **M9** (fig. 4): oxidation at the nitrogen of the benzisothiazole ring to form *N*-oxide **1**; aromatic hydroxylation of the benzisothiazole moiety **2**; and reductive cleavage of the benzisothiazole followed by methylation of the resulting thiophenol to form **3**.

Treatment of the purified metabolite **M9** with aqueous TiCl_3 did not change the HPLC retention time, the molecular ion, or the CID spectrum of metabolite **M9**. This eliminated an *N*-oxide as a possible structure for **M9**. Reaction of the purified metabolite **M9** with MTBSTFA or diazomethane also resulted in no change in the retention time or MS data, suggesting that a free hydroxyl group was not present. Based on these data, **M9** was tentatively identified as *S*-methyl-dihydro-ZIP-3 (fig. 4).

Metabolite **M6** showed a protonated molecular ion at m/z 445, 32 mass units higher than the parent drug. Its CID spectrum showed fragment ions at m/z 280, 263, 209, 194, 177, 166, and 109, suggesting

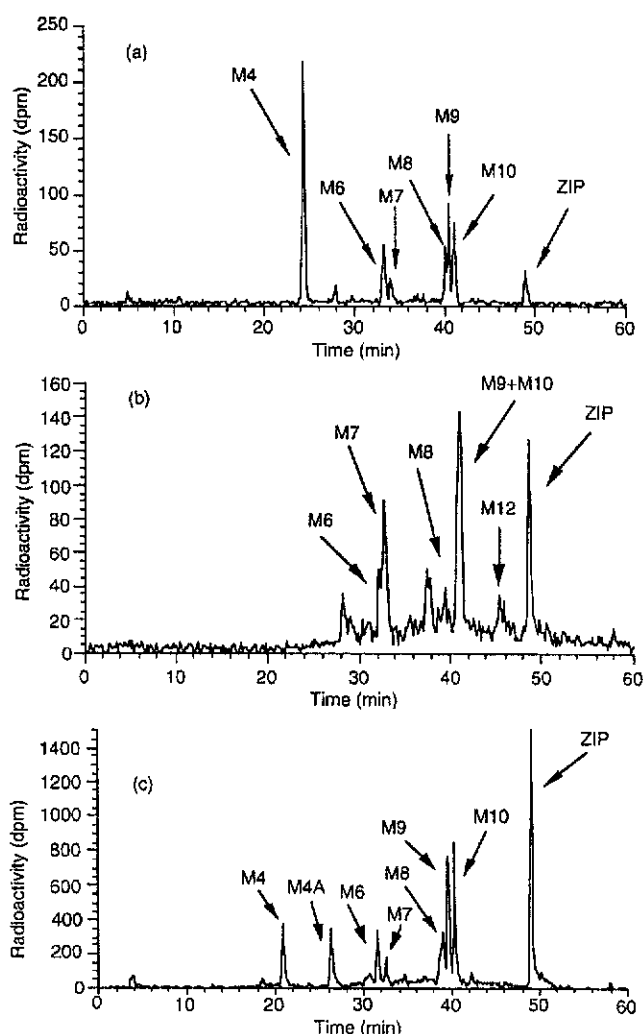


FIG. 2. HPLC radiochromatograms of ZIP metabolites from (a) rat urine, (b) rat bile, and (c) human liver homogenate (S-9).

that the 32 mass units were added on the benzisothiazole moiety (fig. 3*b*). **M6** did not coelute with synthetic ZIP-SO₂ on HPLC and thus sulfur dioxygenation of the intact molecule was eliminated as a possible structure. Treatment of **M6** with MTBSTFA or diazomethane did not change the HPLC retention time, or the molecular ion of metabolite **M6**, indicating the absence of a free hydroxyl group. Treatment of **M6** with aqueous TiCl_3 resulted in the disappearance of **M6** and the appearance of a new peak that had a retention time and MS data similar to those of **M9**. Based on these results, redox relationship between metabolite **M6** and **M9** was established. It was thus concluded that **M6** was a sulfur oxidation product of **M9** and was tentatively identified as *S*-methyl-dihydro-ZIP-sulfoxide.

In an attempt to confirm further the structures of **M6** and **M9**, a series of *in vitro* investigations were attempted. Incubations of ZIP with rat or human liver microsomes did not generate these metabolites (9). However, when microsomes were fortified with SAM, a small amount of metabolite **M9** was detected. Incubation of ^{14}C -ZIP with S-9 plus an NADPH regenerating system and SAM resulted in the formation of both metabolites **M6** and **M9** (fig. 2*c*). These metabolites showed the HPLC retention times and mass spectral characteristics similar to those of **M6** and **M9** obtained from rat urine as shown in fig. 3*c* for **M9**. Additional experiments using ^3H -SAM and unlabeled ZIP revealed that the formation of these metabolites required the presence

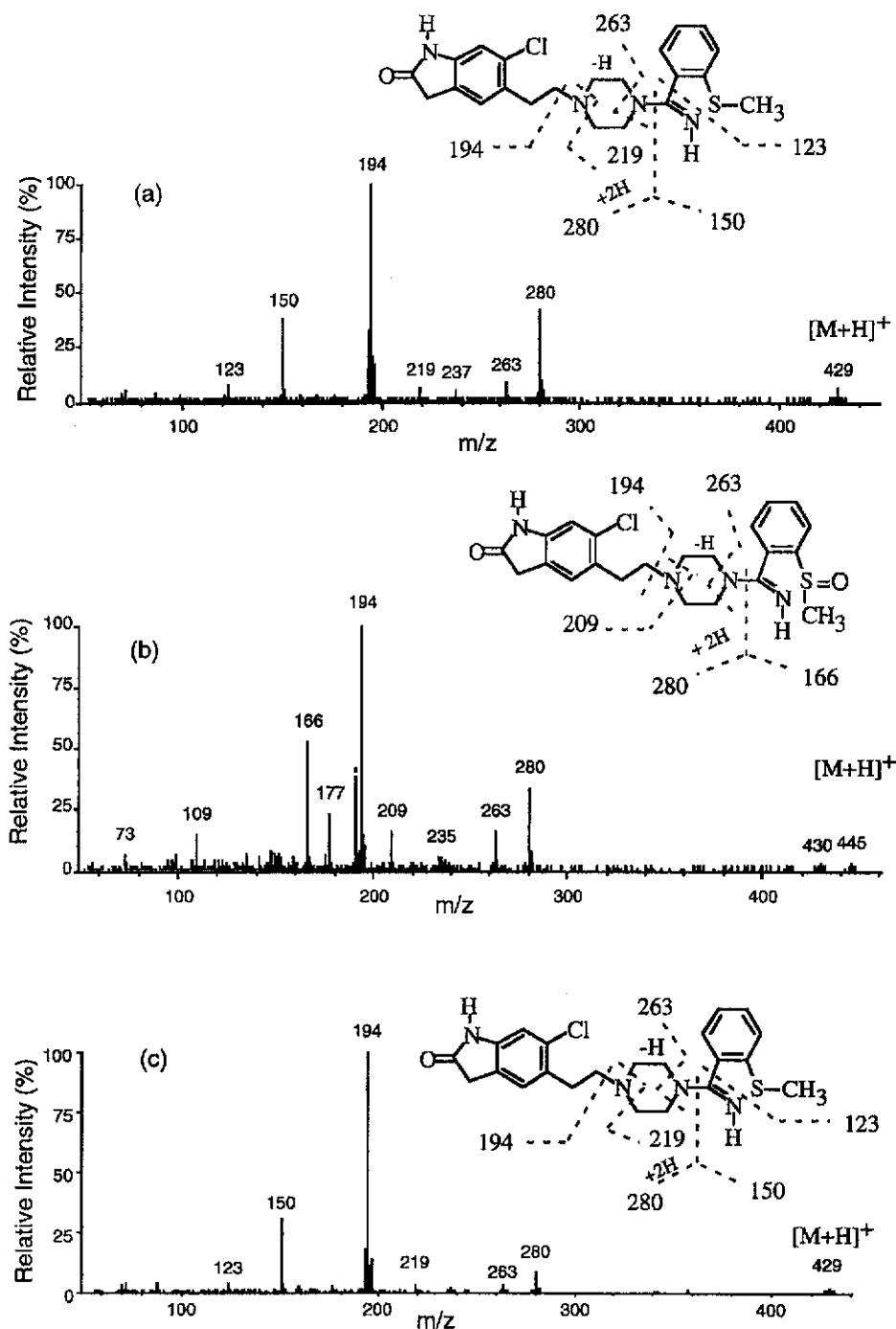


FIG. 3. CID product ion spectra of (a) urinary metabolite M9, (b) urinary metabolite M6, and (c) M9 from in vitro incubations.

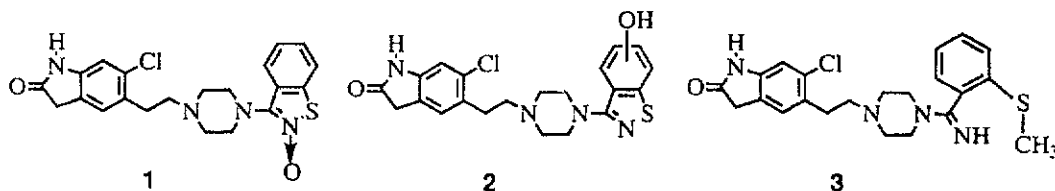


FIG. 4. Possible structures for metabolite M9.

of SAM, an essential cofactor for the methylation of thiols, in the incubation medium (10). Attempts to isolate enough amounts of M6 and M9 for NMR were unsuccessful. Therefore, M9 was synthesized

by treatment of dihydro-ZIP with diazomethane or CH₃I/KOH. M9 coeluted with synthetic standard on HPLC and had an identical CID spectrum.

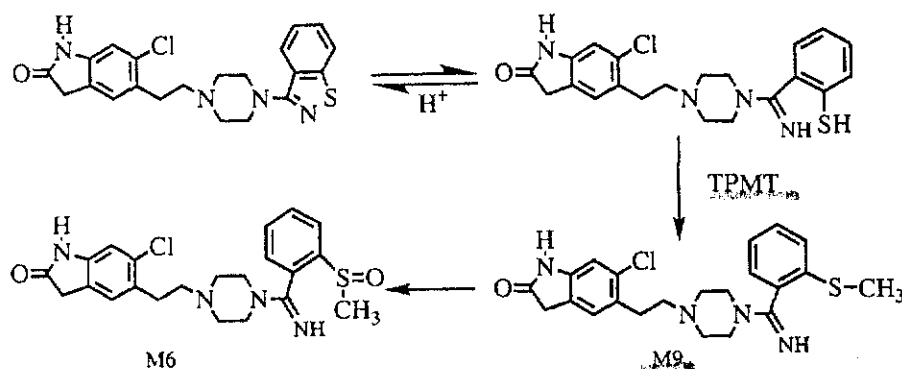


FIG. 5. Proposed pathway for the formation of M6 and M9.

Based on these data, metabolites M6 and M9 were identified as benzisothiazole ring-cleaved products. The formation pathway of metabolites M6 and M9 is speculated to involve an initial reductive cleavage of the benzisothiazole moiety to give an intermediate with a free thiol function and an amidine. The thiol can be further converted to a methyl thioether by methylation with TMT or TPMT to form M9 (fig. 5). Confirmation of this hypothesis was obtained by incubation of dihydro-ZIP with S-9 in the presence of SAM, resulting in the formation of M9. M6 was formed by oxidation of M9 at the sulfur of the S-methyl moiety of benzisothiazole ring.

Although there are several investigational pharmaceutical compounds containing a benzisothiazole structure (11–13), aromatic hydroxylation, N-oxidation, or cleavage of the benzisothiazole have not been reported. N-oxides of 1,2-benzisothiazoles have, however, been prepared by the reaction of 1,2-benzisothiazolium chloride with hydroxylamine (14). The common pathway for the metabolism of benzisothiazole analogs involves oxidation at the sulfur resulting in the sequential formation of sulfoxides and sulfones (5, 6), which suggests that the benzisothiazole moiety is more susceptible to oxidation at the sulfur than it is to aromatic hydroxylation. We have also recently demonstrated that oxidation at the sulfur of the benzisothiazole was one of the major pathways for metabolism of ZIP in rats (4). The other pathways involve N-dealkylation of the ethyl side chain attached to the piperazinyl nitrogen atom and hydration of C=N double bond of the benzisothiazole ring. Two metabolites, also modified on the benzisothiazole ring, were not fully characterized earlier (4). We have now identified these two novel metabolites of ZIP, which resulted from the modification of the benzisothiazole ring via a biotransformation not involving oxidation of the sulfur. These metabolites were formed by the reductive cleavage of benzisothiazole moiety. Similar cleavage has been reported for the compounds possessing a 1,2-benzisoxazole ring structure, risperidone (15), zonisamide (16), and iloperidone (17). Reductive cleavage of benzisoxazoles resulted in the formation of an intermediate imine that is hydrolyzed nonenzymatically to a stable ketone. But, in ZIP, the intermediate amidine was not identified due to its instability under acidic conditions.

The formation of metabolite M9 involves two steps that are catalyzed by two different enzymes. Our studies speculate that soluble TPMT enzyme might be involved in the methylation of the intermediate thiophenol, similar to that reported for aromatic sulfhydryl compounds (18). The trace amount of M9 formed in the incubation of ZIP with microsomes may be due to the presence of a small contamination of soluble TPMT in the microsomal preparations. But, we do not presently know which enzymes are involved in reduction of the benzisothiazole. The opening of the benzisoxazole ring of risperidone was attributed to the reduction by gut microflora (15). The reductive

ring opening is a reaction of dihydrogenation and as such must involve transfer of two electrons. It has recently been shown that the reductive ring opening in zonisamide is catalyzed mainly by a specific cytochrome P450 enzyme (CYP3A), in human and rat liver microsomes under anaerobic conditions (19, 20). Because ring-cleaved metabolites of ZIP were found both in urine and bile, we believe that the opening of the benzisothiazole ring is also mediated by liver enzymes. Further studies to determine the enzymes involved in the formation of these metabolites are currently under investigation. Finally, the identification of this novel metabolic pathway of ZIP will have relevance to understanding the metabolism of other benzisothiazole-piperazine drugs.

Acknowledgments. We thank Drs. Keith McCarthy, Harry Howard, C. Sklavounos, and Stan Walinsky for synthesizing radiolabeled ZIP and synthetic standards, and Drs. Hassan Fouda, Larry Tremaine, and Robert Ronfeld for helpful suggestions.

Department of Drug Metabolism,
Central Research Division,
Pfizer, Inc.

CHANDRA PRAKASH
AMIN KAMEL
DONGHUI CUI

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US005935960A

D2-99
100
D3**United States Patent** [19]

Walinsky et al.

[11] **Patent Number:** **5,935,960**[45] **Date of Patent:** **Aug. 10, 1999**

[54] **PRO-DRUGS OF 5-(2-(4-(1,2-BENZISOTHIAZOL-3-YL)-1-PIPERAZINYL)ETHYL)-6-CHLORO-1,3-DIHYDRO-2H-INDOL-2-ONE**

[75] **Inventors:** Stanley W. Walinsky, Mystic, Conn.;
John F. Lambert, Stonington, Conn.

[73] **Assignee:** Pfizer Inc., New York, N.Y.

[21] **Appl. No.:** 08/798,395

[22] **Filed:** Feb. 7, 1997

Related U.S. Application Data

[60] Provisional application No. 60/011,568, Feb. 13, 1996.

[51] **Int. Cl.⁶** **A61K 31/495**; C07D 403/06

[52] **U.S. Cl.** **514/253**; 544/373

[58] **Field of Search** 544/373, 368;
514/253

[56] **References Cited****U.S. PATENT DOCUMENTS**

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Primary Examiner—Richard L. Raymond

Assistant Examiner—Ann M. Kessinger

Attorney, Agent, or Firm—Peter C. Richardson; Paul H. Ginsburg; B. Timothy Creagan

[57] **ABSTRACT**

The present invention relates to a pro-drug of ziprasidone or pharmaceutically acceptable salts thereof, processes for its preparation, and pharmaceutical compositions and methods of treatment comprising said pro-drug.

9 Claims, No Drawings

TABLE 1-continued

Assay Conditions for Radioligand Binding Studies				
Receptor	Ligand concentration	Tissue	Blank	Buffer pH
	ketanserin .4 nM + 1 μ M prazosin + 500 nM mepyramine	cortex	2 μ M	TrisHCl pH 7.7

TABLE 2

Receptor	Radioligand Binding Results
D2	2.3 nM
D3	5.8 nM
D4	59.2 nM
5HT2	0.35 nM (IC ₅₀)
5HT1A	12 nM(IC ₅₀)

Pro-drugs of ziprasidone may be administered as a neuroleptic agent. Administration to a human subject may be alone or, preferably, in combination with pharmaceutically acceptable carriers or diluents in a pharmaceutical composition, in accordance with standard pharmaceutical practice. The pro-drugs of ziprasidone may be administered orally or parenterally including intravenously or intramuscularly. Suitable pharmaceutical carriers include solid diluents or fillers, and sterile aqueous solutions and various organic solvents. The pharmaceutical compositions are then readily administered in a variety of dosage forms, such as tablets, powders, lozenges, syrups, and injectable solutions. These pharmaceutical compositions, if desired, may contain additional ingredients such as flavorings, binders and excipients. Thus, for purposes of oral administration, tablets containing various excipients such as sodium citrate, calcium carbonate and calcium phosphate may be employed along with various disintegrants such as starch, alginate acid and certain complex silicates, together with binding agents such as polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often useful for tableting purposes. Solid compositions of a similar type may also be employed as fillers in soft and hard filled gelatin capsules. Preferred materials for this include lactose or milk sugar and high molecular weight polyethylene glycols. When aqueous suspensions or elixirs are desired for oral administration, the essential active ingredient therein may be combined with various sweetening or flavoring agents, coloring matter or dyes and, if desired, emulsifying or suspending agents, together with diluents such as water, ethanol, propylene glycol, glycerin and combinations thereof.

For parenteral administration, a solution or suspension of a pro-drug of ziprasidone in sesame or peanut oil, aqueous propylene glycol, or in sterile aqueous solution may be employed. Such aqueous solutions should be suitably buffered if necessary and the liquid diluent first rendered isotonic with sufficient saline or glucose. These particular aqueous solutions are especially suitable for intravenous, intramuscular, subcutaneous and intraperitoneal administration. The sterile aqueous media employed are all readily available by standard techniques known to those skilled in the art.

The effective dosage for a pro-drug of ziprasidone depends on the intended route of administration and other factors such as age and weight of the subject, as generally known.

The following Examples illustrate the preparation of the pro-drugs of the present invention. Commercial reagents were utilized without further purification. Melting points are uncorrected. NMR data are reported in parts per million (δ) and are referenced to the deuterium lock signal from the sample solvent. Unless otherwise stated, all mass spectrum were performed using electron impact (EI, 70 eV) conditions. Unless otherwise indicated, chromatography refers to column chromatography performed using 32-63 μ m silica gel and executed under nitrogen pressure (flash chromatography) conditions. High Pressure Liquid Chromatography (HPLC) was performed on a LDC Analytical constaMetric® 3200 HPLC (Thermo Separation Products Co.). A Zorbax® C8, 60Å, 3.9x150 mm column (Mac-Mod Analytical, Inc., Chadds Ford, Pa. 19317) was used for HPLC analysis (mobile phase: 40% acetonitrile, 45% 0.05M potassium phosphate, monobasic (KH₂PO₄) adjusted to pH=6.0 with potassium hydroxide (KOH), 15% methanol; Flow Rate of 1.0 ml/minute; Detector: UV 229 nm; Injector: 10 μ l; Samples are prepared in mobile phase (0.05 mg/ml)). Room temperature refers to 20-25° C.

EXAMPLE 1

1-[2-(6-Chloro-2,3-dihydro-2-oxo-1H-indol-5-yl)ethyl]-4-[(imino(2-mercaptophenyl)methyl)]piperazine

A one-liter, 3-neck round bottom flask equipped with a mechanical stirrer, condenser topped with a nitrogen inlet, and thermometer was purged and then maintained under an inert nitrogen atmosphere. 5-[2-[4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-1,3-dihydro-2H-indol-2-one (60.0 g, 145 mmol), 2-propanol (600 mL), and benzyl mercaptan (45.1 g, 363 mmol) were added to the flask affording a pink slurry which was heated to reflux (83° C.). After 6 hours at reflux, thin layer chromatography (eluted with methylene chloride/isopropanol 4:1) showed that the reaction was complete. The slurry was cooled to 25° C. and then granulated overnight. The slurry was filtered and the filter cake was washed with isopropanol (two times 90 mL). The wet cake was suspended in one liter of tetrahydrofuran (THF) and the resulting slurry was granulated at 25° C. for 7 hours. The slurry was filtered, washed with THF (two times 100 mL), and then dried in vacuo at 42° C. overnight. The title compound (54.4 g) was isolated as a tan solid (mp=224-226° C. with decomposition) in 90.2% yield. ¹³C NMR (DMSO-d₆): δ 176.25, 166.33, 159.16, 143.28, 135.16, 131.84, 131.26, 129.64, 128.65, 126.88, 126.03, 125.21, 116.37, 109.58, 57.65, 51.58, 35.40, and 29.95. Dibenzyl disulfide was isolated as a reaction by-product from the mother liquors.

EXAMPLE 2

1-[2-(6-Chloro-2,3-dihydro-2-oxo-1H-indol-5-yl)ethyl]-4-[(imino(2-mercaptophenyl)methyl)]piperazine dihydrochloride

The compound (5.0 g, 12.1 mmol) from Example 1 was suspended in 75 mL of THF at room temperature, and then 1.97 mL of concentrated hydrochloric acid was slowly added over 30 min affording a gummy solid. Water (5 mL) was added and the gummy solids were stirred for 6 hours to produce a finely divided solid which was granulated overnight. The mixture was filtered and the filter cake was washed with THF (10 mL). The product was dried in vacuo at 25° C. overnight under a nitrogen bleed to give 5.87 g of the title dihydrochloride compound as a tan solid (mp=232-240° C. with decomposition). When the dihydrochloride

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PREPARATION 4

3-(1-Piperazinyl)-1,2-benzisothiazole

3-(2-Cyanophenylthio)-1,2-benzisothiazole (0.25 g, 0.93 mmol), anhydrous piperazine (0.80, 9.32 mmol), and isopropanol (0.25 mL) were added to a 6 mL round bottom flask equipped with a magnetic stirring bar, reflux condenser topped with a nitrogen inlet, and thermometer. The flask was purged with nitrogen and then immersed in a 120° C. oil bath to give a yellow refluxing solution. After heating at 116–120° C. 120° C. for 25 hour, the reddish solution was cooled to 25° C. and 5 mL of methanol was added. Thin-layer chromatography (methylene chloride/isopropanol/triethylamine, 15:5:1) showed that the reaction was essentially complete. The crude reaction solution was analyzed by high-pressure liquid chromatography to show that 3-(1-piperazinyl)-1,2-benzisothiazole was formed in 70% yield.

PREPARATION 5

3-(1-Piperazinyl)-1,2-benzisothiazole

Anhydrous piperazine (17.2 g, 0.20 mol) and isopropanol (3.0 mL) were charged to a round bottom flask equipped with a mechanical stirrer, thermometer, condenser topped with a nitrogen inlet, and an addition funnel. Once the flask was purged and then maintained under nitrogen, the mixture was heated to 90° C. to afford a solution. A solution of 1-(2-cyanophenylthio)piperazine (4.38 g, 20.0 mmol) in isopropanol (2.0 mL) was slowly added to the warm piperazine solution over 1 hour. Once the addition was complete, the solution was heated to reflux (118° C.) for 24 hours. The reddish solution was cooled to room temperature and then analyzed by HPLC. 3-(1-Piperazinyl)-1,2-benzisothiazole was formed in 55% yield by HPLC assay.

PREPARATION 6

3-(2-Cyanophenylthio)-1,2-benzisothiazole
Method A

Bis(2-cyanophenyl)disulfide (1.25 g, 4.66 mmol), anhydrous piperazine (4.01 g, 46.6 mmol), and dimethyl sulfoxide (0.80 g, 10.3 mmol) in 15 mL of tetrahydrofuran were added to a 50 mL round bottom flask equipped with a magnetic stirring bar, thermometer, and condenser topped with a nitrogen inlet. After the flask was purged with nitrogen, the mixture was heated at reflux (75° C.) for 25 hours. The reaction mixture was cooled to 25° C., and the tetrahydrofuran was removed at reduced pressure. The resulting solid was dissolved in a 40 mL of a methylene chloride/water (1:1) mixture, the layers were separated, and the organic layer washed with water (20 mL). The methylene chloride solution was evaporated to afford a crude solid (0.85 g) which was crystallized from isopropanol (17 mL) to give light yellow crystals. After filtration, the product was dried in vacuo at 40° C. to give 0.39 g (31% yield) of 3-(2-cyanophenylthio)-1,2-benzisothiazole. Melting point 115.5–117° C. ¹H NMR (CDCl₃): δ 8.03 (m, 1H), 7.92 (m, 1H), 7.77 (m, 1H), 7.70 (m, 1H), 7.57 (m, 2H), and 7.48 (m, 2H). ¹³C NMR (CDCl₃): δ 154.99, 152.30, 134.83, 134.56, 134.06, 133.24, 129.07, 128.51, 125.33, 123.29, 120.13, 117.13, and 116.95. Analytical calculated for C₁₄H₈N₂S₂: C, 62.66; H, 3.00; N, 10.44; S, 23.90. Found: C, 62.43; H, 3.01; N, 10.68; S, 24.05. A X-ray crystal structure was also obtained to confirm structure.

PREPARATION 7

3-(2-Cyanophenylthio)-1,2-benzisothiazole
Method B

Bis(2-cyanophenyl)disulfide (0.40 g, 1.48 mmol) and 2-mercaptobenzonitrile (0.20 g, 1.48 mmol) were combined

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in 2 mL of isopropanol and were heated at reflux (90° C.) for 25 hours under a nitrogen (N₂) atmosphere. 3-(2-Cyanophenylthio)-1,2-benzisothiazole was formed in 69% yield by HPLC assay.

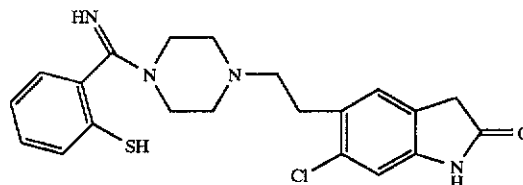
PREPARATION 8

1-(2-Cyanophenylthio)piperazine

Anhydrous piperazine (22.5 g, 261 mmol) and tetrahydrofuran (100 mL) were combined under a nitrogen atmosphere and then heated to 60–65° C. 3-Chloro-1,2-benzisothiazole (10.0 g, 59.0 mmol) was slowly added over one hour to the warm piperazine solution and then the resulting reddish solution was heated at 65° C. for 17 hours. Thin-layer chromatography (ethyl acetate/hexanes/triethylamine, 10:10:1) showed that the reaction was complete. The mixture was cooled to room temperature and then filtered. After toluene (100 mL) was added, the solution was concentrated at reduced pressure (40° C.) to one-half volume. The toluene solution was washed with water (100 mL), and the aqueous layer was extracted with fresh toluene (25 mL). The combined toluene layers were concentrated at reduced pressure to about 30 mL. After cooling the solution to 0–5° C., hexanes (50 mL) was slowly added. The resulting crystals were granulated for 1 hour at 0 to 5° C., filtered, and the cake was washed with fresh hexanes (15 mL). After drying the solids for 18 hours at 23° C., 11.51 grams (89% yield) of a yellow crystalline solid (m.p. = 67–71° C.) was isolated. The crude sulfenamide contained approximately 5% of 1,4-bis(2-cyanophenylthio)piperazine by NMR analysis. Title sulfenamide was stored at 0 to –10° C. to prevent slow conversion to 1,4-bis(2-cyanophenylthio)piperazine with heating or storage at room temperature. ¹H NMR (CDCl₃): δ 7.63 (m, 1H), 7.56 (m, 3H), 7.21 (m, 1H), 2.96 (m, 4H), and 2.87 (m, 4H). ¹³C NMR (CDCl₃): δ 142.69, 133.55, 132.67, 128.14, 126.69, 116.80, 110.24, 57.34, and 47.06. HRMS Found: 220.0878; C₁₁H₁₃N₃S Requires (FAB P+1): 220.0908.

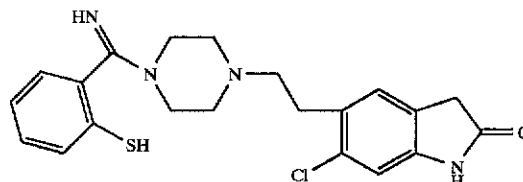
We claim:

1. A compound of the formula



or a pharmaceutically acceptable salt thereof.

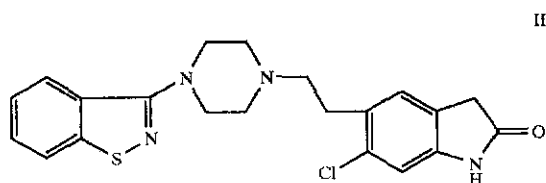
2. A process for preparing a compound of the formula



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comprising, reacting a compound of the formula



with a reducing agent.

3. A process according to claim 2 wherein said reducing agent is benzyl mercaptan.

4. A process according to claim 3 wherein said reducing agent benzyl mercaptan comprises 2.2 equivalents relative to the amount of ziprasidone.

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5. A process for according to claim 4 wherein said reaction is performed in the presence of a solvent.

6. A process according to claim 5 wherein said solvent is isopropanol.

7. A process according to claim 6 wherein said reaction is run at about 85° C. for about 6 hours.

8. A pharmaceutical composition having neuroleptic activity comprising the compound according to claim 1 in an amount effective in the treatment of neuroleptic diseases, and a pharmaceutically acceptable carrier.

9. A method of treating neuroleptic diseases which comprises administering to a subject in need of such treatment a neuroleptic amount of the compound according to claim 1.

* * * * *

103/04

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES

2020
Bogotá, D.C.,

✓
Abogado
CARLOS R. OLARTE
Apoderado

ASUNTO Radicación 02-109196
 Trámite 002
 Evento 001
 Actuación 430
 Oficio No 8687
 Folios 14

Patente de Invención ☒ Patente de Modelo de Utilidad ☐

Vía Nacional ☐

Vía PCT (fase nacional) ☒ Cap. I ☐ Cap. II ☒

No. Sol. Internacional PCT/IB01/00933
Fecha de Presentación Internal. 28 de Mayo de 2001

Como resultado del examen de fondo, realizado con fundamento en el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

1. Documentos estudiados

- 1.1. Descripción: Folios: 27 a 43 y 48 como se radicó inicialmente
- 1.2. Reivindicaciones: Folios 44 a 47 como se radicó inicialmente
 Folios 76 a 79 modificadas
 Folios 92
- 1.3. Prioridad: Folios: 01
 Junio 02 de 2000, Estados Unidos, 60/209,136
 Junio 16 de 2000, Estados Unidos, 60/212,172
- 1.4. Respuesta del solicitante Folios: 89 a 91

2. Análisis de la Prioridad

- La fecha de prioridad del 02 de Junio de 2000 y su correspondiente documento, son aceptados para el estudio de patentabilidad.

3. Objeto de la invención

sales farmacéuticamente aceptables para el tratamiento de los trastornos psiquiátricos, tales como esquizofrenia, trastornos de ansiedad, depresión, trastorno bipolar, trastornos asociados con retraso mental, autismo, conducta, demencia, discinesias inducidas por droga entre otros; y trastornos oculares como glaucoma y retinopatía isquémica.

Reivindicaciones 1-6: Una composición farmacéutica

El problema planteado en esta solicitud es la necesidad de composiciones farmacéuticas útiles para tratamientos psiquiátricos y oculares

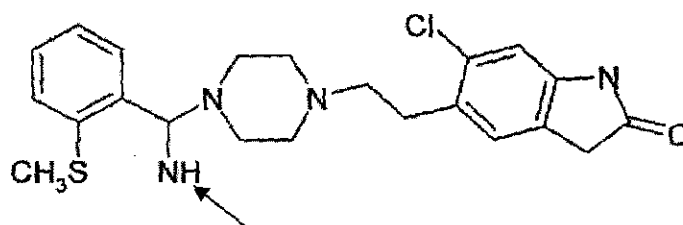
Para solucionar este problema técnico la solicitud en estudio enuncia de forma general una composición farmacéutica que contiene S- Metil-Dihidro-Ziprasidona.

- **Clasificación Internacional de Patentes (IPC):** A61 K 31/496

4. De la solicitud de Patente

4.1. Descripción (artículo 28 D. 486)

- La estructura química del compuesto S-metil-dihidroziprasidona no es clara y precisa, pues posee un grupo amino y le falta un sustituyente. El grupo imino no se encuentra presente. (Ver folio 26)



- Según folio 28, la invención solicitada se refiere a un procedimiento para un trastorno o afección seleccionado de esquizofrenia, trastornos de ansiedad, entre otros y no a composiciones farmacéuticas.
- Según folio 29, este procedimiento se denominará en lo sucesivo "el procedimiento de la invención" y no a composiciones farmacéuticas.
- El ejemplo No 1 corresponde a un procedimiento de síntesis y no a composiciones farmacéuticas.
- No se encontraron datos reportados que presenten el efecto inesperado y superior de la composición farmacéutica frente a las previamente divulgadas para compuestos de ziprasidona.

4.2. Reivindicaciones (artículo 30 D 486)

- Las reivindicaciones 1 a 5 se encuentran de forma general y amplia al referirse al "vehículo" de la composición farmacéutica.
- La reivindicación 6 se encuentra caracterizada por el método de tratamiento terapéutico y no por los elementos constitutivos de la composición farmacéutica.

5. Determinación del Estado de la Técnica

Considerando que la fecha de presentación de la primera solicitud de patente de la cual se reivindica prioridad es: 02/06/2000, se encontraron los siguientes estados de la técnica relacionados que pueden afectar la

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	and Disposition Vol 25 No 7	Benzithiazole Ring-Cleaved Products of the Antipsychotic Drug Ziprasidone"	
D2	US 5,935,960	Prodrugs of 5-(2-(4-(1,2- benzisothiazol-3-yl)-1- piperazinyl)ethyl)-6-chloro- 1,3dihydro-2H-indol-2-one	10/08/1999

6. Análisis de patentabilidad (artículo 14 D486)

6.1. Nivel inventivo (artículo 18 D486)

La reivindicación 1 se refiere a una composición farmacéutica para el tratamiento de los trastornos psiquiátricos y/o oculares caracterizada porque comprende 6-cloro-5-(2-{4-[imino-(2-metilsulfanilfenil)-metil] piperazin-1-il}-etil)-1,3-dihidro-indol-2-ona o una de sus sales farmacéuticamente aceptables, donde la relación en peso del ingrediente activo:vehículo varía en el intervalo de 1:6 a 2:1

La reivindicación 2 se refiere al compuesto activo, en una proporción entre 5-70% en peso

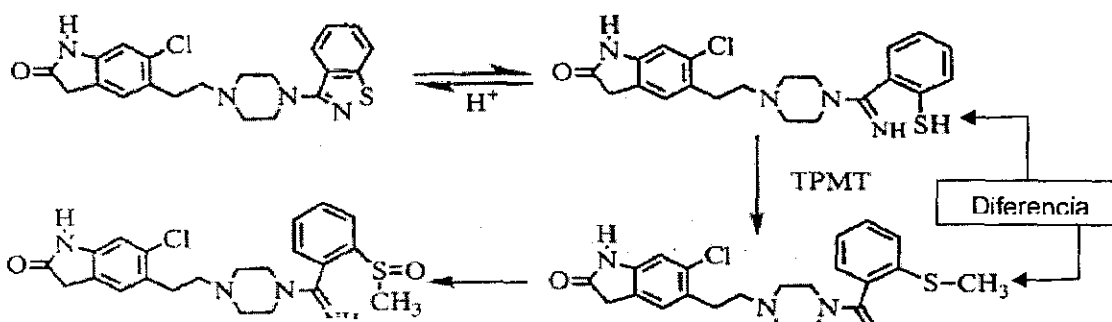
La reivindicación 3 la relación en peso del ingrediente activo:vehículo se encuentra 1:4 a :1

La reivindicación 4 se refiere a la dosis diaria de agente activo de 0.5 a 500 mg, en cantidades de 10mg a 80mg por Kg de peso corporal/día

La reivindicación 5 se refiere a los vehículos constituidos por diluyentes o cargas sólidas, medios acuosos estériles y diversos disolventes orgánicos no tóxicos y similares

D1 previamente divulgaba el compuesto "**S-metil-dihidro-ziprasidona**" caracterizado por ser un producto obtenido del metabolismo del compuesto **ziprasidona**. (Ver resumen, columna 2, líneas 5-6) Los metabolitos de ziprasidona respectivamente **fueron aislados de orina de rata y bilis** (Ver página 897, línea 1)

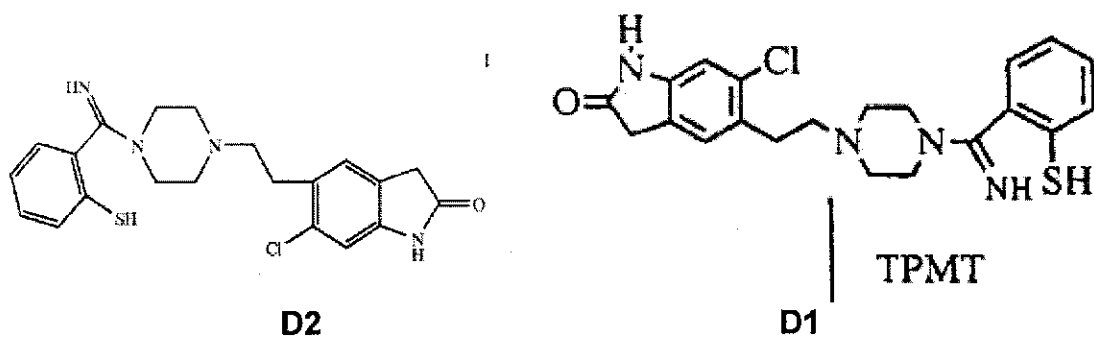
El **metabolito M9** ha sido identificado como **S-metil-dihidro-ziprasidona**. (Ver página 898, columna 1, líneas 56-57), cuya estructura se encuentra descrita en la Figura 5 de **D1**: (Ver página 900)



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D2 enseña previamente pro-fármacos de ziprasidona, sus procesos y sus composiciones farmacéuticas. (Ver resumen)

El compuesto referido en **D2** posee la siguiente estructura química según la reivindicación 1 (Ver columna 16):



El compuesto de **D2** corresponde a la estructura tiol-dihidro-ziprasidona, precursor del compuesto **S-metil-dihidro-ziprasidona**, según **D1**-Figura 5.

El compuesto **S-metil-dihidro-ziprasidona** posee un metilo en el grupo tiol.

Los profármacos de ziprasidona son administrados en soportes o diluentes en una composición farmacéutica, los cuales **incluyen soluciones acuosas estériles y varios solventes orgánicos**. Las suspensiones acuosas o elixires pueden **contener** además agentes saborizantes, colorantes, si se desea agentes emulsificantes o agentes suspensores con diluentes tales como **agua, etanol, propilénglicol, glicerina y sus combinaciones**. (Ver columna 11, líneas 63)

La **dosis efectiva** para un profármaco de ziprasidona depende de la ruta de administración y otros factores como edad y peso del sujeto, **generalmente conocidos** (Ver columna 11, líneas 64-67)

Los elementos característicos encontrados en la solicitud son los siguientes y su relación con el estado de la técnica es:

Solicitud	D1	D2
Compuesto de Ziprasidona	SI	NO (Precursor)
Vehículo	NO	SI

El solicitante por lo tanto utiliza **un compuesto obtenido por procesos biológicos de la naturaleza** tales como **el metabolismo humano (D1)** en composiciones farmacéuticas de compuestos con estructura química similar (**D2**), y cuya única diferencia es la presencia de un grupo metilo.

La solicitud no presenta el efecto inesperado y superior de las composiciones farmacéuticas de ziprasidona, en comparación con las previamente divulgadas el estado de la técnica.

El problema técnico planteado en esta solicitud como es **"obtener compuestos**

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El problema técnico planteado en esta solicitud como es obtener **“una composición farmacéutica de S-metil-dihidroziprasidona”**, sería solucionado fácilmente por el experto en la materia con base en la composición farmacéutica divulgada en D2 y el compuesto divulgado en D1, de manera que este lo lograría fácil y obviamente sin necesidad de emplear Habilidad Inventiva.

Por lo tanto las reivindicaciones 1 a 6 carecen de nivel inventivo.

7. Conclusión:

Los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

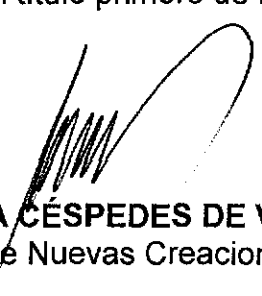
Nº	Documento Nº	Reivindicaciones afectadas	Requisito que afecta
D1	Drug Metabolism and Disposition Vol 25 No 7	1-6	Nivel Inventivo
D2	US 5,935,960	1-6	Nivel Inventivo

8. Respuesta a los argumentos del solicitante:

- El solicitante no presenta el efecto mejorado y superior de las composiciones farmacéuticas de la solicitud presentada, como por ejemplo su farmacocinética comparado con el estado de la técnica.

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de 60 días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única Nº 10 de 2001.


ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe de División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha
04 JUL. 2003

 **CONCEPTO TÉCNICO No. 01610**

EXAMINADOR TÉCNICO
Código No. 202070