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ESCOBAR - URIBE ASOCIADOS
Intellectual Property

As. 2950/PCT.

**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES**

E. S. D.

Ref.: Expediente No. 06-030.456
Solicitud de Patente a nombre de
Janssen Pharmaceutica N.V.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



NO. 06-030456- -00005-0000

2008-05-19 13:20:39 Dep. 2020 NUECREACION
SUPERINTENDENCIA Evt: 378 FASENACIONAL
DIVISION FOLIOS: 2

Yo, **JIMENA ESCOBAR URIBE**, identificada como aparece al pie de mi firma, domiciliada en Bogotá, en la Carrera 11 No. 86-53, piso 6, obrando como apoderada de la sociedad **Janssen Pharmaceutica N.V.**, con domicilio en Beerse, Bélgica, solicitante de la patente de la referencia, pido a usted que se proceda a examinar si la invención, cuya patente se tramita en el expediente de la referencia, es patentable.

Adjunto al presente memorial el recibo No. 08 - 15,069 de 20 de febrero de 2008, por la suma de \$420.000.00, con lo cual queda cubierta la tasa oficial correspondiente a dicho estudio.

Señor Superintendente,


JIMENA ESCOBAR URIBE
C.C.39.779.452 de Usaquén
T.P.No. 68228
Cód.5376

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 06-030456- -00005-0000

Fecha: 2008-03-19 13:20:39 Dep. 2020 NUECREACIONE
Tra 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 538 PETICION Folios: 2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO ESPECIAL DE CAJA : 08 - 15,069
FECHA : FEBRERO 20 DE 2008

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CLARKE MODET Y CO. COLOMBIA	CONSIGNACION	BANCO DE BOGOTA	062754387	2926010	20/02/2008	15,845,000.00

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

CANT.	RENTISTAS	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01	SOLICITUDES	
		85 EXAMEN DE PATENTABILIDAD DE INVEN	420,000.00
		TOTAL :	\$ 420,000.00

CINCUENTA Y DOS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

DIVISIÓN DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 06-30456

EL EXTRACTO DE LA PRESENTE SOLICITUD DE **PATENTE DE INVENCION**

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **580** DE

FECHA **28 DE SEPTIEMBRE DE 2007** EL TÉRMINO HÁBIL SEÑALADO POR

LA LEY EXPIRA EL **27 DE DICIEMBRE DE 2007**

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 X



US006057325A

D1
538**United States Patent** [19]

Kenniss et al.

[11] **Patent Number:** 6,057,325[45] **Date of Patent:** May 2, 2000[54] **HEXAHYDRO-PYRIDO(4,3-B)INDOLE
DERIVATIVES AS ANTIPSYCHOTIC DRUGS**[75] **Inventors:** Ludo Edmond Josephine Kennis,
Turnhout; Josephus Carolus Mertens,
Oud-Turnhout, both of Belgium[73] **Assignee:** Janssen Pharmaceutia, N.V., Beerse,
Belgium[21] **Appl. No.:** 09/180,366[22] **PCT Filed:** May 15, 1997[86] **PCT No.:** PCT/EP97/02710§ 371 **Date:** Nov. 9, 1998§ 102(e) **Date:** Nov. 9, 1998[87] **PCT Pub. No.:** WO97/44040**PCT Pub. Date:** Nov. 27, 1997[30] **Foreign Application Priority Data**

May 23, 1996 [EP] European Pat. Off. 96201450

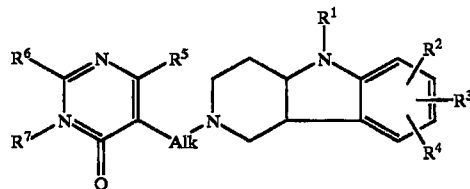
[51] **Int. Cl.⁷** A61K 31/513; A61K 31/519;
C07D 471/04; C07D 519/00[52] **U.S. Cl.** 514/258; 514/269; 544/278;
544/279; 544/281; 544/282; 544/311; 544/319;
544/321; 546/85; 546/86[58] **Field of Search** 544/281, 282,
544/311, 319, 321, 278, 279, 28; 546/85,
86; 514/258, 269[56] **References Cited****U.S. PATENT DOCUMENTS**3,991,199 11/1976 Berger 544/316
4,337,250 6/1982 Welch et al. 544/316**FOREIGN PATENT DOCUMENTS**

24 57 305 12/1975 Germany .

OTHER PUBLICATIONSWelch et al. Neuroleotics from the 4a,9b-trans-2,3,4,4a,5,
9b-hexahJ. Med. Chem 29,2108-2111, 1986.Welch et al. Neuroleotics from the 4a,9b-trans-2,3,4,4a,5,
9b-hexa.. J.Med. Chem 29,2093-209908-2111, 1986.Welch et al.
4a,9b-trans-8-fluoro-5-(fluorophenyl)-2-4-(4-fluoro- . .
J.Med. Chem 23, 994-952, 1980.Nagai et al. Synthesis of 2,3,4,4a,5,
9b-Hexahydro-1H-pyrido[4,3-b].J.Med. Chem. 23,
677-683, 1979.Nagai, Yasutake et al.: "Synthesis of 2,3,4,4a,5,
9b-hexahydro-1H-yrido[4,3-b] in Dole Derivatives and
Their Central Nervous System Activities", J. Med. Chem.
(1979), 22(6), 677-83.**Primary Examiner**—Mukund J. Shah**Assistant Examiner**—V Balasubramanian**Attorney, Agent, or Firm**—Mary A. Apollina[57] **ABSTRACT**

This invention concerns the compounds of formula

(I)



the pharmaceutically acceptable addition salts and the stereochemically isomeric forms thereof, wherein Alk is C₁₋₆alkanediyl; R¹ is hydrogen, C₁₋₆alkyl, aryl or aryl C₁₋₆alkyl; R², R³ and R⁴ are each independently selected from hydrogen, halo, hydroxy, nitro, cyano, C₁₋₆alkyl, C₁₋₆alkyloxy, trifluoromethyl, C₁₋₆alkylthio, mercapto, amino, mono- and di(C₁₋₆alkyl)amino, carboxyl, C₁₋₆alkyloxycarbonyl or C₁₋₆alkylcarbonyl; R⁵ is hydrogen, C₁₋₆alkyl, phenyl or phenylC₁₋₆alkyl; R⁶ is hydrogen, C₁₋₆alkyl, C₁₋₆alkyloxy, C₁₋₆alkylthio, or a radical of formula —NR⁸R⁹, wherein R⁸ and R⁹ are each independently selected from hydrogen, C₁₋₆alkyl, phenyl or phenylC₁₋₆alkyl; R⁷ is hydrogen or C₁₋₆alkyl; or R⁶ and R⁷ taken together may form a bivalent radical of formula —R⁶—R⁷—; having central dopamine and serotonin antagonistic activity; their preparation, compositions containing them and their use as a medicine.

10 Claims, No Drawings

6,057,325

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HEXAHYDRO-PYRIDO(4,3-B)INDOLE DERIVATIVES AS ANTIPSYCHOTIC DRUGS

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a National Stage application under 35 U.S.C. § 371 of PCT/EP97/02710 filed May 15, 1997, which claims priority from EP 96.201.450.2, filed May 23, 1996.

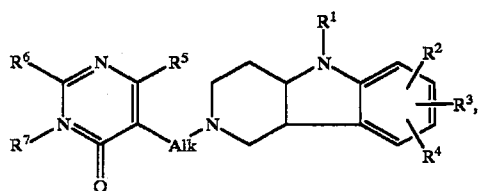
This invention relates to hexahydro-pyrido[4,3-b]indole derivatives having therapeutic potential in psychotic disorders, and processes for their preparation; it further relates to compositions comprising these derivatives, as well as their use as a medicine.

A number of hexahydro-pyrido[4,3-b]indole compounds substituted on the 2-position with an alkyl group bearing a substituted phenyl and an hydroxy, which have antipsychotic properties as evidenced by their ability to block the action of dopamine receptors of the central nervous system, are disclosed in *J. Med. Chem.* 22:677-683 (1979) and *J. Med. Chem.* 29:2093-2099 (1986). *J. Med. Chem.* 23:949-952 (1980) describes 4a,9b-trans-8-fluoro-5-(4-fluorophenyl)-2-[4-(4-fluorophenyl)-4-hydroxy-butyl]-2,3,4,4a,5,9b-hexahydro-1H-pyrido[4,3-b]indole hydrochloride as a neuroleptic agent capable of blocking dopamine receptors.

The problem which this invention sets out to solve is to provide compounds having besides central dopamine antagonistic activity also central serotonin antagonistic activity at the same dosage, a combination which is considered advantageous in potential antipsychotic drugs.

The compounds of the present invention differ from the cited art compounds structurally, by the fact that the tricyclic hexahydro-pyrido[4,3-b]indole moiety, also known as a hexahydro γ -carboline moiety, is invariably substituted on the 2-position with an alkyl group bearing a pyrimidinyl derivative, and by their favourable pharmacological properties, in particular by the fact that in addition to their excellent central dopamine antagonistic activity the compounds of the present invention also have potent central serotonin antagonistic activity.

The present invention concerns the compounds of formula



the N-oxide forms, the pharmaceutically acceptable addition salts and the stereochemically isomeric forms thereof, wherein

Alk is C₁₋₆alkanediyl;

R¹ is hydrogen, C₁₋₆alkyl, aryl or arylC₁₋₆alkyl;

R², R³ and R⁴ are each independently selected from hydrogen, halo, hydroxy, nitro, cyano, trifluoromethyl, C₁₋₆alkyl, C₁₋₆alkyloxy, C₁₋₆alkylthio, mercapto, amino, mono- and di(C₁₋₆alkyl)amino, carboxyl, C₁₋₆alkyloxycarbonyl and C₁₋₆alkylcarbonyl;

R⁵ is hydrogen, C₁₋₆alkyl, phenyl or phenylC₁₋₆alkyl;

R⁶ is hydrogen, C₁₋₆alkyl, C₁₋₆alkyloxy, C₁₋₆alkylthio, or a radical of formula —NR⁸R⁹, wherein R⁸ and R⁹ are

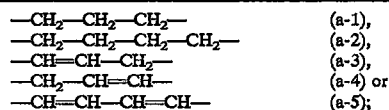
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each independently selected from hydrogen, C₁₋₆alkyl, phenyl or phenylC₁₋₆alkyl;

R⁷ is hydrogen or C₁₋₆alkyl; or

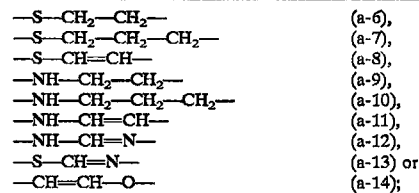
R⁶ and R⁷ taken together may form a bivalent radical of formula —R⁶—R⁷—,

wherein —R⁶—R⁷—represents



wherein one or two hydrogen atoms of said radicals (a-1) to (a-5) each independently may be replaced by halo, C₁₋₆alkyl, arylC₁₋₆alkyl, trifluoromethyl, amino, hydroxy, C₁₋₆alkyloxy or C₁₋₁₀alkylcarbonyloxy; or where possible, two geminal hydrogen atoms may be replaced by C₁₋₆alkylidene or arylC₁₋₆alkylidene; or

—R⁶—R⁷— may also be



wherein one or where possible two or three hydrogen atoms in said radicals (a-6) to (a-14) each independently may be replaced by C₁₋₆alkyl or aryl; and

aryl is phenyl or phenyl substituted with one, two or three substituents selected from halo, hydroxy, nitro, cyano, trifluoromethyl, C₁₋₆alkyl, C₁₋₆alkyloxy, C₁₋₆alkylthio, mercapto, amino, mono- and di(C₁₋₆alkyl)amino, carboxyl, C₁₋₆alkyloxycarbonyl and C₁₋₆alkylcarbonyl.

As used in the foregoing definitions and hereinafter, halo is generic to fluoro, chloro, bromo and iodo; C₁₋₆alkyl defines straight and branched chain saturated hydrocarbon radicals having from 1 to 6 carbon atoms such as, for example, methyl, ethyl, propyl, butyl, 1-methylethyl, 2-methylpropyl, 2,2-dimethylethyl, pentyl, hexyl, 3-methylbutyl, 2-methylpentyl and the like; C₁₋₁₀alkyl is meant to comprise C₁₋₆alkyl and the higher homologues thereof having from 7 to 10 carbon atoms such as, for example, heptyl, octyl, nonyl, decyl and the like; C₁₋₂alkanediyl defines bivalent straight chain saturated hydrocarbon radicals having 1 or 2 carbon atoms such as, for example, methylene and 1,2-ethanediyl; C₁₋₆alkanediyl is meant to comprise C₁₋₂alkanediyl and the higher straight and branched chain saturated hydrocarbon homologues thereof having from 3 to 6 carbon atoms such as, for example, 1,3-propanediyl, 1,4-butanediyl, 1,5-pentanedyl, 1,6-hexanedyl and the like; the term C₁₋₆alkylidene defines bivalent straight or branch chained alkylidene radicals having from 1 to 6 carbon atoms such as, for example, methylene, ethylidene, 1-propylidene, 1-butylidene, 1-pentylidene, 1-hexylidene and the like.

The pharmaceutically acceptable addition salts as mentioned hereinabove are meant to comprise the therapeutically active non-toxic acid and non-toxic base addition salt forms which the compounds of formula (I) are able to form.

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evoked by the above-mentioned challenging substances. Column APO lists the results of the apomorphine challenge, indicating central dopamine antagonistic activity. Column TRY convulsions and TRY hyperaemia list the results of the tryptamine challenge, indicating central and peripheral serotonin antagonistic activity respectively. Column NOR lists the results of the norepinephrine challenge, indicating α -adrenergic antagonist activity. The favourable pharmacological properties of the compounds of formula (I) lie in their potent central dopamine (column APO) and serotonin (column TRY convulsions) antagonistic activity.

TABLE 3

Compound Number	Combined test in rats, ED ₅₀ in mg/kg			
	APO	TRY convulsions	TRY hyperaemia	NOR
11	0.31	0.31	≤0.04	>10
12	1.25	1.25	0.02	>10
13	2.5	5	≤0.04	>10
14	0.31	1.25	≤0.16	>10
15	0.31	0.31	≤0.0025	>10
16	0.25	0.45	0.015	>10
17	0.08	0.5	≤0.04	≥10
18	0.31	2	0.02	>10
19	8	1.25	0.31	5
20	1.25	1.25	≤0.63	5
22	1.25	1.25	0.08	0.5
23	0.12	0.08	≤0.01	0.03
24	5	1.25	≤0.04	0.31
25	0.31	0.12	0.02	0.08
26	0.03	0.02	0.005	>10
27	0.31	0.31	0.005	>10
28	0.08	0.12	0.005	>10
29	5	5	0.02	≥10
30	≥10	2	≤0.16	>10
31	1.25	≥10	≤0.16	>10

D. Composition Examples

"Active ingredient" (A.I.) as used throughout these examples relates to a compound of formula (I), a pharmaceutically acceptable addition salt or a stereochemically isomeric form thereof.

EXAMPLE D.1

Capsules

20 g of the A.I., 6 g sodium lauryl sulfate, 56 g starch, 56 g lactose, 0.8 g colloidal silicon dioxide, and 1.2 g magnesium stearate are vigorously stirred together. The resulting mixture is subsequently filled into 1000 suitable hardened gelatin capsules, each comprising 20 mg of the A.I.

EXAMPLE D.2

Film-Coated Tablets

Preparation of Tablet Core

A mixture of 100 g of the A.I., 570 g lactose and 200 g starch is mixed well and thereafter humidified with a solution of 5 g sodium dodecyl sulfate and 10 g polyvinylpyrrolidone in about 200 ml of water. The wet powder mixture is sieved, dried and sieved again. Then there are added 100 g microcrystalline cellulose and 15 g hydrogenated vegetable oil. The whole is mixed well and compressed into tablets, giving 10,000 tablets, each comprising 10 mg of the active ingredient.

Coating

To a solution of 10 g methyl cellulose in 75 ml of denaturated ethanol there is added a solution of 5 g of ethyl

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cellulose in 150 ml of dichloromethane. Then there are added 75 ml of dichloromethane and 2.5 ml 1,2,3-propanetriol. 10 g of polyethylene glycol is molten and dissolved in 75 ml of dichloromethane. The latter solution is added to the former and then there are added 2.5 g of magnesium octadecanoate, 5 g of polyvinylpyrrolidone and 30 ml of concentrated colour suspension and the whole is homogenated. The tablet cores are coated with the thus obtained mixture in a coating apparatus.

EXAMPLE D.3

Oral Solution

9 Grams of methyl 4-hydroxybenzoate and 1 gram of propyl 4-hydroxybenzoate were dissolved in 4 l of boiling purified water. In 3 l of this solution were dissolved first 10 grams of 2,3-dihydroxybutanedioic acid and thereafter 20 grams of the A.I. The latter solution was combined with the remaining part of the former solution and 12 l 1,2,3-propanetriol and 3 l of sorbitol 70% solution were added thereto. 40 Grams of sodium saccharin were dissolved in 0.5 l of water and 2 ml of raspberry and 2 ml of gooseberry essence were added. The latter solution was combined with the former, water was added q.s. to a volume of 20 l providing an oral solution comprising 5 mg of the active ingredient per teaspoonful (5 ml). The resulting solution was filled in suitable containers.

EXAMPLE D.4

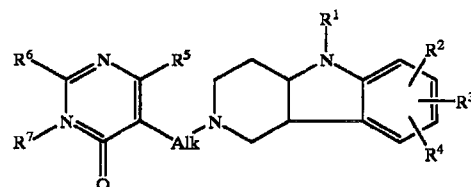
Injectable Solution

1.8 Grams methyl 4-hydroxybenzoate and 0.2 grams propyl 4-hydroxybenzoate were dissolved in about 0.5 l of boiling water for injection. After cooling to about 50° C. there were added while stirring 4 grams lactic acid, 0.05 grams propylene glycol and 4 grams of the A.I. The solution was cooled to room temperature and supplemented with water for injection q.s. ad 1 l, giving a solution comprising 4 mg/ml of A.I. The solution was sterilized by filtration and filled in sterile containers.

We claim:

1. A compound of formula (I)

(I)



a N-oxide form, a pharmaceutically acceptable addition salt or a stereochemically isomeric form thereof, wherein

Alk is C₁₋₆alkanediyl;

R¹ is hydrogen, C₁₋₆alkyl, aryl or arylC₁₋₆alkyl;

R², R³ and R⁴ are each independently selected from hydrogen, halo, hydroxy, nitro, cyano, trifluoromethyl, C₁₋₆alkyl, C₁₋₆alkyloxy, C₁₋₆alkylthio, mercapto, amino, mono- and di(C₁₋₆alkyl)amino, carboxyl, C₁₋₆alkyloxycarbonyl or C₁₋₆alkylcarbonyl;

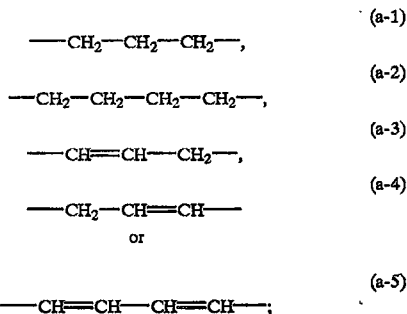
R⁵ is hydrogen, C₁₋₆alkyl, phenyl or phenylC₁₋₆alkyl;

R⁶ is hydrogen, C₁₋₆alkyl, C₁₋₆alkyloxy, C₁₋₆alkylthio, or a radical of formula -NR⁸R⁹, wherein R⁸ and R⁹ are each independently selected from hydrogen, C₁₋₆alkyl, phenyl or phenylC₁₋₆alkyl;

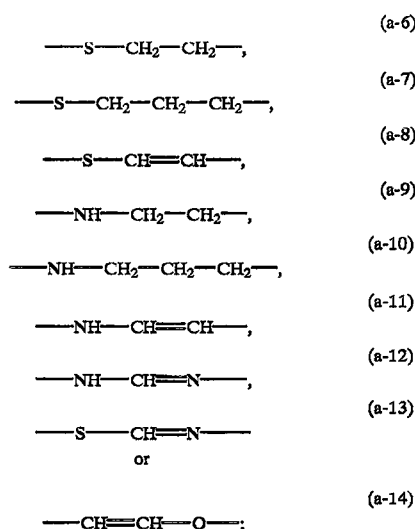
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R⁷ is hydrogen or C₁₋₆alkyl; or
 R⁶ and R⁷ taken together may form a bivalent radical
 $\text{—R}^6\text{—R}^7\text{—}$,
 wherein $\text{—R}^6\text{—R}^7\text{—}$ represents



wherein one or two hydrogen atoms of said radicals (a-1) to (a-5) each independently may be replaced by halo, C₁₋₆alkyl, arylC₁₋₆alkyl, trifluoromethyl, amino, hydroxy, C₁₋₆alkyloxy or C₁₋₁₀alkylcarbonyloxy; or where possible, two geminal hydrogen atoms may be replaced by C₁₋₆alkylidene or arylC₁₋₆alkylidene; or $\text{—R}^6\text{—R}^7\text{—}$ may also be



wherein one or where possible two or three hydrogen atoms in said radicals (a-6) to (a-14) each independently may be replaced by C₁₋₆alkyl or aryl; and

aryl is phenyl or phenyl substituted with one, two or three substituents selected from halo, hydroxy, nitro, cyano,

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trifluoromethyl, C₁₋₆alkyl, C₁₋₆alkyloxy, C₁₋₆alkylthio, mercapto, amino, mono- and di(C₁₋₆alkyl)amino, carboxyl, C₁₋₆alkyloxycarbonyl and C₁₋₆alkylcarbonyl.

2. A compound according to claim 1 wherein one or two hydrogen atoms of the radicals (a-1) to (a-5) each independently are replaced by C₁₋₆alkyl, C₁₋₆alkyloxy, hydroxy or C₁₋₁₀alkylcarbonyloxy; and one or where possible two hydrogen atoms in the radicals (a-6) to (a-14) each independently are replaced by C₁₋₆alkyl.

3. A compound according to claim 1 wherein the configuration between the hydrogen atom on carbon atom 4a and the hydrogen atom on carbon atom 9b of the hexahydro-pyrido[4,3-b]indole moiety is defined as trans.

4. A compound according to claim 1 wherein R⁶ and R⁷ are taken together to form a bivalent radical of formula (a1), (a-5), (a-6) or (a-8) wherein one of the hydrogen atoms may be replaced by C₁₋₆alkyl; and R⁵ is phenyl or C₁₋₆alkyl.

5. A compound according to claim 1 wherein R¹ is hydrogen, R² is halo, R³ and R⁴ are both hydrogen; Alk is C₁₋₂alkanediyl, R⁵ is phenyl or C₁₋₆alkyl; and R⁶ and R⁷ are taken together to form a bivalent radical of formula (a-1), (a-5), (a-6) or (a-8) wherein one of the hydrogen atoms may be replaced by C₁₋₆alkyl.

6. A compound according to claim 1 wherein the compound is 3-[2-(8-fluoro-1,3,4,4a,5,9b-hexahydro-2H-pyrido[4,3-b]indol-2-yl)ethyl]-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one; or

6-[2-(8-fluoro-1,3,4,4a,5,9b-hexahydro-2H-pyrido[4,3-b]indol-2-yl)ethyl]-7-methyl-5H-thiazolo[3,2-a]pyrimidin-5-one; or

6-[2-(8-chloro-1,3,4,4a,5,9b-tetrahydro-2H-pyrido[4,3-b]indol-2-yl)ethyl]-7-methyl-5H-thiazolo[3,2-a]pyrimidin-5-one; the stereoisomeric forms and the pharmaceutically acceptable addition salts thereof, or an N-oxide form thereof.

7. A pharmaceutical composition comprising a pharmaceutically acceptable carrier, and as active ingredient a therapeutically effective amount of a compound as claimed in claim 1.

8. A process of preparing a pharmaceutical composition comprising intimately mixing a therapeutically effective amount of a compound as claimed in claim 1 with a pharmaceutically acceptable carrier.

9. A method of treating a warm-blooded animal suffering from a psychotic disorder comprising administering to the warm-blooded animal a therapeutically effective amount of the compound of claim 1.

10. The method of claim 9, wherein the psychotic disorder is schizophrenia.

* * * * *

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(19)  **Europäisches Patentamt**
European Patent Office
Office européen des brevets



(11) **EP 0 905 136 A1**

(12) **EUROPEAN PATENT APPLICATION**

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(51) Int. Cl.⁶: **C07D 471/04**, A61K 31/435,
C07D 519/00

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(22) Date of filing: **08.09.1997**

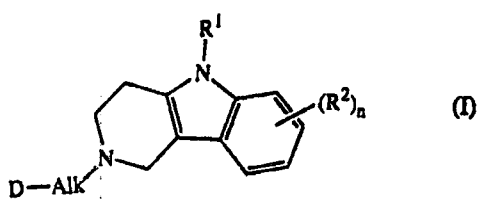
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2340 Beerse (BE)
• **Mertens, Josephus Carolus**
2340 Beerse (BE)

(54) **Tetrahydro gamma-carbolines**

(57) The present invention concerns the compounds of formula



the *N*-oxide forms, the pharmaceutically acceptable addition salts and the stereochemically isomeric forms thereof, wherein R¹ is hydrogen, optionally substituted C₁₋₆alkyl, aryl; R² is each independently a halogen, hydroxy, C₁₋₆alkyl, C₁₋₆alkyloxy or nitro; n is 0, 1, 2 or 3; Alk is C₁₋₆alkanediyl; D is an optionally substituted saturated or unsaturated nitrogen containing heterocycle; and aryl is optionally substituted phenyl; having an affinity for the serotonin receptors. It further relates to their use as a medicine, their preparation as well as compositions containing them.

EP 0 905 136 A1

EP 0 905 136 A1

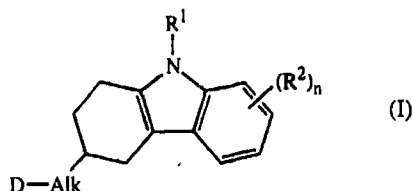
Description

[0001] The present invention concerns tetrahydro γ -carbolines having therapeutic potential in serotonin related disorders. It further relates to their preparation, compositions comprising them and their use as a medicine.

[0002] US-4,636,563, published on January 13, 1987, and US-4,672,117, published on June 9, 1987, disclose 2-(heteroaryl-alkyl)-tetrahydro- γ carbolines having antipsychotic activity.

[0003] The compounds of the present invention are novel and have an interesting broad-spectrum receptor-binding profile. In comparison to the structurally related known compounds, they surprisingly exhibit a greater therapeutic breadth.

[0004] The present invention concerns the compounds of formula



the *N*-oxide forms, the pharmaceutically acceptable addition salts and the stereochemically isomeric forms thereof, wherein :

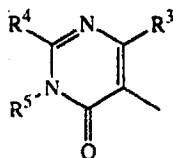
R^1 is hydrogen, C_{1-6} alkyl, aryl or C_{1-6} alkyl substituted with aryl;

R^2 is each independently a halogen, hydroxy, C_{1-6} alkyl, C_{1-6} alkyloxy or nitro;

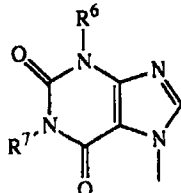
n is 0, 1, 2 or 3;

Alk is C_{1-6} alkanediyl;

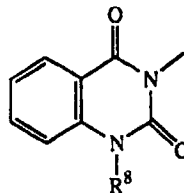
D is 1- or 2-benzimidazolyl, 2(3*H*)-benzoxazolone-3-yl or a radical of formula



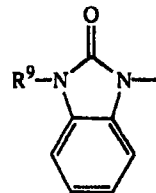
(a)



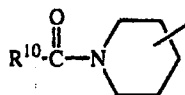
(b)



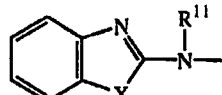
(c)



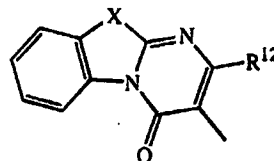
(d)



(e)



(f)



(g)

wherein

each X independently represents O, S or NR^{13} ;

R^3 is hydrogen, C_{1-6} alkyl, aryl or aryl C_{1-6} alkyl;

R^4 is hydrogen, C_{1-6} alkyl, C_{1-6} alkyloxy, C_{1-6} alkylthio, amino, mono- or di(C_{1-6} alkyl)amino or mono- or di(aryl C_{1-6} alkyl)amino;

R^5 , R^6 , R^7 , R^9 , R^{11} , R^{12} and R^{13} each independently are hydrogen or C_{1-6} alkyl;

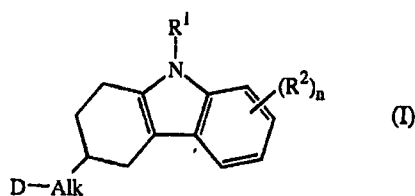
R^8 and R^{10} each independently are hydrogen, C_{1-6} alkyl or aryl; or

R^4 and R^5 taken together may form a bivalent radical $-R^4-R^5-$ of formula

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Claims

1. A compound of formula



a *N*-oxide form, a pharmaceutically acceptable addition salt or a stereochemically isomeric form thereof, wherein :

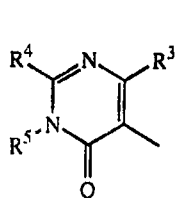
R^1 is hydrogen, C_{1-6} alkyl, aryl or C_{1-6} alkyl substituted with aryl;

R^2 is each independently a halogen, hydroxy, C_{1-6} alkyl, C_{1-6} alkyloxy or nitro;

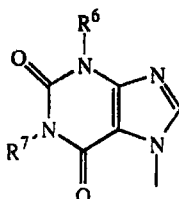
n is 0, 1, 2 or 3;

Alk is C_{1-6} alkanediyl;

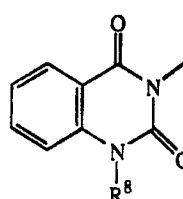
D is 1- or 2-benzimidazolyl, 2(3*H*)benzoxazolone-3-yl or a radical of formula



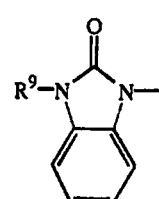
(a)



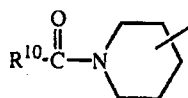
(b)



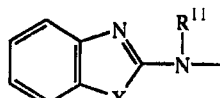
(c)



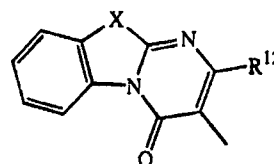
(d)



(e)



(f)



(g)

wherein

each X independently represents O, S or NR^{13} ;

R^3 is hydrogen, C_{1-6} alkyl, aryl or aryl C_{1-6} alkyl;

R^4 is hydrogen, C_{1-6} alkyl, C_{1-6} alkyloxy, C_{1-6} alkylthio, amino, mono- or di(C_{1-6} alkyl)amino or mono- or di(aryl C_{1-6} alkyl)amino;

R^5 , R^6 , R^7 , R^9 , R^{11} , R^{12} and R^{13} each independently are hydrogen or C_{1-6} alkyl;

R^8 and R^{10} each independently are hydrogen, C_{1-6} alkyl or aryl; or

R^4 and R^5 taken together may form a bivalent radical $-R^4-R^5-$ of formula



wherein one or two hydrogen atoms of said radicals (a-1) to (a-5) each independently may be replaced

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by halogen, C₁₋₆alkyl, arylC₁₋₆alkyl, trifluoromethyl, amino, hydroxy, C₁₋₆alkyloxy or C₁₋₁₀alkylcarbonyloxy; or where possible, two geminal hydrogen atoms may be replaced by C₁₋₆alkylidene or arylC₁₋₆alkylidene; or -R⁴-R⁵- may also be

5	-S-CH ₂ -CH ₂ -	(a-6);
	-S-CH ₂ -CH ₂ -CH ₂ -	(a-7);
	-S-CH=CH-	(a-8);
10	-NH-CH ₂ -CH ₂ -	(a-9);
	-NH-CH ₂ -CH ₂ -CH ₂ -	(a-10);
15	-NH-CH=CH-	(a-11);
	-NH-CH=N-	(a-12);
	-S-CH=N-	(a-13) or
20	-CH=CH-O-	(a-14);

wherein one or where possible two or three hydrogen atoms in said radicals (a-6) to (a-14) each independently may be replaced by C₁₋₆alkyl or aryl; and
 25 aryl is phenyl or phenyl substituted with a halogen or C₁₋₆alkyl.

2. A compound according to claim 1 wherein n is 0 or 1 and R² is positioned in the 6-, 7- or 8-position of the γ -carboline moiety.
- 30 3. A compound according to claims 1 or 2 wherein R² is halogen, hydroxy, C₁₋₆alkyl or C₁₋₆alkyloxy; n is 0 or 1, Alk is C₁₋₄alkanediyl; D is a radical of formula (a) wherein R³ is C₁₋₆alkyl; R⁴ is amino; or -R⁴-R⁵- is a radical of formula (a-2) or (a-5) wherein one or two hydrogen atoms each independently may be replaced by halogen, C₁₋₆alkyl, trifluoromethyl or C₁₋₆alkyloxy, or -R⁴-R⁵- is a radical of formula (a-6), (a-7), (a-8), (a-11), (a-13) or (a-14) wherein one or where possible two hydrogen atoms each independently may be replaced by C₁₋₆alkyl; or D is a radical of formula (d) (f) wherein X is S or NR¹³ and R¹¹ is hydrogen; or a radical of formula (g) wherein X is S or NR¹³.
- 35 4. A compound according to claims 1 or 2 wherein R¹ is hydrogen; n is 0 or n is 1 whereby R² is a halogen, C₁₋₆alkyl, or C₁₋₆alkoxy; Alk is 1,2-ethanediyl and D is a radical of formula (a) wherein R³ is C₁₋₆alkyl; R⁴ is amino; R⁵ is C₁₋₆alkyl; or -R⁴-R⁵- is a radical of formula (a-2), (a-5), (a-6), (a-7), (a-8) or (a-11) wherein one hydrogen atom may be replaced by C₁₋₆alkyl; or D is a radical of formula (g) wherein X is NR¹³ and R¹² is C₁₋₆alkyl.
- 40 5. A compound according to claims 1 or 2 wherein R¹ is hydrogen; n is 0 or n is 1 whereby R² is a halogen or C₁₋₆alkyl, Alk is 1,2-ethanediyl and D is a radical of formula (a) wherein R³ is C₁₋₆alkyl; R⁴ and R⁵ are taken together to form -R⁴-R⁵- of formula (a-2), (a-5), (a-6), (a-7) or (a-8) wherein one hydrogen atom may be replaced by C₁₋₆alkyl.
- 45 6. A compound according to any one of claims 1 to 5 for use as a medicine.
7. The use of a compound as claimed in any one of claims 1 to 5 in the manufacture of a medicament for treating serotonin related disorders.
- 50 8. A composition comprising a pharmaceutically acceptable carrier and, as active ingredient, a therapeutically effective amount of a compound as claimed in any one of claims 1 to 5.
9. A process for preparing a composition according to claim 8 by combining a compound as defined in any one of claims 1 to 5 as the active ingredient in intimate admixture with a pharmaceutically acceptable carrier.
- 55 10. A process for preparing a compound according to claim 1, characterized by,

**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIRECCION DE NUEVAS CREACIONES**

2020
Bogotá, D.C.,

Abogado:
JIMENA ESCOBAR URIBE

ASUNTO:	Radicación No.	06 03 0456
	Trámite	011
	Evento	378
	Actuación	430
	Oficio	
	Folios	473

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 comunica:

Documentos estudiados:

Descripción:	Folios 6 a 374 como se radicó inicialmente.
Reivindicaciones:	Folios 375 a 472 modificadas en fase nacional.
Prioridad:	US 60/504,528 (17/09/03); US 60/552,673 (11/03/04)

Objeto de la Invención

Título de la invención: "Compuestos heterocíclicos fusionados"

Problema Técnico Planteado: "Necesidad de obtener compuestos moduladores del receptor de serotonina y alcanzar mecanismos terapéuticos múltiples y mejorar las respuestas clínicas con un solo fármaco"

Solución: "Proveer compuestos de acuerdo a las fórmulas I, II y III"

IPC: C07D 487/00; C07D 487/04; A61K 31/55; A61K 31/435; A61P 25/00

Excepciones a la Patentabilidad (Art 20 D 486 literal d)

Las reivindicaciones 36 a 41 y 48 se refieren a un método de tratamiento por lo cual se considera materia no patentable.

Dichas reivindicaciones deben ser retiradas del capítulo reivindicatorio.

Análisis de la Solicitud de Patente

Reivindicaciones (Art 30 D 486, Art 22 PCT)

Concisión: El capítulo reivindicatorio no es conciso en tanto define un alto número de sustituyentes sobre el núcleo estructural y además presenta en la reivindicación 1 tres grupos de moléculas que poseen un diferente núcleo. Se requiere al solicitante modificar las reivindicaciones de manera que se defina concisamente la materia reclamada.

Soporte en la descripción: La forma en que se ha redactado el capítulo reivindicatorio abarca una gran cantidad de compuestos, algunos que probablemente no han sido probados o ensayados por parte del solicitante. Se sugiere restringir el alcance del capítulo teniendo en cuenta los grupos que fueron ensayados.

Determinación del Estado de la Técnica

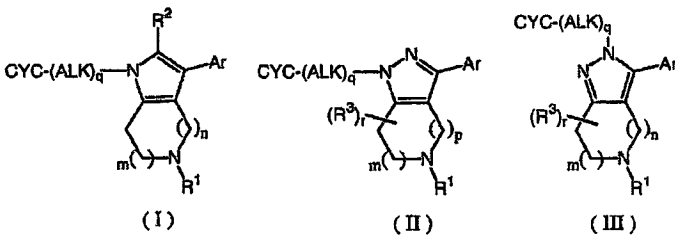
El Estado de la Técnica se determinó con base en la fecha de prioridad 17/09/03 y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

Item	Documento	Título	Fecha de Publicación
D1	US6057325	Hexahydro-pyrido(4,3-B) indole derivatives as antipsychotic drugs	27.11.1997
D2	EP0905136	Tetrahydro gamma-carbolines	08.09.1999

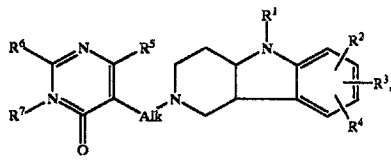
Análisis de Patentabilidad (Art 14 D486)

Nivel inventivo (Art18 D486)

La reivindicación 1 dice: “Un compuesto que tiene actividad moduladora del receptor de serotonina, de fórmula (I), (II) o (III): en donde: m es 0, 1 o 2; n es 1, 2 o 3; p es 1, 2 o 3, con la condición de que cuando m es 1, p no es 1; m+n es menor o igual que 4; m+p es menor o igual que 4; q es 0 o 1; r es 0,1,2,3,4, o 5; R³ es –alquilo de C₁₋₄, propargilo, o bencilo, cada uno sustituido opcionalmente con –alquilo,...” lo demás como el folio 375.



D1 presenta compuestos que presentan actividad serotonina antagonista, en cual se revelan compuestos heterociclos derivados de la fórmula I, derecha, en donde Alk está definido como C1-6 alquediil, R1 es hidrógeno, alquilo c1-6, arilo o aril



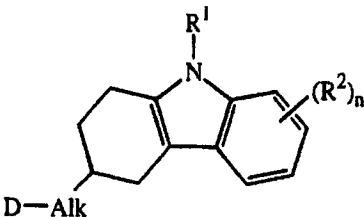
C1-6 alquilo. Además, describe composiciones farmacéuticas para la administración de los mismos (columna 20, líneas 38 a 42).

La solicitud se diferencia de D1 en la ausencia del anillo de benceno que se encuentra fusionado con el heterociclo aromático de 5 miembros, y en el número de miembros posibles en el heterociclo que esta representado por 6 miembros en las figuras I, II y III.

El efecto que logra la diferencia es obtener compuestos alternativos para el tratamiento de las patologías relacionadas con el receptor de serotonina, de los cuales algunos poseen una capacidad de modular la actividad del receptor de 5-HT más alta de los que son provistos por D2.

El problema técnico de la solicitud es la necesidad de obtener compuestos moduladores del receptor de serotonina y alcanzar mecanismos terapéuticos múltiples y mejorar las respuestas clínicas con un solo fármaco

D2 revela tetrahidrogamacarbolinas con potencial terapéutico en los desordenes relacionados con serotonina(párrafo 1), de acuerdo a la fórmula I, derecha, en donde R1 es definido como H, alquilo C1-6, arilo o alquilo C1-6 sustituido con arilo, Alk es Alcanedienil C1-6, D es 1- o 2- benzimidazolil, 2(3H)benzoxazolona-3-il o un radical de fórmula a – g; y n, puede ser 0 (párrafo 4).



También revela composiciones farmacéuticas que contienen a estos agentes terapéuticos.

La persona versada en la materia habría sido sugerida por D2 a incluir en los compuestos de D1 radicales definidos para D, Alk, y R1. Sin embargo, no es sugerido por D1 ni D2 el incluir 1, 2 o 3 átomos de carbono en el heteroanillo no aromático de las figuras I, II y III de la presente solicitud, pero dentro de la actividad científica desarrollada por parte del experto, hubiese sido obvio pensar en modificar el número de miembros del heterociclo para llegar al resultado de la presente solicitud.

Se concluye que el contenido de la presente solicitud carece de nivel inventivo.

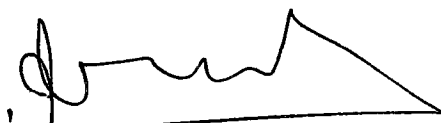
Conclusión

Los requisitos de Patentabilidad de la presente Solicitud se encuentran afectados así:

	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	US6057325	1-35, 42-47	Nivel inventivo
D2	EP0905136	1-35, 42-47	Nivel inventivo

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 N° 10 de 2001.


JESUS FERNEL GARCIA GARCIA
Director de Nuevas Creaciones (E)

El anterior requerimiento fue notificado por fijación en lista, de fecha
_____, 15 ENE. 2010

CONCEPTO TECNICO NUMERO: 4158	EXAMINADOR TÉCNICO Código:202092
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