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Señora Jefe de la
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Superintendencia de Industria y Comercio
E. S. D.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 07-099086- -00004-0000

Fecha: 2008-11-19 09:51:16 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 538 PETICION Folios: 2

Trámite : 011

Evento : 378

Actuación : 538

Referencia : Expediente No. 07.099.086
Asunto : Solicitud de Patente para **DERIVADOS DE
TETRAHIDROINDOLONAS Y DE
TETRAHIDROINDAZOLONAS FENIL-SUSTITUIDOS
ÚTILES PARA EL TRATAMIENTO DE CÁNCER.**
Solicitante : **SERENEX INC.**
Clase : A61K 031/416, A61P 035/000, C07D 209/14
Publicada en : La Gaceta No. **592** Del 30 de mayo de 2008
Fecha de Solicitud : 24 de septiembre de 2007

1. Yo, Emilio FERRERO, identificado como aparece al pie de mi firma, actuando como apoderado en el asunto de la referencia, atentamente, solicito se efectúe el examen de patentabilidad de la solicitud en referencia presentada de acuerdo con el Capítulo I del PCT y según lo establecido en el artículo 44 de la Decisión 486 de la Comisión de la Comunidad Andina. Para tal efecto presento junto con este escrito el recibo por valor de \$420.000.00, que corresponde a la tasa fijada según lo dispuesto en la resolución No. 44372 de 26 de diciembre de 2007.

2. Ruego atentamente a la Señora Jefe se sirva ordenar que se anexe este recibo para que se efectúe dicho examen y se continúe con el trámite de la solicitud.

Señora Jefe,

EMILIO FERRERO

T.P.A. No. 31.929

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ASG\JMS\ID-138608\WPC16097
No. M-2008-138608\ASG

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 538 PETICION Folios: 2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 08 - 86,876
FECHA : NOVIEMBRE 4 DE 2008

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CAVELIER ABOGADOS	CONSIGNACION	BANCO DE BOGOTA	062754387	10528361	04/11/2008	50,330,000.00

***** CONCEPTO *****

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

SON: CUATROCIENTOS VEINTE MIL PESOS

RESPONSABLE : _____

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(12) **United States Patent**
Broughton et al.

(10) **Patent No.:** **US 6,395,766 B1**(45) **Date of Patent:** **May 28, 2002**

(54) **TETRAHYDROINDOLONE DERIVATIVES AS
GABAAALPHA5 LIGANDS FOR
ENHANCING COGNITION**

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(GB)

(73) **Assignee:** **Merck Sharp & Dohme Limited**,
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(*) **Notice:** Subject to any disclaimer, the term of this
patent is extended or adjusted under 35
U.S.C. 154(b) by 0 days.

(21) **Appl. No.:** **09/674,740**

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(2), (4) **Date:** **Nov. 6, 2000**

(87) **PCT Pub. No.:** **WO99/62899**

PCT Pub. Date: **Dec. 9, 1999**

(30) **Foreign Application Priority Data**

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(51) **Int. Cl.⁷** **A61K 31/404**; A61K 31/4439;
A61P 25/00; C07D 209/08; C07D 209/30

(52) **U.S. Cl.** **514/411**; 514/412; 548/427;
548/450; 548/466; 548/467; 548/512; 548/516

(58) **Field of Search** 548/516, 512,
548/466, 467, 450, 427; 514/412, 411

(56) **References Cited**

U.S. PATENT DOCUMENTS

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Primary Examiner—Mark L Berch

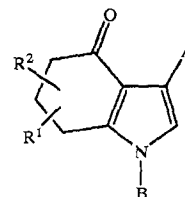
Assistant Examiner—Al Kahsay Habte

(74) *Attorney, Agent, or Firm*—J. Eric Thies; Shu Muk Lee;
David L. Rose

(57) **ABSTRACT**

Compounds according to Formula (I) or a pharmaceutically
acceptable salt thereof are GABA-A Alpha 5 ligands useful
for enhancing cognition:

(I)



where A is C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl,
C₃₋₆cycloalkyl, arylC₁₋₆alkyl, or aryl wherein the aryl group
is optionally substituted by halogen, C₁₋₆alkyl, CF₃, CN,
NO₂ or NH₂, NR¹R₁₀, S(O)_pR¹, heteroarylC₁₋₆alkyl or
heteroaryl where heteroaryl is a 5- or 6-membered het-
eroaromatic ring as defined for B; and B is phenyl or a
5-membered ring having one or two unsaturations contain-
ing 1, 2, 3, or 4 heteroatoms chosen from O, N and S
provided that not more than one heteroatom is other than N,
a 6-membered heteroaromatic ring containing 1, 2, 3 or 4
nitrogen atoms, each of which rings is optionally substituted
by one or more substituents.

7 Claims, No Drawings

TETRAHYDROINDOLONE DERIVATIVES AS GABAA ALPHA5 LIGANDS FOR ENHANCING COGNITION

This is an application under 35 U.S.C. 371 of PCT/GB99/01799 and claims priority from Great Britain Application No. 9812038.9, filed Jun. 4, 1998.

BACKGROUND

The present invention relates to tetrahydroindolone derivatives, pharmaceutical compositions comprising them and to their use in therapy. More particularly, this invention is concerned with substituted derivatives which are ligands for GABA_A receptors, in particular for GABA_A $\alpha 5$ receptors and are therefore useful in therapy particularly where cognition enhancement is required.

Receptors for the major inhibitory neurotransmitter, gamma-aminobutyric acid (GABA), are divided into two main classes: (1) GABA_A receptors, which are members of the ligand-gated ion channel superfamily; and (2) GABA_B receptors, which may be members of the G-protein linked receptor superfamily. Since the first cDNAs encoding individual GABA_A receptor subunits were cloned the number of known members of the mammalian family has grown to thirteen (six α subunits, three β subunits, three γ subunits and one δ subunit). It may be that further subunits remain to be discovered; however, none has been reported since 1993.

Although knowledge of the diversity of the GABA_A receptor gene family represents a huge step forward in our understanding of this ligand-gated ion channel, insight into the extent of subtype diversity is still at an early stage. It has been indicated that an α subunit, $\alpha \beta$ subunit and a γ subunit constitute the minimum requirement for forming a fully functional GABA_A receptor expressed by transiently transfecting cDNAs into cells. As indicated above, a δ subunit also exists, but is apparently uncommon in the native receptor.

Studies of receptor size and visualisation by electron microscopy conclude that, like other members of the ligand-gated ion channel family, the native GABA_A receptor exists in pentameric form. The selection of at least one α , one β and one γ subunit from a repertoire of thirteen allows for the possible existence of more than 10,000 pentameric subunit combinations. Moreover, this calculation overlooks the additional permutations that would be possible if the arrangement of subunits around the ion channel had no constraints (i.e. there could be 120 possible variants for a receptor composed of five different subunits).

Receptor subtype assemblies which do exist include $\alpha 1 \beta 2 \gamma 2$, $\alpha 2 \beta 2 / 3 \gamma 2$, $\alpha 3 \beta 2 / 3$, $\alpha 2 \beta \gamma 1$, $\alpha 5 \beta 3 \gamma 2 / 3$, $\alpha 6 \beta \gamma 2$, $\alpha 6$ and $\alpha 4 \beta \delta$. Subtype assemblies containing an $\alpha 1$ subunit are present in most areas of the brain and account for over 40% of GABA_A receptors in the rat. Subtype assemblies containing $\alpha 2$ and $\alpha 3$ subunits respectively account for about 25% and 17% of GABA_A receptors in the rat. Subtype assemblies containing an $\alpha 5$ subunit are primarily hippocampal and represent about 4% of receptors in the rat.

A characteristic property of some GABA_A receptors is the presence of a number of modulatory sites, of which the most explored is the benzodiazepine (BZ) binding site through which anxiolytic drugs such as diazepam and temazepam exert their effect. Before the cloning of the GABA_A receptor gene family, the benzodiazepine binding site was historically subdivided into two subtypes, BZ1 and BZ2, on the basis of radioligand binding studies. The BZ1 subtype has been shown to be pharmacologically equivalent to a GABA_A

receptor comprising the $\alpha 1$ subunit in combination with $\beta 2$ and $\gamma 2$. This is the most abundant GABA_A receptor subtype, representing almost half of all GABA_A receptors in the brain.

Two other major populations are the $\alpha 2 \beta \gamma 2$ and $\alpha 3 \beta \gamma 2 / 3$ subtypes. Together these constitute approximately a further 35% of the total GABA_A receptor repertoire. Pharmacologically this combination appears to be equivalent to the BZ2 subtype as defined previously by radioligand binding, although the BZ2 subtype may also include certain $\alpha 5$ -containing subtype assemblies. The physiological role of these subtypes has hitherto been unclear because no sufficiently selective agonists or antagonists were known.

It is now believed that agents acting as BZ agonists at $\alpha 1 \beta \gamma 2$, $\alpha 2 \beta \gamma 2$ or $\alpha 3 \beta \gamma 2$ subunits will possess desirable anxiolytic properties. The $\alpha 1$ -selective GABA_A receptor agonists alpidem and zolpidem are clinically prescribed as hypnotic agents, suggesting that at least some of the sedation associated with known anxiolytic drugs which act at the BZ1 binding site is mediated through GABA_A receptors containing the $\alpha 1$ subunit. Accordingly, it is considered that GABA_A receptor agonists which bind more effectively to the $\alpha 2$ and/or $\alpha 3$ subunit than to $\alpha 1$ will be effective in the treatment of anxiety with a reduced propensity to cause sedation. Also, agents which are antagonists or inverse agonists at $\alpha 1$ might be employed to reverse sedation or hypnosis caused by $\alpha 1$ agonists.

A number of dementing illnesses such as Alzheimer's disease are characterised by a progressive deterioration in cognition in the sufferer. It would clearly be desirable to enhance cognition in subjects desirous of such treatment, for example for subjects suffering from a dementing illness. It is believed this can be done utilising compounds which are ligands for the GABA_A $\alpha 5$ receptor subtype.

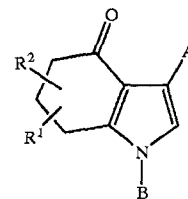
WO-A-9616954 mentions three thienylcyclohexanone derivatives in substituted by substituted arylaminocarbonyl on the thiophene ring as fungicides.

Van Rhee et al, *J. Med. Chem.*, 1996, 39, 398-406 discloses related compounds as adenosine receptor antagonists which differ in having an ester group on the thiophene ring.

SUMMARY OF THE INVENTION

The present invention is directed to compounds according to Formula (I) or a pharmaceutically acceptable salt thereof that are GABA-A Alpha 5 ligands useful for enhancing cognition:

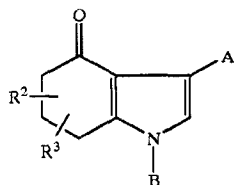
(I)



DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof.

3



where A is C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, arylC₁₋₆alkyl, or aryl wherein the aryl group is optionally substituted by halogen, C₁₋₆alkyl, CF₃, CN, NO₂ or NH₂, NR¹R¹⁰, S(O)_pR¹, heteroarylC₁₋₆alkyl or heteroaryl where heteroaryl is a 5- or 6-membered heteroaromatic ring as defined for B below;

B is phenyl or a 5-membered ring having one or two unsaturations containing 1, 2, 3 or 4 heteroatoms chosen from O, N and S provided that not more than one heteroatom is other than N, a 6-membered heteroaromatic ring containing 1, 2, 3 or 4 nitrogen atoms, each of which rings is optionally substituted by one or more substituents independently chosen from: cyano; C₁₋₆alkyl; C₁₋₆haloalkyl; halogen; S(O)_pR⁴; COR⁵; and aryl, arylC₁₋₆alkyl or a 5-membered ring having one or two unsaturations containing 1, 2, 3 or 4 heteroatoms chosen from O, N and S provided that not more than one heteroatom is other than N wherein the aryl ring or 5-membered ring is optionally substituted by one, two or three substituents independently chosen from halogen, CF₃, OCH₃, nitro and cyano; and when a nitrogen ring atom is present it is optionally substituted by oxygen;

R¹ is hydrogen; C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl or C₃₋₆cycloalkenyl each of which is optionally substituted by amino, C₁₋₆alkylamino, di(C₁₋₆alkyl)amino, C₁₋₆alkoxy, C₁₋₆alkylaminocarbonyl, one, two or three hydroxy groups, one, two or three halogen atoms or a four, five or six-membered saturated heterocyclic ring containing a nitrogen atom and optionally either an oxygen atom or a further nitrogen atom which ring is optionally substituted by C₁₋₆alkyl on the further nitrogen atom; aryl, arylC₁₋₆alkyl, arylC₂₋₆alkenyl or arylC₂₋₆alkynyl optionally substituted on the aryl ring by halogen, nitro, cyano, C₁₋₆alkylcarbonylamino, hydroxy or C₁₋₆alkoxy; or a five-membered aromatic ring containing 1, 2, 3 or 4 heteroatoms chosen from O, N and S provided that not more than one heteroatom is other than N, or a six-membered aromatic ring containing 1, 2, 3 or 4 nitrogen atoms, which ring is optionally substituted by halogen, C₁₋₆alkoxy, C₁₋₆alkylthio, aryl, C₁₋₆alkyl, C₂₋₆alkenyl or C₂₋₆alkynyl;

R² and R³ are independently hydrogen or C₁₋₆alkyl or together with the carbon atom to which they are attached form a C₃₋₈ cycloalkyl group;

R⁴ is hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, aryl or CH₂(CO)_mNR⁸R⁹;

R⁵ is NR⁶R⁷, C₁₋₆alkyl or C₁₋₆alkoxy;

R⁶ is independently as defined for R⁴;

R⁷ is aryl optionally substituted by halogen, nitro or cyano;

R⁸ is hydrogen, C₁₋₆alkyl, C₃₋₆cycloalkyl, C₃₋₆cycloalkenyl, C₂₋₆alkenyl, C₂₋₆alkynyl; arylC₁₋₆alkyl, arylC₂₋₆alkenyl or arylC₂₋₆alkynyl optionally

4

substituted on the aryl ring by halogen, nitro or cyano; thiophene or pyridine;

R⁹ is C₁₋₆alkyl; C₂₋₆alkenyl; C₂₋₆alkynyl; or phenyl optionally substituted by one, two or three substituents independently chosen from halogen, CF₃, OCH₃, nitro and cyano;

R¹⁰ is hydrogen or C₁₋₆alkyl;

R¹⁴ is hydrogen or C₁₋₆alkyl;

m is zero or 1;

p is zero, 1 or 2;

q is 1 or 2;

r is 0, 1 or 2;

s is 0, 1 or 2; and

t is 0, 1 or 2.

B may be phenyl or a 5-membered ring having one or two unsaturations containing 1, 2, 3 or 4 heteroatoms chosen from O, N and S provided that not more than one heteroatom is other than N, or a 6-membered aromatic ring containing 1, 2, 3 or 4 nitrogen atoms, which ring is optionally substituted by one or more substituents independently chosen from: C₁₋₆alkyl; C₁₋₆haloalkyl; halogen; S(O)_pR⁴; COR⁵; and aryl or arylC₁₋₆alkyl wherein the aryl ring is optionally substituted by one, two or three substituents independently chosen from halogen, CF₃, OCH₃, nitro and cyano; and when a nitrogen ring atom is present it is optionally substituted by oxygen.

B is preferably an optionally substituted phenyl or optionally substituted 6-membered heteroaromatic ring. The optional substituents are preferably one or two groups independently chosen from halogen, C₁₋₆alkyl, trifluoromethyl, cyano and an unsubstituted 5-membered heteroaromatic ring containing 1, 2, 3 or 4 heteroatoms chosen from O, N and S in which not more than one heteroatom is other than N. The optional substituent is preferably chosen from halogen, C₁₋₆alkyl, trifluoromethyl and cyano.

B is most particularly optionally substituted phenyl or pyridine. In particular B may be pyridine and preferably pyridin-2-yl.

Thus when B is a heteroaromatic ring it may be a thiazole, pyrazole, pyrimidine, tetrazole, triazole, oxadiazole, oxazole, pyridine, imidazole or pyrazine which is unsubstituted or substituted by C₁₋₆alkyl, halogen, SR⁴, COR⁵ or benzyl optionally substituted by halogen. When B is a 5- or 6-membered ring having one unsaturation it is preferably oxazolidinyl or imidazolynyl optionally substituted by halogen or C₁₋₆alkyl.

Particular embodiments of B are (1-phenylsulphonyl)pyrazol-3-yl, 1-acetylpyrazol-3-yl, (3-ethoxycarbonyl)isoxazol-5-yl, (3-isopropyl)-1,2,4-oxadiazol-5-yl, imidazolin-2-yl, pyrazol-4-yl, 2-methyl-1,3,4-oxadiazol-5-yl, oxazolidin-2-yl, 2-methyltetrazol-5-yl, pyrazol-3-yl, 2-propyltetrazol-5-yl, thiazol-2-yl, 4-methyl-1,2,4-triazol-3-yl, (4-ethoxycarbonyl)thiazol-2-yl, (4-trifluoromethyl)thiazol-2-yl, (4-acetyl)thiazol-2-yl, (4-methyl)thiazol-2-yl, pyrrol-2-yl, pyrid-2-yl, 3-methyl-1,2,4-oxadiazol-5-yl, 4-benzyl-1,2,4-triazol-3-yl, 1-methyl-1,2,4-triazol-3-yl, oxazol-2-yl, pyrazin-2-yl, pyrimidin-5-yl, 3-(N-methylaminocarbonyl)thiazol-2-yl, thiazol-5-yl, isoxazol-5-yl, pyrid-3-yl, pyrid-4-yl, 1,3,4-oxadiazol-5-yl and 1-methylsulphonylpyrazol-3-yl.

Other particular embodiments of B are pyridin-2-yl, 6-methyl pyridin-2-yl, thiazol-2-yl, 4-chlorophenyl, 4-fluorophenyl, 3-fluorophenyl, 4-trifluoromethylphenyl, 4-methylphenyl, 3-methylphenyl, pyrimidin-2-yl, pyridin-3-yl, 2-cyanophenyl, 5-chloropyridin-2-yl and 6-(thiazol-2-yl)pyridin-2-yl.

5

R^1 is preferably C_{1-6} alkyl, C_{2-6} alkenyl or C_{3-6} cycloalkyl each of which is optionally substituted by amino, di(C_{1-6} alkyl)amino, hydroxy, C_{1-6} alkoxy, C_{1-6} alkylaminocarbonyl or one, two or three halogen atoms; aryl or aryl- C_{1-6} alkyl optionally substituted on the aryl ring by halogen, C_{1-6} alkylcarbonylamino or C_{1-6} alkoxy; or a five-membered aromatic ring containing 1, 2 or 3 heteroatoms chosen from O, N and S provided that not more than one heteroatom is other than N, or a six-membered aromatic ring containing 1 or 2 nitrogen atoms, which ring is optionally substituted by halogen, C_{1-6} alkoxy, C_{1-6} alkylthio, aryl or C_{1-6} alkyl.

More preferably R^1 is C_{1-6} alkyl, C_{1-4} alkenyl, or C_{3-6} cycloalkyl each of which is optionally substituted by di(C_{1-4} alkyl)amino, C_{1-4} alkoxy, C_{1-4} alkylaminocarbonyl, one or two hydroxy groups or three fluorine atoms; phenyl or phenyl- C_{1-4} alkyl optionally substituted on the phenyl ring by chlorine, fluorine, C_{1-4} alkoxy or C_{1-4} alkylcarbonylamino; or a pyridine, thiophene, furan, pyrimidine, thiazole, imidazole, triazole or thiadiazole, each of which is unsubstituted or substituted by C_{1-4} alkyl, phenyl, fluorine or C_{1-4} alkylthio. In particular R^1 is C_{1-6} alkyl, phenyl, benzyl or pyridyl.

A may be C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, aryl- C_{1-6} alkyl, aryl, $S(O)_pR^1$, heteroaryl- C_{1-6} alkyl or heteroaryl where heteroaryl is a 5-membered ring having one or two unsaturations containing 1, 2, 3 or 4 heteroatoms chosen from O, N and S provided that not more than one heteroatom is other than N, or a 6-membered aromatic ring containing 1, 2, 3 or 4 nitrogen atoms, which ring is optionally substituted by one or more substituents independently chosen from: C_{1-6} alkyl; C_{1-6} haloalkyl; halogen; $S(O)_pR^4$; COR^5 ; and aryl or aryl- C_{1-6} alkyl wherein the aryl ring is optionally substituted by one, two or three substituents independently chosen from halogen, CF_3 , OCH_3 , nitro and cyano; and when a nitrogen ring atom is present it is optionally substituted by oxygen.

When A is not $S(O)_pR^1$ it is preferably C_{1-6} alkyl, C_{2-6} alkenyl or C_{3-6} cycloalkyl. A may be C_{1-6} alkyl such as ethyl.

A is preferably C_{1-6} alkyl, C_{2-6} alkenyl, aryl- C_{1-6} alkyl or aryl wherein the aryl group is optionally substituted by a halogen atom or a C_{1-6} alkyl group, a 5- or 6-membered heteroaromatic ring optionally substituted by a halogen atom or C_{1-6} alkyl, NHR^1 or SR^1 .

Particular embodiments of A include ethyl, 1,1-dimethylethyl, cyclopropyl, thiazol-2-yl, ethylthio, benzyl, phenyl, methylthio, ethenyl, phenylamino, pyridin-2-ylamino, phenylthio, pyrid-2-yl, benzylthio, oxazol-2-yl, 3-methyl-1,2,4-oxadiazol-5-yl, thiazol-5-yl, 4-chlorophenyl, 4-methylthiazol-2-yl, 3-chlorophenyl and 2-chlorophenyl.

Particular embodiments of A are phenyl, cyclohexyl, 2-methylprop-1-enyl, methylthio, ethyl, isopropyl, propyl, cyclobutyl, but-3-enyl, cyclopropyl, methanesulphonyl, methyl, benzyl, methanesulphinyl, (1,1-dimethylethyl)thio, pentylthio, (4-methyl-1,2,4-triazol-3-yl)thio, hexylthio, benzylamino, (3-imidazol-1-ylpropyl)amino, (pyrid-2-yl)amino, 2-methylprop-1-yl, [3-(4-methylpiperazin-1-yl)propyl]amino, methylamino, (2-hydroxyethyl)amino, azetidin-1-yl, tert-butylamino, isopropylthio, (2-hydroxyethyl)thio, methoxy, dimethylamino, cyclobutoxy, phenoxy, butylthio, (3-chloropropyl)thio, (2-phenylethyl)thio, propylthio, (2-methylbutyl)thio, (2,2,2-trifluoroethyl)thio, (1-methylpropyl)thio, (4-chlorophenyl)thio, (3-fluorophenyl)thio, (4-acetylamino)phenylthio, (4-methoxyphenyl)thio, (1-methylimidazol-2-yl)thio, (thiophen-2-yl)thio, (imidazol-2-yl)thio, (4-phenylthiazol-2-

6

yl)thio, (1,2,4-triazol-3-yl)thio, (5-methyl-1,3,4-thiadiazol-2-yl)thio, (5-methylthio-1,3,4-thiadiazol-2-yl)thio, benzylthio, cyclopentylthio, (2-methylpropyl)thio, (furan-2-ylmethyl)thio, (2-hydroxy-1-methylpropyl)thio, (2,3-dihydroxypropyl)thio, (2-hydroxypropyl)thio, ((N-methylaminocarbonyl)methyl)thio, (pyrid-4-yl)thio, (pyrimidin-2-yl)thio, (thiazol-2-yl)thio, prop-2-enylthio, (pyrid-2-yl)thio, ethylthio, phenylthio, (N,N-dimethyl-2-aminoethyl)thio, (2-methoxyethyl)thio, (furan-2-ylmethyl)amino, (2-methylpropyl)amino, propylamino, (2-methoxyethyl)amino, cyclopropylamino, isopropylamino, ethylamino, cyclobutylamino and isopropoxy.

When A is heteroaryl it may be a thiazole, pyrazole, pyrimidine, tetrazole, triazole, oxadiazole, oxazole, pyridine, imidazole or pyrazine.

R^2 and R^3 are preferably independently chosen from hydrogen, methyl and propyl or are attached to the same carbon atom and together with that atom form a C_{3-6} cycloalkyl group. Alternatively R^2 and R^3 are independently chosen from hydrogen and methyl. R^2 may be hydrogen with R^3 being hydrogen, methyl or isopropyl. Preferably both are methyl. Preferably R^2 and R^3 are geminal to each other, preferably at the 6-position, i.e. beta to the carbonyl group in formula I.

R^4 may be hydrogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, aryl or $CH_2(CO)_mNR^8R^9$. R^4 is preferably hydrogen, C_{1-4} alkyl or $CH_2(CO)_mNR^8R^9$, more preferably hydrogen, methyl or $CH_2CONR^8R^9$ and most preferably methyl or $CH_2CONR^8R^9$.

R^5 is preferably methyl, methoxy, ethoxy or NR^6R^7 and most preferably methyl, ethoxy or NR^6R^7 .

R^6 may be hydrogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, aryl or $CH_2(CO)_mNR^8R^9$. R^6 is preferably hydrogen or C_{1-4} alkyl and most preferably hydrogen.

R^1 is preferably phenyl unsubstituted or substituted by halogen, nitro or cyano, more preferably optionally substituted by halogen, such as chlorine.

R^8 is preferably hydrogen or C_{1-6} alkyl and most preferably hydrogen.

R^9 is preferably C_{1-6} alkyl or phenyl unsubstituted or substituted by one, two or three substituents independently chosen from halogen, nitro and cyano, more preferably C_{1-6} alkyl or phenyl optionally substituted by one or two substituents independently chosen from halogen and nitro and most preferably tert-butyl or phenyl optionally substituted with one or two substituents chosen from chlorine and nitro, such as 4-chlorophenyl.

R^{10} is preferably hydrogen or methyl, particularly hydrogen.

R^{14} is generally hydrogen or C_{1-4} alkyl and most preferably hydrogen.

m is preferably 1.

p is preferably zero or two, most preferably zero.

q is preferably 1.

r is preferably 1.

s is preferably 0 or 1. s may be 1. s may be 0.

t is preferably 0 or 1. t may be 1. t may be 0.

A specific Example of a compound according to the present invention is:

6,6-dimethyl 3-ethyl-1-(pyridin-2-yl)-4,5,6,7-tetrahydroindol-4-one and the pharmaceutically acceptable salts thereof.

Further specific Examples of compounds according to the present invention are:

6,6-dimethyl-3-(1,1-dimethylethyl)-1-(pyridin-2-yl)-4,5,6,7-tetrahydroindol-4-one;

31

R² and R³ are independently hydrogen or C₁₋₆alkyl or together with the carbon atom to which they are attached form a C₃₋₆cycloalkyl group;

R⁴ is hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, aryl or CH₂(CO)_mNR⁶R⁷;

R⁵ is NR⁶R⁷, C₁₋₆alkyl or C₁₋₆alkoxy;

R⁶ is independently as defined for R⁴;

R⁷ is aryl optionally substituted by halogen, nitro or cyano;

R⁸ is hydrogen, C₁₋₆alkyl, C₃₋₆cycloalkyl, C₃₋₆cycloalkenyl, C₂₋₆alkenyl, C₂₋₆alkynyl; arylC₁₋₆alkyl, arylC₂₋₆alkenyl or arylC₂₋₆alkynyl optionally substituted on the aryl ring by halogen, nitro or cyano; thiophene or pyridine;

R⁹ is C₁₋₆alkyl; C₂₋₆alkenyl; C₂₋₆alkynyl; or phenyl optionally substituted by one, two or three substituents independently chosen from halogen, CF₃, OCH₃, nitro and cyano;

R¹⁰ is hydrogen or C₁₋₆alkyl;

R¹⁴ is hydrogen or C₁₋₆alkyl;

m is zero or 1;

p is zero, 1 or 2;

q is 1 or 2;

r is 0, 1 or 2;

s is 0, 1 or 2; and

t is 0, 1 or 2.

2. A compound according to claim 1 wherein B is phenyl or 6-membered heteroaromatic ring optionally substituted with one or two substituent groups independently chosen

32

from halogen, C₁₋₆alkyl, trifluoromethyl, cyano or unsubstituted 5-membered heteroaromatic ring substituent containing 1, 2, 3 or 4 heteroatoms chosen from O, N and S in which not more than one heteroatom is other than N.

3. A composition according to claim 1 wherein A is C₁₋₆alkyl, C₂₋₆alkenyl, aryl C₁₋₆alkyl or aryl wherein the aryl group is optionally substituted by a halogen atom or a C₁₋₆alkyl group, a 5- or 6-membered heteroaromatic ring optionally substituted by a halogen atom or C₁₋₆alkyl, NHR¹ or SR¹.

4. A composition according to claim 1, wherein R¹ is C₁₋₆alkyl, C₁₋₄alkenyl, or C₃₋₆cycloalkyl each of which is optionally substituted by di(C₁₋₄alkyl)amino, C₁₋₄alkoxy, C₁₋₄alkylaminocarbonyl, one or two hydroxy groups or three fluorine atoms; phenol or phenylC₁₋₄alkyl optionally substituted on the phenyl ring by chlorine, fluorine, C₁₋₄alkoxy or C₁₋₄alkylcarbonylamino; or a pyridine, thiophene, furan, pyrimidine, thiazole, imidazole, triazole or thiadiazole, each of which is unsubstituted or substituted by C₁₋₄alkyl, phenyl, fluorine or C₁₋₄alkylthio.

5. A compound according to claim 1 wherein R² and R³ are independently chosen from hydrogen and methyl.

6. A pharmaceutical composition comprising a compound according to claim 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

7. A compound as defined in any one of claims 1 to 5 or a pharmaceutically acceptable salt thereof, with the exception of 6,7-dihydro-3-methyl-1-phenylindol-4(5H)-one and 1,5,6,7-tetrahydro-3,6,6-trimethyl-1-phenylindol-4-one.

* * * * *

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIRECCIÓN DE NUEVAS CREACIONES

2020
Bogotá, D.C.,

Abogado
EMILIO FERRERO

ASUNTO

Radicación 07 099086
Trámite 011
Evento 378
Actuación 519
Oficio
Folios 009

05880

Patente de Invención



Patente de Modelo de Utilidad

☐

Vía Nacional



Vía PCT (Fase Nacional)



Cap. I



Cap. II

☐

No. Solicitud Internacional PCT/US20061/006988

Fecha de Presentación Internacional 27/Febrero/2006

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:

1. Documentos estudiados

Descripción: Folios 265 a 449 como se radicó inicialmente.

Reivindicaciones: Folios 450 a 524 como se radicó inicialmente

Prioridad: US 60 /656,230 de Febrero 25 de 2005
US 60 /705,715 de Agosto 04 de 2005
US 60 /727,965 de Octubre 18 de 2005

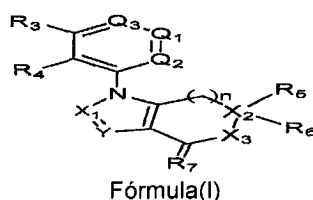
2. Objeto de la invención

Objeto: La invención se relaciona con derivados de benceno, piridina y piridazina útiles en el tratamiento y/o condiciones relacionadas con la proliferación celular, tal como cáncer; también útiles en el tratamiento de infecciones fúngicas (folio 265, campo de la invención).

Título de la solicitud: "DERIVADOS DE TETRAHIDROINDAZOL Y DE TETRAHIDROINDOLONA"

El problema planteado en esta solicitud es la necesidad de proporcionar compuestos útiles para tratar el cáncer, inflamación y trastornos asociados con la inflamación y condiciones o enfermedades relacionadas con angiogénesis no controlada.

Para resolver este problema técnico la solicitud en estudio proporciona un compuesto de la fórmula (I) y composiciones que lo contienen.



El objeto de la presente Solicitud se relaciona con la Clasificación Internacional de Patentes (CIP): C07D231/56, 209/14, A61K31/416, A61P35/00.

3. Excepción a la Patentabilidad (Art 20 D 486 literal (d))

El objeto de las reivindicaciones 93, 94, 96-104, 120, no es patentable porque se refieren a un método de tratamiento.

4. Reivindicaciones relativas a un uso o a un segundo uso (Art 14 y 21 D 486)

Las reivindicaciones 106, 108-118 no son patentables porque corresponden a un uso.

5. De la Solicitud de Patente

Reivindicaciones (Art 30 D 486, Art 22 PCT)

En el capítulo reivindicatorio la reivindicación 94, esta numerada dos veces, una como un paquete y otra como un método de tratamiento, por lo tanto no hay claridad al respecto.

La Reivindicaciones 94, 107, no son claras porque reclaman la misma materia.

La reivindicación 70 no es clara porque no se sabe de cual reivindicación depende, ya que menciona que depende de la reivindicación "6469".

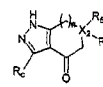
Las reivindicaciones 92 y 105 no son claras porque reclaman la misma materia,

La Reivindicación 1 y sus dependientes no son concisas, porque presentan una excesiva complejidad, lo cual dificulta determinar la extensión del objeto que se busca proteger. Por Ejemplo cuando $n = 0-4$, la gran cantidad de significados para R_3 y R_4 , asimismo la extensa variabilidad de Q_1 , Q_2 y Q_3 , entre otros. Conforme a lo mencionado antes es necesario, que los sustituyentes de cada variable sean definidos de forma específica, y que se haga una generalización razonable de los compuestos reclamados, tomando en cuenta los ejemplos, que resuelvan el problema planteado, con la actividad biológica que se les atribuye.

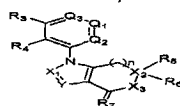
Se requiere al Solicitante hacer las aclaraciones necesarias.

6. Unidad de invención (Art 25 D 486)

El compuesto de la reivindicación 119, tiene la estructura



, la cual es muy



diferente a la estructura de la reivindicación 1; además no presenta alguna de las actividades asignadas a los compuestos que están

comprendidos en la fórmula (I) de la reivindicación 1 (ver tablas descripción pgs 185 y 186); por lo cual, dicha reivindicación no cumple con el requisito de unidad de invención.

7. Determinación del Estado de la Técnica

El Estado de la Técnica se determinó con base en la
Fecha de Presentación de la Solicitud de Prioridad: Febrero 25 de 2005.
y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

Item	Documento	Título	Fecha de Publicación*
D1	US5104442	Tetarhydroindolone Derivatives as Gabaalphas ligands for enhancing cognition	Mayo 28 de 2002

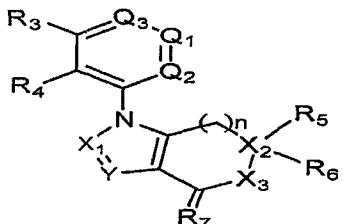
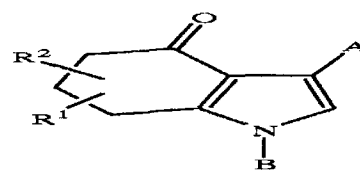
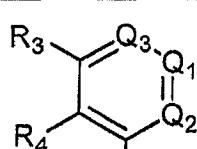
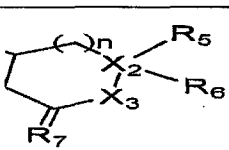
D1 divulga (folios 589-593) un compuesto de la fórmula (I), sus sales y composiciones que los contienen.

8. Examen de Patentabilidad (Art 14 D486)

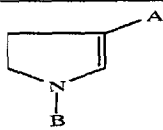
Novedad (artículo 16 D486)

La reivindicación 1, reclama un compuesto de formula (I), y las composiciones farmacéuticas que los contienen.

Comparación de las características técnicas **esenciales**, con las del estado de la Técnica:

Características esenciales	D1 US5104442
Compuesto de fórmula (I) y sus sales: 	Compuesto de fórmula (I) 
Donde las variables a continuación significan:	sus sales y las composiciones farmacéuticas que los contienen (folio 593, columna 32, reiv 7 y 8) Donde las variables a continuación significan:
 Q3=N Q1= CRa siendo Ra= H Q2= CR21 siendo R21=ciano, COR5, R5= C1-6 alcoxy R3 y R4= halo, alquilo C1-6	Si B= fenil que contiene un heteroatomo N, H el fenil esta sustituido por ciano, COR5, R5= C1-6 alcoxy (folio 591, columna 3, líneas 18-67)
 n=1 R7=O X2=C X3=C R5 y R6=H, C1-6 alquilo	Si 1 O C C R2 y R3= H, C1-6 alquilo (folio 591, columna 3, líneas 1-11 y 56)

599
598
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 X1= CRc, Rc=H Y= CRc, Rc=C1-6 alquil, C2-6alquenil, C2-6alquinil, C3-6cicloalquil, aril; sustituido por C1-6 alquil, halo, amino, ciano, nitro, heteroarilo.	 CH A= C1-6 alquil, C2-6alquenil, C2-6alquinil, C3-6cicloalquil, aril; sustituido por C1-6 alquil, halo, amino, ciano, nitro, heteroarilo (folio 591, columna 3, líneas 12-15)
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Las características esenciales del compuesto de la reivindicación 1, habían sido divulgadas previamente en D1, como se observa en la tabla comparativa anterior.

En consecuencia, la reivindicación 1 carece de novedad, según lo divulgado en el documento D1.

Las reivindicaciones dependientes 2-69, 71-91, 95, 97-105, 11 no mencionan alguna característica que haga nueva a la composición de la reivindicación 1, por lo cual se considera que no son nuevas.

9. Conclusión

Los requisitos de Patentabilidad de la presente Solicitud están afectados así:

Item	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	US 5'789.567	1-69, 71-91, 95, 97-105	Novedad

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 sesenta (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.



JOSÉ LUIS SALAZAR LÓPEZ
Director de Nuevas Creaciones (C)

El anterior requerimiento fue notificado por fijación en lista, de fecha

10 1 ABR. 2011

CONCEPTO TÉCNICO No.487	EXAMINADOR TÉCNICO Código No.202078
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