

Señor

SUPERINTENDENTE DELEGADO PARA LA PROPIEDAD INDUSTRIAL
DIVISION DE NUEVAS CREACIONES

E. _____ S _____ D.

Ref: **P1.-PHARMACIA & UPJOHN COMPANY.-Expediente**
No 02-083.633 -

- 1 Me refiero al asunto de la referencia
- 2 Por medio del presente, atentamente me permito manifestar que hubo un **cambio** de apoderado para todos los asuntos de la Propiedad Industrial en Bogotá de la sociedad **PHARMACIA & UPJOHN COMPANY.**
- 3 En consecuencia, atentamente solicito a ese Despacho reconocirme personería en este asunto, de conformidad con la sustitución de poder adjunta, otorgada a favor de la SUSCRITA
4. Por lo tanto, ruego a usted **notificarme de las providencias expedidas dentro de este expediente** y notificadas al anterior apoderado, que actualmente se encuentran pendientes de cumplimiento o de respuesta.
- 5 Solicito a ese Despacho proceder de conformidad.

Atentamente,



ALICIA LLOREDA RICAURTE

T.P. 53.215

Código 231

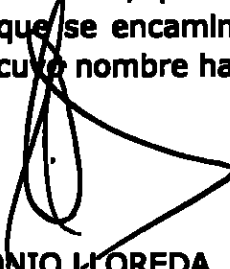
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Señor
SUPERINTENDENTE DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
E. _____ S. _____ D. _____

Ref: P1.-PHARMACIA & UPJOHN COMPANY.-Expediente No. 02-083.633.-

Yo, **JOSE ANTONIO LLOREDA**, mayor de edad y vecino de esta ciudad, abogado titulado e inscrito, identificado como aparece al ple de mi firma, actuando en mi carácter de Representante Legal en Bogotá para asuntos relacionados con la propiedad industrial de **PHARMACIA & UPJOHN COMPANY**, sociedad organizada y existente de conformidad con las leyes del Estado de Delaware, Estados Unidos de América, domiciliada en Kalamazoo, Estado de Michigan, Estados Unidos de América, tal y como consta en este expediente, atentamente manifiesto a usted que **SUSTITUYO** el poder a mi conferido a la doctora **ALICIA LLOREDA RICAURTE**, abogada titulada e inscrita, identificada con la cédula de ciudadanía No. 39.690 713 de Usaquén, para que continúe representandola en el expediente de la referencia

El mencionado apoderado tendrá las mismas facultades a mi conferidas, en especial, renunciar, recibir, sustituir, desistir, presentar recursos, conciliar, transigir, y en fin, para todo lo que se encamine a la correcta defensa de los intereses de la sociedad en cuyo nombre hablo.

Atentamente, 

NOTARIA DE BOGOTA
RECONOCIMIENTO Y PRESENTACION DE **JOSE ANTONIO LLOREDA**
Bogotá, D.C., **25 ABO 2004** T.P. 10784
Ante mí **PABLO MENDEZ BARRAJAS** Código 231
NOTARIO SEXTO(2) DEL CIRCULO DE BOGOTA
Comparecieron **JOSE ANTONIO LLOREDA**

quien (as) exhibió(aron) la(s) C.C.
17.159.681
y declaró(aron) que es (son) el (los) propietario(s) de la(s) firma(s) que se exhibió(aron) y
en el presente documento, y
que el contenido es verdadero y correcto.
En constancia de lo anterior, se otorga el presente documento y se imprime el presente documento.

JOSE ANTONIO LLOREDA
C.C. No. 17.159.681 de Bogotá



D1 145/138



Publication number

0 277 791
A2

②

EUROPEAN PATENT APPLICATION

④ Application number 88300823.7

⑤ Date of filing 01.09.88

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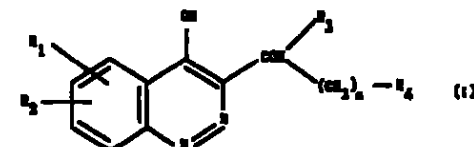
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⑫ Cinnoline-carbonamides and process for their preparation.

⑬ The invention relates to compounds having the general formula (I)



wherein

n is zero, 1 or 2;

each of R₁ and R₂ is independently

- a) hydrogen, halogen, trifluoromethyl or C₁-C₆ alkyl,
- b) hydroxy, C₁-C₆ alkoxy or C₃-C₄ alkenyloxy;
- c) nitro, amino, formylamino or C₃-C₆ alkanoylamino,

R₃ represents hydrogen or C₁-C₆ alkyl,

R₄ is

- a') C₁-C₆ alkyl, unsubstituted or substituted by



- e') pyridyl, unsubstituted or substituted by one or two

wherein each of R₅ and R₆ is independently phenyl or C₁-C₆ alkyl, or R₅ and R₆, taken together with the nitrogen atom to which they are linked, form a N-pyrrolidyl, N-piperidyl, hexahydroazepin-1-yl, thiomorpholino, morpholino or piperidino ring, wherein said heterocyclic rings may be unsubstituted or substituted by C₁-C₆ alkyl or phenyl;

b') C₃-C₁₆ cycloalkyl, unsubstituted or substituted by methyl,

c') 2- or 3-pyrrolidyl, piperidyl or 2-piperidyl, wherein said heterocyclic rings may be unsubstituted or substituted by C₁-C₆ alkyl,

d') isoxazolyl or thiazolyl, wherein said heterocyclic rings may be unsubstituted or substituted by C₁-C₆ alkyl; substituents chosen independently from halogen, C₁-C₆ alkyl and C₁-C₆ alkoxy or

f') phenyl, unsubstituted or substituted by one or two substituents chosen independently from halogen, CF₃, C₁-C₆ alkyl, C₁-C₆ alkoxy, amino, nitro, formylamino and C₃-C₆ alkanoylamino, and the pharmaceutically acceptable salts thereof, which possess immunomodulating activity and are useful e.g. in the treatment of neoplastic diseases and acute and chronic infections of both bacterial and viral origin in mammals.

Structural Formula

EP 0 277 791 A2

Description

"CINNOLINE-CARBOXAMIDES AND PROCESS FOR THEIR PREPARATION

The present invention relates to 4-hydroxycinnoline-carboxamides, to their use as immunomodulating agents, to a method for their preparation and pharmaceutical compositions containing them.

The preparation of cinnoline compounds, including 4-hydroxycinnoline-3-carboxylic acids, is described in "A new Cinnoline synthesis. Part I. Cyclization of Mescalyl Chloride to give substituted 4-hydroxycinnoline-3-carboxylic acids" J. Chem. Soc. 2828 (1931)

The synthesis of 4-hydroxycinnoline-3-carboxylic alkyl esters, useful as intermediate compounds for the preparation of piazolo-cinnolines having antitumor properties, is also described in French patent No. 2 548 633.

Additionally 4-hydroxy-3-cinnoline carboxamides are described in U.S. patent No. 3 657 241. However no utility is attributed to such compounds, which are intermediate compounds in the preparation of the corresponding 4-halocinnolines useful as herbicides, fungicides and insecticides.

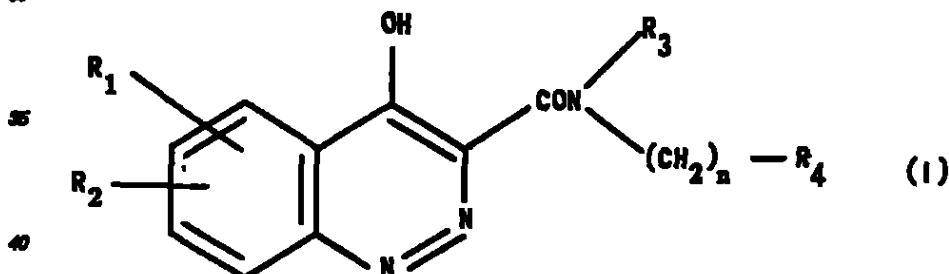
The broad general formula of the compounds object of European patent application publication No. 205272 embraces 4-amino- and 4-hydroxy-cinnoline-3-carboxylic acid derivatives, to which CN8 depressant activity is attributed. However, besides the sole compounds 4-hydroxy-N,6-dipropyl-cinnoline-3-carboxamide and 6-chloro-4-hydroxy-N-propyl-cinnoline-3-carboxamide, no further 4-hydroxycinnoline-3-carboxamide derivative is specifically mentioned in the European document.

Moreover none of the foregoing prior-art documents discloses or suggests the use of the compounds of the present invention as immunomodulating agents or their use in the preparation of a pharmaceutical composition having immunomodulating activity.

It has now been found that 4-hydroxy-3-cinnoline carboxamides of general formula (I), as herein defined, and the pharmaceutically acceptable salts thereof possess immunomodulating activity.

The present invention therefore relates, as a first object, to the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as immunomodulator, to pharmaceutical compositions having immunomodulating activity containing a compound of formula (I), or a pharmaceutically acceptable salt thereof, as active principle and to the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, for the preparation of these pharmaceutical compositions.

The compounds of formula (I) have the following general formula



wherein

n is zero, 1 or 2,

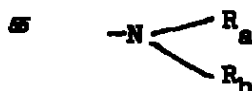
each of R₁ and R₂ is independently

- a) hydrogen, halogen, trifluoromethyl or C₁-C₆ alkyl,
- b) hydroxy, C₁-C₆ alkoxy or C₂-C₄ alkenyloxy;
- c) nitro, amino, formylamino or C₂-C₆ alkanylamino,

R₃ represents hydrogen or C₁-3 alkyl,

R₄ is

- a') C₁-C₆ alkyl, unsubstituted or substituted by



wherein each of R_a and R_b is independently phenyl or C₁-C₆ alkyl, or R_a and R_b, taken together with the nitrogen atom to which they are linked, form a N-pyrrolidinyl, N-piperidinyl, hexahydroazepin-1-yl, thiomorpholino, morpholino or piperidino ring, wherein said heterocyclic rings may be unsubstituted or substituted by C₁-C₆ alkyl or phenyl,

b') C₆-C₁₀ cycloalkyl, unsubstituted or substituted by methyl,
 c') 2- or 3-pyrrolidinyl, piperidyl or 2-piperazinyl, wherein said heterocyclic rings may be unsubstituted or substituted by C₁-C₆ alkyl,

d') isoxazolyl or thiazolyl, wherein said heterocyclic rings may be unsubstituted or substituted by C₁-C₆ alkyl,

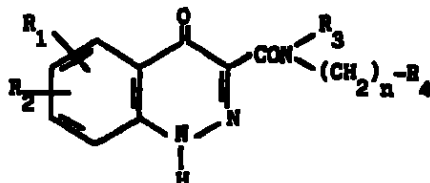
e') pyridyl, unsubstituted or substituted by one or two substituents chosen independently from halogen, C₁-C₆ alkyl and C₁-C₆ alkoxy, or

f') phenyl, unsubstituted or substituted by one or two substituents chosen independently from halogen, CF₃, C₁-C₆ alkyl, C₁-C₆ alkoxy, amino, nitro, formylamino and C₂-C₆ alkenoylamino.

These compounds and their salts are hereafter referred to as the "active compounds" and as the "compounds of the invention"

By evaluating the prior-art references cited above, it appears clear that two of the compounds, falling within the general formula (I) above, are known compounds previously mentioned in EP-A-205272, others are embraced by the broad general formula of the European document, but therein not specifically mentioned whereas other compounds of general formula (I) are not covered by the foregoing prior-art documents.

It has to be noticed that the 4-hydroxy-cinnoline derivatives of general formula (I) may exist also in the tautomeric cinnoline form of general formula



Nevertheless all the compounds of the present invention are named as 4-hydroxy-cinnoline derivatives. The invention also includes within its scope all the possible isomers, stereoisomers and optical isomers and their mixtures, and the metabolites and the metabolic precursors or bioprecursors of the compounds of formula (I)

A halogen atom is preferably chlorine or fluorine. The alkyl, alkenyl, alkoxy and alkenoylamino groups may be branched or straight chain groups.

A C₁-C₁₀ alkyl group is preferably a C₁-C₆ in particular C₁-C₄ alkyl group.

A C₁-C₆ alkyl group is preferably a C₁-C₄ alkyl group.

A C₁-C₆ alkyl group is, e.g., methyl, ethyl, propyl, isopropyl, butyl or tert.butyl, more preferably, methyl, ethyl or tert. butyl

A C₂-C₄ alkenyl group is preferably allyl

A C₁-C₆ alkoxy group is, e.g., methoxy, ethoxy, propoxy, isopropoxy, butoxy or tert.butoxy, preferably it is methoxy, ethoxy or propoxy

A C₆-C₁₀ cycloalkyl group is preferably cyclopentyl, cyclohexyl or cycloheptyl.

A C₂-C₆ alkenoylamino group is preferably acetylamino or propionylamino.

Examples of pharmaceutically acceptable salts are either those with inorganic bases, such as sodium, potassium, calcium and aluminium hydroxides or with organic bases, such as lysine, triethylamine, triethanolamine, diisopropylamine, methylbenzylamine, di-(2-ethyl-hexyl)-amine, piperidine, N-ethylpiperidine, N,N-diethylaminoethylamine, N-ethylmorpholine, β-phenethylamine, N-benzyl-β-phenethylamine, N-benzyl-N,N-dimethylamine and the other acceptable organic amines, as well as the salts with inorganic acids, e.g. hydrochloric, hydrobromic and sulphuric acids and with organic acids, e.g. citric, tartaric, maleic, malic, fumaric, methanesulphonic and ethanesulphonic acids.

Preferred salts of the compounds of formula (I) are the sodium and the potassium salts thereof

As stated above, the present invention also includes within its scope pharmaceutically acceptable bioprecursors (otherwise known as pro-drugs) of the compounds of formula (I), i.e. compounds which have a different formula to formula (I) above but which nevertheless upon administration to a human being are converted directly or indirectly *in vivo* into a compound of formula (I)

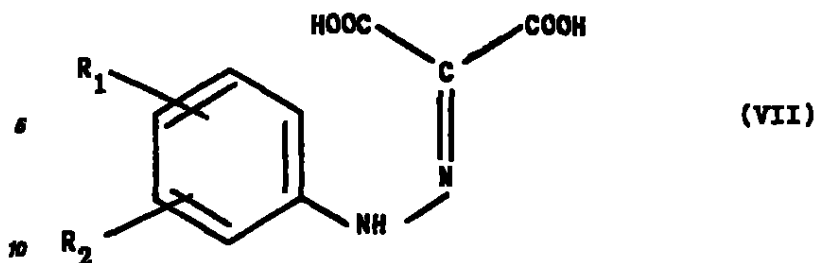
Preferred compounds of the invention are those of formula (I) wherein

n is zero, 1 or 2,

each of R₁ and R₂ is independently hydrogen, halogen, trifluoromethyl, C₁-C₄ alkyl, nitro, amino or C₁-C₄ alkoxy, R₃ represents hydrogen or C₁-C₄ alkyl, preferably hydrogen or C₁ or C₂ alkyl,

R₄ is

a") C₁-C₁₀ alkyl, preferably C₁-C₆ alkyl, unsubstituted or substituted by



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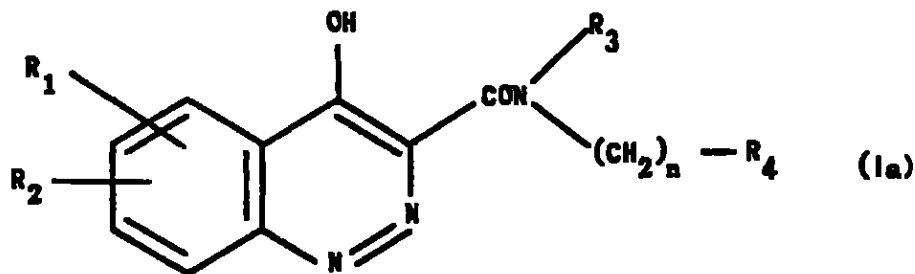
8-fluoro-4-hydroxy-N-(2-pyridyl)-cinnoline-3-carboxamide,
 N-benzyl-6-fluoro-4-hydroxy-cinnoline-3-carboxamide,
 6-fluoro-N-(4-fluoro-phenyl)-4-hydroxy-cinnoline-3-carboxamide,
 6-fluoro-N-(3-fluoro-phenyl)-4-hydroxy-cinnoline-3-carboxamide,
 6-fluoro-4-hydroxy-N-(8-methyl-2-pyridyl)-cinnoline-3-carboxamide,
 N-(3-chloro-phenyl)-6-fluoro-4-hydroxy-cinnoline-3-carboxamide,
 4-hydroxy-N-(3-dimethylamino-propyl)-cinnoline-3-carboxamide,
 4-hydroxy-N-(2-dimethylamino-ethyl)-cinnoline-3-carboxamide,
 4-hydroxy-N-(2-morpholino-ethyl)-cinnoline-3-carboxamide,
 4-hydroxy-N-(2-(1-methyl-pyrrolidin-2-yl)-ethyl)-cinnoline-3-carboxamide,
 N-[(1-ethyl-pyrrolidin-2-yl)-methyl]-4-hydroxy-cinnoline-3-carboxamide.

5. The use of a compound of formula (I) or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 4 in the preparation of a pharmaceutical composition having immunostimulant activity

6. The use of a compound of formula (I) or a pharmaceutically acceptable salt thereof, according to claim 5, in the preparation of a pharmaceutical composition for the treatment of acute and chronic infections of both bacterial and viral origin in mammals.

7. The use of a compound of formula (I) or a pharmaceutically acceptable salt thereof, according to claim 5, in the preparation of a pharmaceutical composition for the treatment of neoplastic diseases in mammals.

8. A compound of general formula (Ia)



wherein

n is zero, 1 or 2,

each of R₁ and R₂ is independently

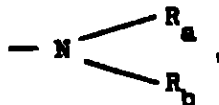
a) hydrogen, halogen, trifluoromethyl or C₁-C₆ alkyl,

b) hydroxy, C₁-C₆ alkoxy or C₂-C₄ alkanoyloxy;

c) nitro, amino, formylamino or C₂-C₆ alkanoylamino,
 R₃ represents hydrogen or C₁-C₆ alkyl.

R₄ is

a') C₁-C₂₀ alkyl, unsubstituted or substituted by



wherein each of R_a and R_b is independently phenyl or C₁-C₆ alkyl, or R_a and R_b, taken together with the nitrogen atom to which they are linked, form a N-pyrrolidinyl, N-piperazinyl, hexahydroazepin-1-yl, thiomorpholino, morpholino or piperidino ring, wherein said heterocyclic rings may be unsubstituted or substituted by C₁-C₆ alkyl or phenyl,

b') C₂-C₁₀ cycloalkyl, unsubstituted or substituted by methyl,

c') 2- or 3-pyrrolidinyl, piperidinyl or 2-piperazinyl, wherein said heterocyclic rings may be unsubstituted or substituted by C₁-C₆ alkyl,

d') isoxazolyl or thiazolyl, wherein said heterocyclic rings may be unsubstituted or substituted by C₁-C₆ alkyl,

e') pyridyl, unsubstituted or substituted by one or two substituents chosen independently from halogen, C₁-C₆ alkyl and C₁-C₆ alkoxy, or

f') phenyl, unsubstituted or substituted by one or two substituents chosen independently from halogen, CF₃, C₁-C₆ alkyl, C₁-C₆ alkoxy, amino, nitro, formylamino and C₂-C₆ alkanoylamino, and the pharmaceutically acceptable salts thereof, and wherein, when R₄ is unsubstituted C₁-C₁₀ alkyl or unsubstituted C₂-C₆ cycloalkyl, then at least one of R₁ and R₂ is formylamino or C₂-C₆

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 EUROPEAN PATENT APPLICATION

 Application number 8530393.2

 Int. Cl. **C 07 D 237/28**
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 Designated Contracting States
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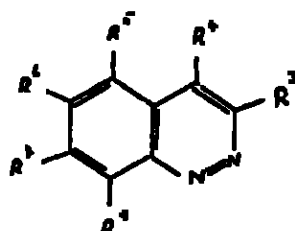
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 Classifications

 Compounds of the formula:-



Independently represent hydrogen, alkyl, acyl or cycloalkyl(alkyl) and the pharmaceutically acceptable salts and 1- or 2-position N-oxides thereof possess anxiolytic activity

(wherein R^3 represents $-\text{CONRR}^9$, $-\text{COOR}^9$ or $-\text{COC(R}^{10})$ (R^{11}), R^4 represents $-\text{NR}^{12}\text{R}^{13}$ or $-\text{OR}^{12}$, R^5 , R^6 , R^7 and R^8 each independently represent hydrogen, alkyl, alkenyl, althynyl, cycloalkyl, cycloalkylalkyl, optionally substituted aryl, (optionally substituted aryl)alkyl, fluoroalkyl, haloalkenyl, alkoxyalkyl, hydroxyalkyl, halogen, alkoxy, alkenyloxy, hydroxy, nitro, cyano or optionally substituted amino, R and R^9 each independently represent hydrogen, alkyl, alkenyl, althynyl, cycloalkyl, cycloalkylalkyl, optionally substituted aryl, (optionally substituted aryl) alkyl, 4,5-dihydro-2-thiazolyl, alkoxyalkyl, hydroxyalkyl, fluoroalkyl or haloalkenyl, or R and R^9 together form an alkylene group optionally interrupted by an oxygen atom or an alkenylene group, R^{10} and R^{11} each independently represent hydrogen or alkyl, R^{12} and R^{13} each

EP 0 205 272 A2

CINNOLINE COMPOUNDSBACKGROUND OF THE INVENTION

5 The present invention comprises certain
amide and ester derivatives of 4-substituted-cinno-
line-3-carboxylic acids and 3-acyl-4-substituted-cin-
noline derivatives, their use as central nervous
system (CNS) depressants (especially anxiolytics) and
10 pharmacological tools, methods for their preparation,
pharmaceutical compositions containing them and inter-
mediates used in their preparation.

 Selected cinnoline compounds including
selected 4-amino- and 4-oxo-cinnoline-3-carboxamides
15 are disclosed in East German Patent 123525 (Verfahren
zur Herstellung von substituierten 4-Aminocinnolinen);
U.S. Patent 4,379,929 to Conrad et al; Daunis et al.,
"Préparation et propriétés de cinnolones-3 et cinno-
lones-4," Bull. de la Société Chimique de France,
20 8:3198-3202 (1972); Lunt et al. "A New Cinnoline Syn-
thesis," J. Chem. Soc. (C), 687-695 (1968); Gevald,
et al., "Synthese von 4-Aminocinnolinen aus (Arylh-
drazono)(cyan)-essigsäurederivaten," Liebigs Ann.
Chem., 1390-1394 (1984); and U.S. Patent 3,657,241 to
25 Kurihara. Additionally, selected cinnoline compounds,
including 3-acyl-4-substituted cinnoline derivatives
are disclosed in Liebigs Ann. Chem. 1390-1394 (1984)
supra and Sandison, et al., "A New Heterocyclisation
Reaction Leading to Cinnolin-4(1H)-one Derivatives,"
30 J. Chem. Soc. Chem. Comm., 752-753 (1974). However,
none of the foregoing discloses or suggests the novel

compounds of the present invention or suggests their use as CNS depressants.

SUMMARY OF THE INVENTION

5

The compounds of the present invention are amide and ester derivatives of 4-substituted cinnoline-3-carboxylic acids and 3-acyl-4-substituted-cinnoline derivatives. These compounds have been
10 found to possess utility as anxiolytics in animals. }
Also included as part of the invention are pharmaceutical compositions containing one or more of the compounds for administration to an animal in need of an
15 anxiety-reducing medication, such a method of treatment, and methods for the synthesis of the compounds as well as novel intermediates used in the syntheses.

DETAILED DESCRIPTION OF THE INVENTION

20

The compounds of the invention are cinnolines of the following formula (I):

25

(Formula set out on pages following Examples) I

wherein:

30

R^3 is an amide of the formula (II):

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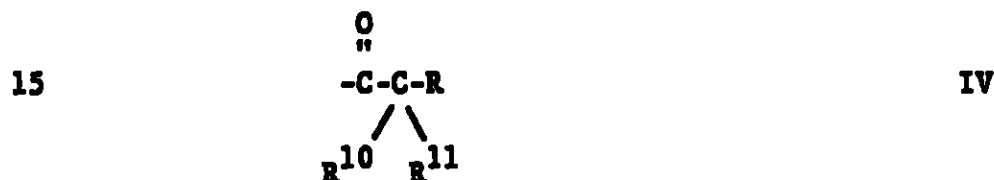
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5 an ester of the formula (III):



10 or a ketone of the formula (IV):



20 R^4 is $-\text{NR}^{12}\text{R}^{13}$ or $-\text{OR}^{12}$,
 R^5 , R^6 , R^7 and R^8 may be the same or different and are each hydrogen, (1-10C)alkyl, (2-10C)alkenyl, (2-10C)alkynyl, (3-6C)cycloalkyl, (4-10C)cycloalkylalkyl, (1-10C)aryl, (1-10C)substituted aryl, (2-11C)arylalkyl, (2-11C)(substituted aryl)alkyl, (1-10C)-fluoroalkyl having at least one fluorine, (2-10C)haloalkenyl having at least one halogen, (2-10C)alkoxyalkyl, (1-10C)hydroxyalkyl, halogeno, (1-10C)alkoxy, (3-10C)alkenyl-oxy, hydroxy, nitro, cyano or amino including substituted amino;

30 R and R^9 may be the same or different and may each be hydrogen (provided that R^3 is not an ester of formula III) except that R and R^9 cannot both be hydrogen at the same time, (1-10C)alkyl, (3-10C)alkenyl, (3-10C)alkynyl, (3-6C)cycloalkyl, (4-10C)(cyclo-

-4-

alkyl)alkyl, (1-10C)aryl, (1-10C)substituted aryl,
(2-11C)arylalkyl, (2-11C)(substituted aryl)alkyl, 4,5-
dihydro-2-thiazolyl of the following formula (V):

5

(Formula set out on pages following Examples) V

10

(2-10C)alkoxyalkyl, (1-10C)hydroxyalkyl, (1-10C)-
fluoroalkyl having at least one fluorine provided that
no fluorine is on a carbon bonded to a nitrogen,
(2-10C)haloalkenyl having at least one halogen pro-
vided that no halogen is on a carbon bonded to a
nitrogen; or R and R⁹ when taken together form a
(4-6C)alkylene group wherein one of the carbons may
optionally be replaced by an oxygen, or, when taken
together, form a (4-6C)alkenylene group;

15

20

R¹⁰ and R¹¹ may be the same or different and
are each hydrogen or (1-4C)alkyl:

25

R¹² and R¹³ may be the same or different and
are each hydrogen, (1-4C)alkyl, (2-10C)acyl, or (4-
10C)cycloalkylalkyl, provided that R¹² may not be hy-
drogen when R³ is of formula (III) and R⁴ is OR¹²; and
pharmaceutically acceptable salts and 1- or
2-position N-oxides thereof.

30

Unless otherwise specified, the alkyls, al-
kenyls and alkynyls described for this invention may
be straight or branched chain. Aryl shall mean an
organic radical derived from an aromatic hydrocarbon,

e.g., phenyl. Aryl shall also include heterocyclic radicals, e.g., those derived from pyrrole, furan, thiophene, pyridine, thiazole or indole. Substituted amino includes mono- or di-substituted amines. Substituted aryls may be substituted with, for example, (1-4C)alkyl, (1-4C)alkoxy, or halogeno. The number of substitutions on an aryl may vary. For example, where the aryl has only one ring, for example phenyl, the number of substituents may be from 1 to 3. All of the substitutions are taken independently of each other; thus, a three member substitution from a listed group may include three different members, two of the same members or all identical members. The term halogeno includes fluoro, chloro, bromo and iodo. These definitions shall apply throughout this specification except where specifically indicated otherwise.

Particular values for the groups defined above are as follows:

R^3 selected from the group consisting of the group as defined above;

R^4 selected from the group consisting of $-NR^{12}R^{13}$ and OR^{12} in which R^{12} and R^{13} are each independently selected from the group consisting of hydrogen, (1-4C)alkyl, (2-4C)acyl and (4-8C)cycloalkyl-alkyl;

R^5 , R^6 , R^7 and R^8 (each independently) selected from the group consisting of hydrogen, (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (3-6C)cycloalkyl, (4-8C)cycloalkylalkyl, (2-8C)aryl, (3-9C)aryl-alkyl, (1-6C)hydroxyalkyl, halogeno, and (1-8C)alkoxy;

Example 52

4-Hydroxy-N,8-dipropyl-3-cinnolinacarboxamide (Formula 1, R³-CONRR⁹, R⁴-OH, R⁵-R⁶-R⁷-R⁸-H, R⁸-propyl, R⁹-propyl)

To a solution of a portion of the title 4-amino product of Example 24 (0.64 g) in absolute ethanol (20 ml) was added solid potassium hydroxide (3.22 g). The mixture was heated to reflux with stirring under nitrogen for 42 hours. On cooling to room temperature, the mixture was diluted with water (50 ml) and stirred with ethyl ether (50 ml). The organic layer was separated and then discarded. The aqueous phase was treated with acetic acid until pH 6.0 was reached; the precipitate which deposited on cooling to 0° was collected by filtration and washed with water. The precipitate was then dissolved in boiling methanol (250 ml) and evaporated onto flash silica gel (12 g). This was loaded atop a column of flash silica gel (40 g) in chloroform, and the product was eluted with chloroform/methanol (93:7 v/v). The resulting white solid was recrystallized by slow evaporation of a methanol solution, providing the title compound, 0.15 g (23% yield) as a white solid, m.p. 241-245°. ¹H NMR (DMSO-d₆, characteristic peaks only): 3.32 (d of t, 2H), 7.51 (d of d, 1H), 7.73 (d, 1H), 8.09 (d, 1H), 9.69 (t, exchangeable, 1H), 10.87 (s, exchangeable, 1H) ppm.

Example 68

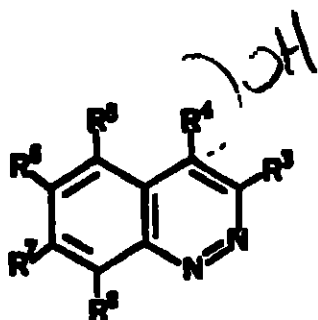
8-Chloro-4-hydroxy-N-propyl-3-cinnolinacarboxamide
(Formula I, R³-CONRR⁹, R⁴-OH, R⁵-R⁶-R⁷-R-H, R⁸-chloro,
5 R⁹-propyl)

To a suspension of a portion of the product
of Example 33(a) (0.98 g) in absolute ethanol (25 ml)
was added solid potassium hydroxide (3.0 g). The mix-
10 ture was stirred and heated to reflux under nitrogen
for 48 hours. The mixture was poured into water (100
ml) and the resulting suspension was extracted twice
with ethyl ether (100 ml each); these ether extracts
were discarded. The residual aqueous suspension was
15 acidified to a final pH of 5.5 (to test papers) by the
dropwise addition of glacial acetic acid with stirring.
After chilling to 0° with stirring for three hours,
the precipitated product was collected by filtration,
washed with water, and dried in vacuo at 40° over
20 phosphorus pentoxide. This provided 0.80 grams (80%
yield) of the title compound as a white solid. Re-
crystallization from boiling methanol provided an
analytical sample of white felt-like fine needles,
m.p. 237-239°. ¹H NMR (DMSO-d₆, characteristic peaks
25 only): 3.31(t,2H), 7.55(t,d of d,1H), 8.05(d of d,1H),
8.16(d of d,1H), 9.45(t, exchangeable, 1H), 14.12(s,
exchangeable, 1H) ppm.

Calculated for

C₁₂H₁₂N₃O₂Cl: C, 54.25; H, 4.55; N, 15.81

30 Found: C, 53.93; H, 4.44; N, 15.60



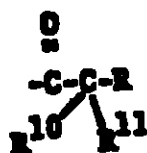
I }



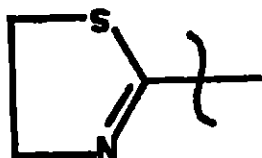
II



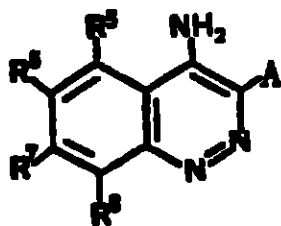
III



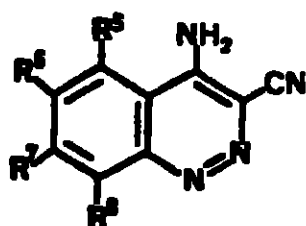
IV



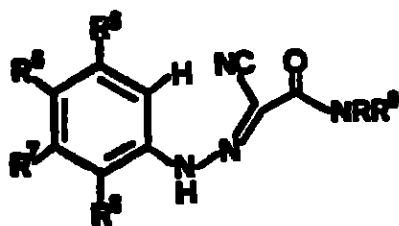
V



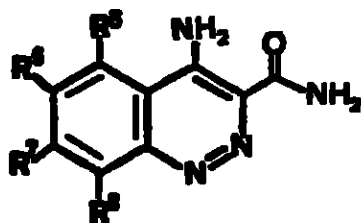
VI



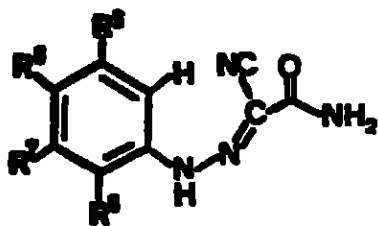
VII



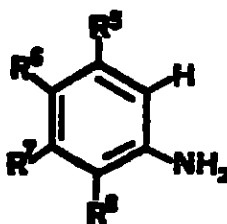
VIII



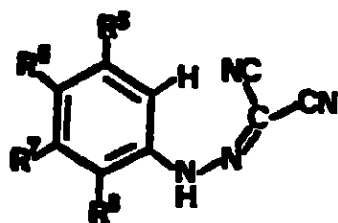
IX



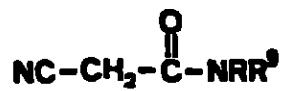
X



XI



XII



XIII

CLAIMS

1. A compound of formula I

5

(Formula set out on pages following Examples) I

wherein:

10

R^3 is an amide of the formula (II):

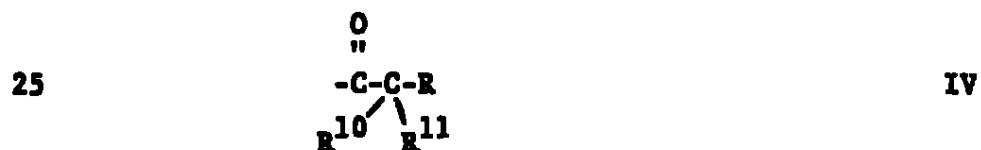


15 an ester of the formula (III):



20

or a ketone of the formula (IV):



25

30 R^4 is $-\text{NR}^{12}\text{R}^{13}$ or $-\text{OR}^{12}$ or $-\text{OH}$
 R^5, R^6, R^7 and R^8 may be the same or different and are each selected from the group consisting of hydrogen, (1-10C)alkyl, (2-10C)alkenyl, (2-10C)alk-

-125-

R and R⁹ are each independently selected⁴
from the group consisting of hydrogen, (1-4C)alkyl,
(3-4C)alkenyl, (3-4C)alkynyl, (4-5C)cycloalkylalkyl,
(1-4C) fluoroalkyl having 1-4 fluoros, 4,5-dihydrothi-
5 azol-2-yl, (2-4C)hydroxyalkyl, phenylmethyl, or R and
R⁹, when taken together, form a (4-5C)alkylene in
which one of the carbons may optionally be replaced by
an oxygen, or, when taken together, form a 4 carbon
alkenylene;
10 R¹⁰ and R¹¹ are each hydrogen;
R¹² and R¹³ are each independently selected
from the group consisting of hydrogen, (1-4C)alkyl,
(4-6C)cycloalkylalkyl and (2-4C)acyl,
or a pharmaceutically acceptable salt
15 thereof.

4. A compound as claimed in any one of
Claims 1-3 wherein R⁵ is hydrogen or chloro; R⁶ is
hydrogen, chloro, methoxy or butyl; R⁷ is hydrogen,
20 chloro, methyl, methoxy or pentyl; R⁸ is hydrogen,
fluoro, chloro, bromo, iodo, methyl, ethyl, propyl,
butyl, pentyl, methoxy, cyclopropyl, 2-methylpropyl,
3-methylbutyl, cyclopentylmethyl, 3-butenyl, 3-hydroxy-
butyl, phenyl, phenylmethyl or 3-pentynyl; R is
25 hydrogen, methyl, ethyl, propyl, butyl, cyclopropyl-
methyl, 2-propenyl or phenylmethyl; R⁹ is methyl,
ethyl, propyl, butyl, 2-methylpropyl, cyclopropyl-
methyl, cyclobutylmethyl 2-propenyl, 2-propynyl, 2-

30 EPO-5

butynyl, propargyl, cyclopropyl, 2,2,2-trifluoroethyl,
phenyl, phenylmethyl, 3-hydroxypropyl, or 4,5-dihydro-
thiazol-2-yl; R¹⁰ is hydrogen; R¹¹ is hydrogen.

5 5. A compound as claimed in any one of
Claims 1-4 wherein R is hydrogen; R³ is CONRR⁹; R⁵ is
hydrogen; R⁶ is hydrogen; R⁷ is hydrogen or halogen;
R⁸ is (3-5C)alkyl; and R⁹ is (2-4C)alkyl, (3-4C)alk-
10 enyl, or (4-5C)(cycloalkyl)alkyl, or a pharmaceutic-
ally acceptable salt thereof.

6. A compound as claimed in any one of
Claims 1-5 selected from the group consisting of 4-
amino-N,8-dipropyl-3-cinnolinecarboxamide; 4-amino-8-
15 butyl-N-(2-propenyl)-3-cinnolinecarboxamide; 4-amino-
8-pentyl-N-(2-propenyl)-3-cinnolinecarboxamide; 4-
amino-8-butyl-N-cyclopropylmethyl-3-cinnolinecarbox-
amide; 4-amino-N-cyclopropylmethyl-8-propyl-3-cinno-
linecarboxamide; 4-amino-8-butyl-N-cyclobutylmethyl-3-
20 cinnolinecarboxamide; 4-amino-8-butyl-N-cyclopropyl-3-
cinnolinecarboxamide; 4-amino-8-(3-methylbutyl)-N-
propyl-3-cinnolinecarboxamide; and 4-amino-8-cyclo-
pentylmethyl-N-propyl-3-cinnolinecarboxamide; or a
pharmaceutically acceptable salt thereof.

25 7. A compound as claimed in any one of
Claims 1-3 wherein said compound is 4-amino-N-cyclo-
propylmethyl-8-propyl-3-cinnolinecarboxamide or a
pharmaceutically acceptable salt thereof.

30

EPO-6

8. A compound as claimed in any one of Claims 1-3 wherein said compound is 4-amino-8-butyl-N-cyclopropylmethyl-3-cinnolinecarboxamide or a pharmaceutically acceptable salt thereof.

5

9. A pharmaceutically acceptable salt as claimed in any one of Claims 1-8 wherein said salt is an acid addition salt. }

10. A process for making a compound as claimed in Claim 1 wherein said process comprises a method selected from the group consisting of

(a) For those compounds of formula (I) in which R^3 is an amide of formula (II) and R^4 is NH_2 ,
15 reacting a compound of formula (VI):

(Formula set out on pages following Examples) VI

20

where A is selected from the group consisting of a carboxylic acid or an acid derivative having a dis-
25 placeable substituent with an amine of formula $NHRR^9$;

(b) For those compounds of formula (I) in which R^3 is an ester of formula (III) and R^4 is NH_2 ,
reacting a compound of formula (VI) with an alcohol of
formula ROH where R has a value as defined in Claim 1

30

EPO-7

that R and R⁹ are not both hydrogen at the same time),
(1-6C)alkyl, (3-6C)alkenyl, (3-6C)alkynyl, (3-6C)-
cycloalkyl, (4-8C)(cycloalkyl)alkyl, (2-8C)aryl, (3-
9C)arylalkyl, 4,5-dihydrothiazol-2-yl, (1-6C)hydroxy-
5 alkyl, (1-6C)fluoroalkyl having at least one fluorine
provided no fluorine is on a carbon bonded to a nitro-
gen; or R and R⁹, when taken together form a (4-6C)-
alkylene wherein one of the carbons may optionally be
replaced by an oxygen or when taken together form a
10 (4-6C)alkenylene; and
R¹⁰ and R¹¹ are each independently selected
from the group consisting of hydrogen and (1-4C)alkyl,
or a pharmaceutically acceptable salt
thereof.

15

3. A compound as claimed in Claim 2
wherein

R³ is selected from the group consisting of
an amide of formula II and a ketone of formula IV;

20 R⁴ is selected from the group consisting
of -NR¹²R¹³ and OH;

R⁵, R⁶ and R⁷ are each independently
selected from the group consisting of hydrogen,
(1-5C)alkyl, chloro and methoxy;

25 R⁸ is selected from the group consisting of
(1-5C)alkyl, (2-4C)alkenyl, (2-5C)alkynyl, (3-6C)cyclo-
alkyl, (4-7C)cycloalkylalkyl, phenyl, phenylmethyl,
(1-4C)hydroxyalkyl, and halogeno;

30 EPO-4

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(4-6C)alkylene group wherein one of the carbons may optionally be replaced by an oxygen; or, when taken together, form a (4-6C)alkenylene group;

5 R^{10} and R^{11} may be the same or different and are each selected from the group consisting of hydrogen and (1-4C)alkyl;

R^{12} and R^{13} may be the same or different and are each selected from the group consisting of hydrogen, (1-4C)alkyl, (2-10C)acyl, and (4-10C)cycloalkyl-
10 alkyl, provided that R^{12} may not be hydrogen when R^3 is of formula (III) and R^4 is OR^{12} ; and

 pharmaceutically acceptable salts and 1- or 2-position N-oxides thereof.

15 2. A compound as claimed in Claim 1 wherein R^3 has a value as defined in Claim 1; R^4 selected from the group consisting of
 $-NR^{12}R^{13}$ and OR^{12} in which R^{12} and R^{13} are each inde-
20 pendently selected from the group consisting of hydrogen, (1-4C)alkyl, (2-4C)acyl and (4-8C)cycloalkyl-
 alkyl;

R^5 , R^6 , R^7 and R^8 are each independently selected from the group consisting of hydrogen, (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (3-6C)cyclo-
25 alkyl, (4-8C)cycloalkylalkyl, (2-8C)aryl, (3-9C)aryl-
 alkyl, (1-6C)hydroxyalkyl, halogeno, and (1-8C)alkoxy;

R and R^9 are each independently selected from the group consisting of hydrogen (provided that R^3 is not an ester of formula III and further provided

30

EPO-3

12. A pharmaceutical composition comprising
a compound of any one of Claims 1-8 or a salt thereof
in association with a non-toxic pharmaceutically,
acceptable diluent or carrier. }

5

ynyl, (3-6C)cycloalkyl, (4-10C)cycloalkylalkyl, (1-10C)aryl, (1-10C)substituted aryl, (2-11C)arylalkyl, (2-11C)(substituted aryl)alkyl, (1-10C)fluoroalkyl having at least one fluorine, (2-10C)haloalkenyl
5 having at least one halogen, (2-10C)alkoxyalkyl, (1-10C)hydroxyalkyl, halogeno, (1-10C)alkoxy, (3-10C)-alkenyl-oxy, hydroxy, nitro, cyano, amino and substituted amino;

R and R⁹ may be the same or different and
10 are each selected from the group consisting of hydrogen (provided that R³ is not an ester of formula III and R and R⁹ cannot both be hydrogen at the same time), (1-10C)alkyl, (3-10C)alkenyl, (3-10C)alkynyl, (3-6C)cycloalkyl, (4-10C)(cycloalkyl)alkyl, (1-10C)-
15 aryl, (1-10C)substituted aryl, (2-11C)arylalkyl, (2-11C)(substituted aryl)alkyl, 4,5-dihydrothiazol-2-yl of the following formula (V):

20 (Formula set out on pages following Examples) V

(2-10C)alkoxyalkyl, (1-10C)hydroxyalkyl, (1-10C)-
25 fluoroalkyl having at least one fluorine provided that no fluorine is on a carbon bonded to a nitrogen, (2-10C)haloalkenyl having at least one halogen provided that no halogen is on a carbon bonded to a nitrogen; or when taken together, R and R⁹ form a

30

EPO-2

or its geometric isomer, with a Lewis acid catalyst in an inert solvent;

5 (e) For those compounds of formula (I) in which R^4 is $NR^{12}R^{13}$ and one or both of R^{12} and R^{13} are alkyl, alkylating a compound of formula (I) in which R^4 is NH_2 ;

10 (f) For those compounds of formula (I) in which R^4 is $NR^{12}R^{13}$ and one or both of R^{12} and R^{13} are acyl, acylating a compound of formula (I) in which R^4 is NH_2 ;

(g) For those compounds of formula (I) in which R^4 is OR^{12} , reacting a compound of formula (I) in which R^4 is NH_2 with a compound of formula MOR^{12} in which M is an alkali metal, or with a compound of formula $L(OR^{12})_2$ in which L is an alkaline earth;

15 (h) For those compounds of formula (I) in which R^8 is alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, aryl or arylalkyl, reacting an organometallic derivative of a compound R^8X in which X is a halogen with a compound of formula (I) in which R^8 is initially chlorine, bromine, or iodine, in the presence of a suitable transition metal catalyst; and, whereafter, when the compound of formula (I) is obtained as a base and an acid addition salt is re-

20
25 required, reacting said compound of formula (I) obtained in the form of a base with an acid to afford a pharmaceutically acceptable anion.

30 11. The process of Claim 10 further characterized by the use of one or more intermediates having a protecting group on one or more of said intermediate(s).

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

2020

Bogotá, D C , Febrero 16 de 2007

Abogada

ALICIA LLOREDA RICAURTE**ASUNTO**

Radicación No

02 083 633

Trámite

002

Evento

001

Actuación

430

Oficio No

2609

Folios

0

Solicitante: Pharmacia & Upjohn Company**Título de la solicitud:** "4-OXO-1,4-DIHIDRO-3-CINOLINCARBOXAMIDAS COMO AGENTES ANTIVIRALES"

Como resultado del examen de fondo, realizado conforme a lo establecido por el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se notifica el siguiente concepto técnico

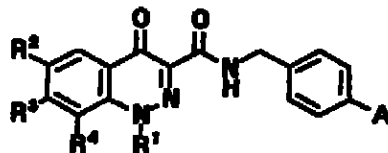
Documentos estudiados

Para el presente estudio se tuvieron en cuenta el capítulo descriptivo comprendido en los folios 51 – 161 y el capítulo reivindicatorio de los folios 162 – 129 de la solicitud en estudio

Objeto de la invención

El objeto de la presente solicitud de patente de invención consiste en

Un compuesto de fórmula I



o una sal farmacéuticamente aceptable (reivindicaciones 1–5, 22), composición que lo contiene (reivindicaciones 6–10), método de tratamiento (reivindicaciones 11–21, 23–24) y el uso(reivindicación 25)

El problema planteado en esta solicitud es la necesidad de compuestos antivirales

Para resolver este problema técnico la solicitud en estudio proporciona compuestos de fórmula I

El objeto de la invención definido anteriormente se clasificó de acuerdo con la IPC A 61 K 31/502, C 07 D 237/00

También se reivindica prioridad de la Solicitud de Patente de los Estados Unidos US 60 191291 de marzo 21 de 2000, con respecto a la cual la fecha de presentación de la actual solicitud cumple el plazo máximo permitido

Excepciones a la Patentabilidad

El artículo 20 de la Decisión 486 establece *"No serán patentables. d) los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnóstico aplicados a los seres humanos o a animales"*

El método de tratamiento de las reivindicaciones 11-21, 23-24, no es patentable de acuerdo con la norma citada, que especifica que *los métodos terapéuticos para el tratamiento humano o animal no son patentables*

En conclusión, el método de tratamiento de las reivindicaciones 11-21, 23-24, que comprende administrar una composición, no es patentable de acuerdo con el Art 20, literal d), de la decisión 486

Usos

El artículo 21 de la Decisión 486 de la Comisión de la Comunidad Andina establece que *"Los productos o procedimientos ya patentados, comprendidos en el estado de la técnica, de conformidad con el artículo 16 de la presente Decisión, no serán objeto de nueva patente, por el simple hecho de atribirse un uso distinto al originalmente comprendido por la patente inicial"*

El artículo 14 de la Decisión 486 de la Comisión de la Comunidad Andina establece que *"Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial"*

El Artículo 19 de la Decisión 486 de la Comisión de la Comunidad Andina establece que *"Se considerará que una invención es susceptible de aplicación industrial, cuando su objeto pueda ser producido o utilizado en cualquier tipo de industria, entendiéndose por industria la referencia a cualquier actividad productiva, incluidos los servicios."*

De acuerdo con el Art 14, no se puede otorgar patente al uso de la reivindicación 25 porque estos no son un producto ni un procedimiento tecnológico

De otro lado, de acuerdo con el Art 19, se considera que los usos no tienen aplicación industrial porque no se refieren a un tipo de producción ó utilización en ningún tipo de industria

Además los usos reivindicados no pueden ser objeto de nueva patente, aunque el solicitante los considere distintos a los originalmente comprendidos por la patente inicial, porque estos se conocían originalmente en EP 0277791 (actividad inmunomoduladora en tratamiento de infecciones bacteriales y virales y de enfermedades neoplásicas, ver pág 2, folio 146) y en EP 0205272 (actividad ansiolítica, ver página 2, folio 152)

Con respecto a los Art. 28 y 30 de la D 486

El artículo 30 de la Decisión 486 establece *"Las reivindicaciones definirán la materia que se desea proteger mediante la patente. Deben ser claras y concisas y estar enteramente sustentadas por la descripción"*

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Las reivindicaciones podrán ser independientes o dependientes. Una reivindicación será independiente cuando defina la materia que se desea proteger sin referencia a otra reivindicación anterior. Una reivindicación será dependiente cuando defina la materia que se desea proteger refiriéndose a una reivindicación anterior. Una reivindicación que se refiera a dos o más reivindicaciones anteriores se considerará una reivindicación dependiente múltiple."

La reivindicación no tiene porqué ser independiente. Debería ser dependiente de la reivindicación 1. Se solicita hacer claridad al respecto.

Determinación del Estado de la Técnica

El artículo 16 de la decisión 486 de la comisión de la Comunidad Andina que establece que "El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida

Solo para el efecto de la determinación de la novedad, también se considerará dentro del estado de la técnica, el contenido de una solicitud de patente en trámite ante la oficina nacional competente, cuya fecha de presentación o de prioridad fuese anterior a la fecha de presentación o de prioridad de la solicitud de patente que se estuviese examinando, siempre que dicho contenido esté incluido en la solicitud de fecha anterior cuando ella se publique o hubiese transcurrido el plazo previsto en el artículo 40"

Considerando que la fecha de presentación de la primera solicitud de patente de la cual se reivindica prioridad es marzo 21 de 2000, se consultaron las bases de datos y los archivos con que cuenta la entidad con fecha de publicación anterior y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud

No	Documento	Título	Fecha de Publicación
D1	EP 0277791	Cinnoline derivatives and process for their preparation	Agosto 10 de 1988
D2	EP 0205272	Cinnoline derivatives	Dic 17 de 1988

Evaluación de los requisitos de Patentabilidad

El artículo 14 de la Decisión 486 de la Comisión de la Comunidad Andina establece que "Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial"

En cumplimiento del artículo 14 de la Decisión 486, se procedió a evaluar el cumplimiento de los requisitos de novedad, nivel inventivo y aplicación industrial, con el fin de establecer la patentabilidad de la invención reivindicada en la solicitud en estudio

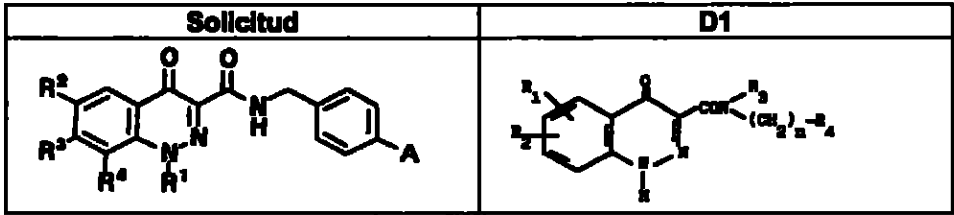
Evaluación de la Novedad

El Art 16 de la Decisión 486 de la Comisión de la Comunidad Andina establece "Una invención se considerará nueva cuando no está comprendida en el estado de la técnica. El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente, o, en su caso, de la prioridad reconocida

Solo para el efecto de la determinación de la novedad, también se considerará dentro del estado de la técnica, el contenido de una solicitud de patente en trámite ante la oficina nacional competente, cuya fecha de presentación o de prioridad fuese anterior a la fecha de presentación o de prioridad de la solicitud de patente que se estuviese examinando, siempre que dicho contenido esté incluido en la solicitud de fecha anterior cuando ella se publique o hubiese transcurrido el plazo previsto en el Art 40"

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D1 enseña que los derivados hidroxi de quinolina pueden existir también en la forma tautómera quinolona (ver folio 147) De manera que su estructura es igual a la de los compuestos reivindicados en esta solicitud Lo cual destruye la novedad



Evaluación del Nivel Inventivo

El artículo 18 de la Decisión 486 de la Comisión de la Comunidad Andina establece que *Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica*

El documento del Estado de la Técnica más próximo es D1 que enseña los derivados de quinolona (ver folio 147), que tienen actividad inmunomoduladora en tratamiento de infecciones bacteriales y virales y de enfermedades neoplásicas, (ver pág 2, folio 146).

La única diferencia con D1 es que esta solicitud no menciona que los compuestos reivindicados son la forma tautómera quinolona de los derivados hidroxi de quinolina. Por lo tanto no se observa un efecto técnico inesperado porque estos compuestos siguen siendo compuestos antivirales.

El hecho de presentarse el compuesto en su forma tautómera no es producto de la habilidad del experto en la materia

Así que el Problema Técnico planteado en esta solicitud la necesidad de compuestos antivirales se había resuelto previamente mediante el mismo tipo de compuestos (compuestos de fórmula I) Por esta razón se considera que la forma tautómera quinolona reivindicada es evidente para un experto en la materia

Además, puesto que D2 divulgaba previamente (ver folios 158 - 162), compuestos derivados de quinolina, una persona conocedora de la materia motivada por tal sugerencia lograría los compuestos de esta solicitud, que son antivirales De manera que para un experto sería obvio combinar estos dos documentos Por lo cual no hay nivel inventivo

Se observa que la composición farmacéutica de las reivindicaciones 6-10 que contiene el compuesto reivindicado estaba sugerida en D2 (ver página 130 en el folio 168) Por lo cual no tiene nivel inventivo

Conclusión

En conclusión, los requisitos de patentabilidad de la presente solicitud están afectados así

Item	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	EP 0277791	1 – 25	Novedad y Nivel inventivo
D2	EP 0205272	1 – 25	Novedad y 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

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sesenta días contados a partir de la fecha de la 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 GESPEDES DE VERGEL

Jefe de la División de Nuevas Creaciones

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

23 FEB. 2007

CONCEPTO TÉCNICO No 183	EXAMINADOR TÉCNICO Código 202007
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EXAMEN TÉCNICO DE FONDO

N° Radicación	02 083 633	Fecha de presentación en Colombia	18-09-2002
N° Prioridad	US 60 191291	Fecha de Prioridad	21-03 -2000

Palabras clave	quinolin	Carboxamida	Antiviral
	quinolona	Carboxamida	

CLASIFICACIONES INTERNACIONALES DE BÚSQUEDA

A 61 K 31/502, C 07 D 237/00

DOCUMENTOS CORRESPONDIENTES EN OTROS PAÍSES

Patente Original	WO 0170706
Otras	WO0170706 (A3) MXPA02009251 (A) EP1265873 (A0) EE200200541 (A) CA2400000 (A1) EP1265873 (B1)

BASES DE DATOS CONSULTADAS

OEPM	Epoline	Espacenet	Oficina US
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INFORMES DE EXÁMENES EN OTRAS OFICINAS

Documento	Fecha	Relv. Afectadas
WO01 70706	Sept 27 de 2001	1-25

ANTERIORIDADES ENCONTRADAS

Documento de Patentes	Relv. Afectadas	Relevancia
EP 0277791	1 - 25	Novedad y Nivel inventivo
EP 0205272	1 - 25	Nivel inventivo

LITERATURA NO PATENTES

Documento no Patentes	Relv. Afectadas	Relevancia

Observaciones

Fecha del examen

Febrero 16 de 2007