

CAVELIER

ABOGADOS

www.cavelier.com
cavelier@cavelier.com

EDIFICIO SISKI
CARRERA 4 No 72 35
BOGOTÁ 8 COLOMBIA

468
Teléfono (57 1) 347 3611
Telefax (57 1) 211 8650
(57 1) 540 0860
Fax in U S A (1 305) 381 9660

Señora Jefe de la
DIVISION DE NUEVAS CREACIONES
Superintendencia de Industria y Comercio
E S D

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad 04-110419- -00005-0000
Fec 2006-08-01 17 11:05 Dep 2020 NUECREACIONES
Tra 11 PATENTEIYII
Eve 379 FASENACIONALI
Act 538 PETICION Folios 2

Trámite 011
Evento 379
Actuacion 538

Referencia Expediente No 04110419
Asunto Solicitud de patente para COMPUESTOS POLICICLICOS COMO
Solicitante POTENTES ANTAGONISTAS DEL ADRENO-RECEPTOR ALFA-2
ORION CORPORATION
Fecha de solicitud 3 de noviembre de 2004
Publicada en La Gaceta No 562 del 31 de marzo de 2006

1 Yo, Emilio FERRERO, identificado como aparece al pie de mi firma, actuando como apoderado en el asunto de la referencia, atentamente, solicito se efectue el examen de patentabilidad de la solicitud en referencia presentada de acuerdo con el Capitulo II del PCT y segun lo establecido en el articulo 44 de la Decision 486 de la Comision de la Comunidad Andina Para tal efecto presento junto con este escrito el recibo por valor de \$ 194 000 00, que corresponde a la tasa fijada segun lo dispuesto en la resolucion No 35582 del 28 de diciembre de 2005

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

Bogotá, 01 AGO 2006
Señora Jefe,



EMILIO FERRERO
T P A No 31 929

COLO 08962 841-001-4
NNJ/NNJ/ID-000093/WPCL8962

469

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad 04-110419- -00005-0000
Fec 2006-08-01 17:11:05 Dep 2020 NUECREACIONES
Tra 11 PATENTEIYII
Evs 370 FASENACIONALII
Act 538 PETICION Fotos 2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT 800176089-2

RECIBO OFICIAL DE CAJA 06 - 51 840
FECHA JULIO 10 DE 2006

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No PAGO	FECHA PAGO	Vr PAGO
CAVELIER ABOGADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	54929896	10/07/2006	42,127,000 00

***** CONCEPTO *****

CANT	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01	SOLICITUDES	
		114 PTC CAP-II EXAMEN DE PATENTIBILIDAD	194,000 00
		TOTAL	\$ 194,000 00

CIENTO NOVENTA Y CUATRO MIL PESOS

RESPONSABLE _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No _____

06 08962-841-001-4

DIVISION DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No 04- 110419

EL EXTRACTO DE LA PRESENTE SOLICITUD DE PATENTE DE INVENCION

- PCT, FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No 562,

DE FECHA 31 DE MARZO DE 2006 EL TERMINO HABIL SEÑALADO POR LA

LEY EXPIRA EL 01 DE AGOSTO DE 2006

NOTA Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicacion 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 ☒ ☐

United States Patent [19]
Huff et al

[11] **Patent Number** **4,686,226**
 [45] **Date of Patent.** **Aug. 11, 1987**

[54] **SUBSTITUTED BENZO[B]FURO- AND BENZO[B]THIENO QUINOLIZINES**
 [75] **Inventors** Joel R. Huff, Lederach John J Baldwin, Gwynedd Valley Fojiro Sakurai, Lansdale Joseph P Vacca, Telford James P Guare, Jr, Quakertown, all of Pa.
 [73] **Assignee** Merck & Co., Inc., Rahway N.J
 [21] **Appl No** 771,927
 [22] **Filed** Sep. 3, 1985
 [51] **Int. Cl.** C07D 491/497, C07D 495/14 A61K 31/38 A61K 31/435
 [52] **U.S. CL.** 514/285; 546/62 546/81 546/82 546/83 546/89 546/95 546/80 546/94
 [58] **Field of Search** 546/94 95 80, 81 546/82 62 514/293 285

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 Szantay et al Chem. Abstracts, vol 96 (1982), entry 6605c
Primary Examiner—Nicholas S Rizzo
Assistant Examiner—William A Teoli, Jr
Attorney, Agent, or Firm—William H Nicholson, Michael C. Sudol

[57] **ABSTRACT**
 Substituted hexahydro arylquinolizines and pharmaceutically acceptable salts thereof are selective α_2 -adrenergic receptor antagonists and thereby useful as antidepressants, antihypertensives, ocular antihypertensives, antidiabetics, antiobesity and platelet aggregation inhibitors and modifiers of gastrointestinal motility

12 Claims, No Drawings

SUBSTITUTED BENZO[B]FURO- AND BENZO[B]THIENO QUINOLIZINES

BACKGROUND OF THE INVENTION

This invention is concerned with novel substituted hexahydro arylquinolizines or pharmaceutically acceptable salts thereof which are selective α_2 -adrenoceptor antagonists and are of value in conditions where selective antagonism of the α_2 -adrenoceptor is desirable for example as antidepressant, antihypertensive, ocular antihypertensive, antidiabetic, antiobesity agents, platelet aggregation inhibitors or modifiers of gastrointestinal motility. It also relates to processes for preparing the novel compounds, pharmaceutical compositions comprising the novel compounds and to a method of antagonizing α_2 -adrenoceptors.

The concept that the complex clinical state of depression is linked to a functional deficiency of monoamines in the central nervous system is now widely accepted. Numerous biochemical and clinical observations support the proposal that many forms of depressive illness are associated with reductions in adrenergic activity at functionally important sites in the brain. Thus, classical antidepressive drugs, such as amitriptyline and imipramine, are believed to act by blocking the neuronal reuptake of norepinephrine and/or serotonin, thereby enhancing the availability of the monoamines as neurotransmitters.

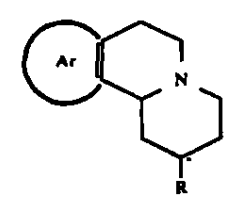
In addition to α_1 -adrenergic receptors which mediate postsynaptic responses to the neurotransmitter norepinephrine, other adrenergic receptors are present at or near sympathetic terminals. These latter receptors, α_2 adrenergic receptors, form part of a negative feedback system which modulates noradrenergic neurotransmission by controlling the impulse-induced release of norepinephrine from presynaptic terminals. Activation of α_2 -adrenergic receptors results in a decrease in the amount of norepinephrine normally released from the nerve terminals by nerve impulses while antagonism of α_2 -adrenergic receptors increases norepinephrine release. Therefore, molecules that block α_2 -adrenergic receptors afford an alternate approach to enhancement of noradrenergic function and the treatment of depression associated with an absolute or relative deficiency of adrenergic function.

α_2 -Adrenergic receptor antagonism is also associated with antidiabetic, antihypertensive, ocular antihypertensive, antiobesity, platelet aggregation inhibition activity and modification of gastrointestinal motility.

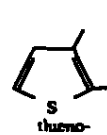
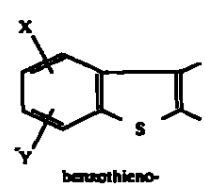
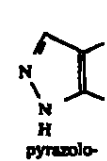
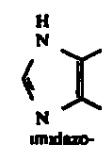
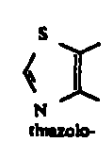
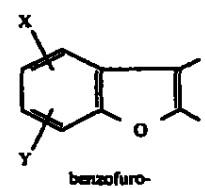
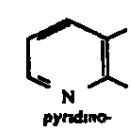
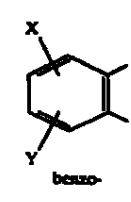
Compounds structurally related to the novel compounds of this invention are disclosed in British Pat Nos 1 435 573 and 2 106,909 of John Wyeth and Brother Ltd.

DETAILED DESCRIPTION OF THE INVENTION

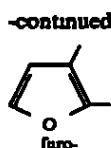
This invention is concerned with a compound of structural formula I



or a pharmaceutical acceptable salt thereof wherein Ar represents an aromatic group such as

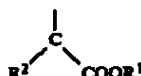


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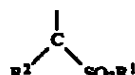
R is

- (1) COOR¹ wherein R¹ is hydrogen or C₁₋₅ alkyl
either straight or branched chain,
(2)

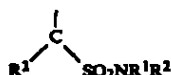


wherein R² is

- (a) hydrogen,
(b) C₁₋₅ alkyl, or
(c) C₁₋₅ alkylidene
(3)



(4)



wherein R¹ and R² can be joined together to form a 5
or 6-membered heterocycle, such as pyrrolidino,
morpholino, piperidino or piperazino;
(5)



wherein Q is

- (a) O or
(b) N-OR¹
(6)



wherein Z is

- (a) -OR³ or -SR³
(b) -NR²R³ wherein R³ is
(i) H,
(ii) C₁₋₅ alkyl, unsubstituted or substituted with
(1) -OH
(2) -COOR¹
(3) -SO₂R²
(4) -N(R²)SO₂R²
(iii) -COOR²
(iv) -SO₂R²
(v) -SO₂NR²R³ and

4

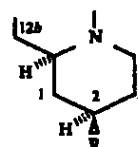
R⁴ is

- (a) C₁₋₅ alkyl or
(b) C₁₋₅ alkylidene, and

the broken lines represent possible double bonds

- 5 The pharmaceutically acceptable salts coming within
the purview of this invention include the pharmaceuti-
cally acceptable acid addition salts. Acids useful for
preparing these acid addition salts include, inter alia,
10 inorganic acids such as the hydrohalic acids (e.g. hy-
drochloric and hydrobromic acid), sulfuric acid, nitric
acid and phosphoric acid and organic acids such as
maleic, fumaric, tartaric, citric, acetic, benzoic, 2-
15 acetoxybenzoic, salicylic, succinic, theophylline, 8-
chlorotheophylline, p-aminobenzoic, p-acetamidoben-
zoic, methanesulfonic, or ethanesulfonic acid

The novel compounds of this invention wherein R is
attached by a single bond are depicted herein as having
20 the configuration in which the hydrogen at C-12b and R
at C-2 are trans



25

- 30 and it is more preferred diastereomer for α₂-adrenocep-
tor blockade activity. However the isomers having the
configuration in which the hydrogen at C-12b and R at
C-2 are cis are also active α₂-adrenoceptor blockers and
35 are considered to be within the scope of this invention.
Each of the 2RS,12bSR and 2RS,12bRS-configura-
tional isomers are racemates capable of being resolved
into dextrorotatory and levorotatory enantiomers. This
40 invention includes these pure enantiomers as well as all
mixtures thereof especially the racemates. However
the (12bS)-enantiomer is preferred.

It is also preferred that Ar be X,Y-benzo, X,Y-ben-
zo[b]furo or X,Y-benzo[b]thieno-. It is even more pre-
ferred that Ar be benzo[b]furo.

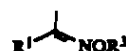
It is further preferred that R be



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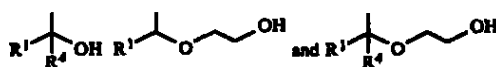
wherein R¹ is C₁₋₅ alkyl

55



wherein R¹ and R³ are independently C₁₋₅ alkyl,

60



- 65 wherein R¹ and R⁴ are C₁₋₅ alkyl or hydrogen. It is most
preferred that R¹, R³ and R⁴ in each of the above is
methyl.

For those compounds wherein R is

Step G Preparation of (2RS,12bSR)-Methyl (1 3,4,6,7 12b-hexahydro-2H benzo[b]furo[2,3 a]quinolizin 2-yl) acetate Hydrochloride

A 1:1 mixture of the E and Z olefins from Step A (700 mg) and 10% Pd on carbon (75 mg) in 100 mL of ethanol were hydrogenated at 40 psi (2.8×10^5 Pa) for 15 hours. After separating the catalyst by filtration, the filtrate was evaporated to dryness. The resulting oil was chromatographed over silica gel, eluting with 40% ethyl acetate/hexane. The product was collected as an oil (370 mg) which crystallized upon standing. The free base was converted to the HCl salt, m.p. 194–195 °C. Starting with optically active 1 3,4,6,7 12b-hexahydro-2H-benzo[b]furo[2,3-a]quinolizin 2-one and employing the procedures in Steps A and B, the enantiomerically pure products are obtained.

EXAMPLE 2

(2RS 12bSR,2 RS) and (2RS 12bSR,2 SR)-Ethyl 2-(1 3,4,6,7 12b-hexahydro-2H benzo[b]furo[2,3-a]quinolizin 2-yl) propionate Hydrochloride

Step A. Preparation of E and Z Ethyl 2-(1 3,4,6,7 12b-hexahydro-2H benzo[b]furo[2,3-a]quinolizin 2-ylidene) propionate

Employing the procedure described in Step F of Example 1 and substituting triethyl 2-phosphonopropionate for trimethyl phosphonoacetate the product was obtained as a mixture of E and Z geometric isomers which were separated by chromatography over silica gel eluting with 20% ethyl acetate/hexane.

Step B Preparation of (2RS 12bSR,2'RS)-Ethyl 2-(1 3,4,6,7 12b-hexahydro-2H benzo[b]furo[2,3-a]quinolizin 2-yl) propionate Hydrochloride

Hydrogenation of the Z olefin (150 mg) obtained in Step A according to the procedure described in Step G of Example 1 yielded the free base of the product (100 mg) after chromatography over silica gel eluting with 20% ethyl acetate/hexane. Conversion of the free base to the HCl salt afforded a white crystalline material, m.p. 251–252 °C.

Step C Preparation of (2RS 12bSR,2 SR)-Ethyl 2-(1 3,4,6,7 12b hexahydro-2H benzo[b]furo[2,3-a]quinolizin 2-yl) propionate Hydrochloride

The E olefin (200 mg) obtained in Step A and 50 mg PtO_2 in 50 mL of ethanol was hydrogenated at 40 psi (2.8×10^5 Pa) for 18 hours. The catalyst was filtered, and the solvent was evaporated. The resultant oil was chromatographed over silica gel, eluting with 20% ethyl acetate/hexane to afford the free base of the product. The free base was converted to the HCl salt m.p. 188–191 °C.

Employing the procedure substantially as described in Examples 1 and 2 but substituting for the Wittig reagents and the benzo[b]furoquinolizin-2-ones used therein, the Wittig reagents and arylquinolizin-2-ones described in Table I there are prepared the acetic acid esters also described in Table I in accordance with the following reaction scheme

TABLE I

Ar	R ²	R ¹
benzo-	H	-C ₂ H ₅
benzo[b]thieno-	-CH ₃	-CH ₃
thieno-	-CH(CH ₃) ₂	-(CH ₂) ₂ CH ₃
furo-	-CH ₂ -CH=CH ₂	-C ₄ H ₉

EXAMPLE 3

E and Z

2-(1 Ethylsulfonylethylidene)-1 3,4,6,7 12b-hexahydro-2H-benzo[b]furo[2,3 a]quinolizine Hydrochloride and 2-(1 Ethylsulfonylethyl)-1 6,7 12b-tetrahydro-3H benzo[b]furo[2,3-a]quinolizine Hydrochloride

α Diethylphosphonoethylsulfone (1.34 g; 5.2 mmol) was dissolved in 20 mL of THF and cooled to -70 °C under N₂ gas. To this solution, n-butyl lithium was added dropwise, and the mixture was stirred for 1 hour. 1,3,4,6,7 12b-Hexahydro-2H benzo[b]furo[2,3-a]quinolizin 2-one (0.96 g, 4 mmol) in 10 mL of THF was added at -70 °C under N₂ gas and the reaction mixture was heated at 50 °C overnight. A saturated NH₄Cl solution and ether were added to the reaction mixture and the ether layer was separated, washed with H₂O, dried over MgSO₄, and evaporated to give an oil. The free base of the products were separated by chromatography over silica gel eluting with 12% ethyl acetate/CH₂Cl₂ and converted to HCl salts to give Z-2-(1 Ethylsulfonylethylidene)-1 3,4,6,7,12b-hexahydro-2H benzo[b]furo[2,3-a]quinolizine Hydrochloride m.p. 210–212 °C. E-2-(1 Ethylsulfonylethylidene)-1 3,4,6,7 12b-hexahydro-2H benzo[b]furo[2,3-a]quinolizine Hydrochloride m.p. 247–248 °C. and 2-(1 Ethylsulfonylethyl)-1 6,7 12b-tetrahydro 3H-benzo[b]furo[2,3-a]quinolizine Hydrochloride m.p. 222–223 °C.

EXAMPLE 4

(2RS 12bSR)-Ethyl

1,3,4,6,7 12b-Hexahydro-2H benzo[b]furo[2,3 a]quinolizine-2-carboxylate Hydrochloride

Step A. Preparation of

(12bSR)-2-(1 3-dithian 2-ylidene)-1 3,4,6,7 12b-hexahydrobenzo[b]furo[2,3 a]quinolizine

2 Trimethylsilyl 1 3-dithiane (0.77 g; 4 mmol) was dissolved in 10 mL dry THF and cooled to -25 °C with a dry ice/CCl₄ bath. To this was added 1.6 mL n-butyl lithium (1.6M solution in hexane) and the solu-

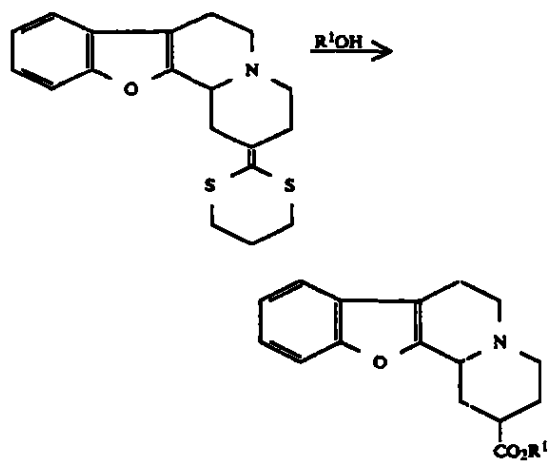
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tion was stirred for 2 hours at -25 C after which time 0.422 g (1.75 mmol) (12bRS)-1,3,4,6,7,12b-hexahydro-2H-benzofuro[2,3-a]quinolizin-2-one was added and the reaction mixture was allowed to warm to room temperature (15 minutes). The reaction mixture was poured into 50 mL H₂O and extracted with 3 x 25 mL CH₂Cl₂. The combined organics were extracted with 5 x 20 mL H₂O, 1 x 25 mL brine, dried (MgSO₄) and the solvent was removed in vacuo. Purification by medium pressure chromatography (CHCl₃) yielded 0.385 g (64%) product as a yellow crystalline solid m.p. 133-134 C.

Step B: Preparation of (2RS,12bSR)-Ethyl 1,3,4,6,7,12b-hexahydro-2H-benzo[b]furo[2,3-a]quinolizine-2-carboxylate Hydrochloride

(12bSR)-2-(1,3-Dithian-2-ylidene)-1,3,4,6,7,12b-hexahydrobenzo[b]furo[2,3-a]quinolizine (0.18 g, 0.524 mmol) was dissolved in 30 mL absolute ethanol which previously had been saturated with HCl gas. The reaction was heated to 50 C for 3 hours; the solvent was removed and the residue was partitioned between 25 mL ethyl acetate and 25 mL 20% NaOH solution. The aqueous layer was separated and the organic layer washed with 1 x 20 mL 20% NaOH, 3 x 25 mL H₂O, 1 x 25 mL brine, dried (MgSO₄) and the solvent was removed in vacuo. Purification by spinning disc chromatography (1% methanol/CHCl₃) yielded 0.12 g (77%) of the product as an oil. The oil was dissolved in 20 mL ethyl acetate and ethanolic HCl was added to give a white solid m.p. 228-230 C (dec).

Employing the procedure substantially as described in Example 4, Step B, but substituting for the ethanol reagent used therein comparable amounts of an alcohol of structure R¹OH, there are produced the esters described below in accordance with the following reaction scheme:



EXAMPLE 5

(2RS,12bSR)-2-Acetyl-1,3,4,6,7,12b-hexahydro-2H-benzo[b]furo[2,3-a]quinolizine Hydrochloride

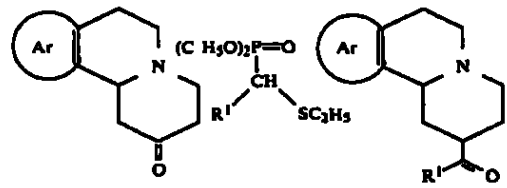
1-Ethylthiotriethylphosphonate (2.34 g, 10.4 mmol) was dissolved in 50 mL of THF and cooled in an acetone-dry ice bath under N₂ gas. To this solution n-butyl lithium (8.8 mmol) was added dropwise. After stirring for 3 hours, (12bRS)-1,3,4,6,7,12b-hexahydro-2H-ben-

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zo[b]furo[2,3-a]quinolizin-2-one (1.93 g, 8 mmol) in 20 mL of THF was added to the solution which then was stirred for 1 hour with cooling, for 1 hour at room temperature, and overnight at 50 C. Water (40 mL) and saturated NH₄Cl solution were added successively to the reaction mixture which was then extracted into ether. The ether layer was washed with saturated NaHCO₃ solution, brine, and water. Evaporation gave an oil. The oil was dissolved in 20 mL of ethanol and to this solution, 20 mL of ethanol saturated with dry HCl gas and 5 drops of H₂O were added with stirring at room temperature. After stirring overnight, the ethanol was evaporated to give a brown residue which was redissolved in ethyl acetate and made basic with dilute NH₄OH. The ethyl acetate layer was separated, washed with H₂O and dried over K₂CO₃. Evaporation gave a dark oil which was subjected to silica gel column chromatography. Ethyl acetate eluted the desired product. The free base was converted to the hydrochloride salt with ethanol/HCl m.p. >260 C.

Employing the procedure substantially as described in Example 5 but substituting for the Wittig reagent and benzo[b]furoquinolizin-2-one used therein the Wittig reagents and arylquinolizin-2-ones described in Table II, there are produced the 2-alkanoyl-arylquinolizines also described in Table II in accordance with the following reaction scheme:

TABLE II

	
Ar	R ¹
benzo-	-CH ₃
pyridino-	-C ₃ H ₇ -n
benzo[b]furo-	-C ₂ H ₅
benzo[b]thieno-	-C ₄ H ₉ -n
thieno-	-CH(CH ₃) ₂
furo-	-CH ₃

EXAMPLE 6

(2RS,12bS)-1,3,4,6,7,12b-Hexahydro-2-(1-hydroxyiminoethyl)-2H-benzo[b]furo[2,3-a]quinolizine Hydrochloride

Into a mixture of 10 mL of ethanol and 3 mL of pyridine, (2RS,12bSR)-2-Acetyl-1,3,4,6,7,12b-hexahydro-2H-benzo[b]furo[2,3-a]quinolizine (0.4 g, 1.5 mmol) and hydroxylamine hydrochloride (0.1 g, 1.5 mmol) were added. After 2 hours stirring, the product precipitated. The solid was collected by filtration and washed with ethyl acetate several times m.p. 280 C.

Employing the procedure substantially as described in Example 6 but substituting for the 2-acetyl benzo[b]furoquinolizine used therein the 2-alkanoyl-arylquinolizines described in Tables II and III, there are produced the oximes described in Table III in accordance with the following reaction scheme:

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Fifteen minutes later the product from Step A (0.23 g) in 2 mL of ether was added and the ice bath was removed. The reaction mixture was heated at reflux for 2 hours. Water (0.2 mL) was added followed by 1 mL of 10% H₂SO₄. A saturated solution of NaHCO₃ was then added until the reaction was basic. The reaction mixture was extracted with ethyl acetate. The extracts were washed with water, dried over MgSO₄, and evaporated to afford an oil. The oil was chromatographed over silica gel and then recrystallized to yield 0.022 g of the product m.p. 116–117 °C.

EXAMPLE 14

(2RS,12bSR)-N-(1,3,4,6,7,12b-Hexahydro-2H-benzo[b]furo[2,3-a]quinolizin-2-yl)methyl-N,N-trimethylsulfamide Hydrochloride

Step A: Preparation of

(2RS,12bSR)-1,3,4,6,7,12b-Hexahydro-2-methoxymethylidene-2H-benzo[b]furo[2,3-a]quinolizine

To a cold (0 °C) solution of diisopropylamine (0.22 g, 2.2 mmole) in 6 mL of tetrahydrofuran (THF) was added n-butyllithium (1 mL of a 2.1 molar solution, 2.1 mmole). After 15 minutes this mixture was added via syringe to a suspension of methoxymethyltriphenylphosphine chloride (0.685 g, 2.0 mmole) in 5 mL of toluene at 0 °C, stirred 15 minutes, and then a solution of (12bRS)-1,3,4,6,7,12b-hexahydro-2H-benzo[b]furo[2,3-a]quinolizin-2-one (0.12 g, 0.5 mmole) in 3 mL of toluene was added. After 30 minutes, the reaction mixture was poured into water (50 mL), washed with ether (2 × 40 mL), the ether washed with brine (40 mL), dried (Na₂SO₄), filtered and concentrated. The oily residue was chromatographed (silica, ethyl acetate/hexanes, 1:1) to give 104 mg of a 1:1 mixture of E and Z enol ethers as an oil. Exact mass: calc. 269.1416, Found 269.14163.

Step B: Preparation of (2RS,12bSR) and

(2SR,12bSR)-1,3,4,6,7,12b-Hexahydro-2H-benzo[b]furo[2,3-a]quinolizin-2-carboxaldehyde

The mixture of enol ethers (104 mg, mmole) from Step A was dissolved in 6 mL of 2N HCl, stirred for 4 hours at 25 °C, made basic and extracted with methylene chloride (2 × 40 mL), dried (Na₂SO₄), filtered and concentrated to give 60 mg of crude aldehyde, a (2:1) mixture of (2RS,12bSR) (2SR,12bSR) aldehydes.

Step C: Preparation of

(2RS,12bSR)-1,3,4,6,7,12b-Hexahydro-1-methylaminomethyl-2H-benzo[b]furo[2,3-a]quinolizine

To a solution of aldehydes from Step B (0.15 g, 0.56 mmole) in 3 mL of methanol was added methylamine hydrochloride (0.18 g, 2.8 mmol) and sodium cyanoborohydride (0.050 g, 0.78 mmole). After 48 hours at 25 °C, the reaction was concentrated to dryness, 5 mL of 6N HCl added, stirred 30 minutes, diluted with 30 mL of water, made basic and extracted with methylene chloride (2 × 30 mL), dried (Na₂SO₄), filtered and concentrated to an oil which was chromatographed (silica, NH₃ saturated CHCl₃/1% MeOH) to give 65 mg of product.

Step D: Preparation of

(2RS,12bSR)-N-(1,3,4,6,7,12b-Hexahydro-2H-benzo[b]furo[2,3-a]quinolizin-2-yl)methyl-N,N-trimethylsulfamide Hydrochloride

To a solution of the amine from Step C (0.065 g, 0.24 mmole) in 2 mL of methylene chloride was added

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0.050 g (0.48 mmole) of triethylamine and 0.070 g (0.48 mmole) of dimethylsulfamoyl chloride. After 18 hours at 25 °C, this was poured into 10 mL of saturated NaHCO₃, extracted into methylene chloride (2 × 20 mL), dried (Na₂SO₄), filtered and concentrated to give an oil which was chromatographed (silica, ethyl acetate) to give 0.05 mg of the free base of the product. The HCl·½H₂O salt was generated in ethyl acetate and ethanolic HCl, m.p. 242–245 °C.

EXAMPLE 15

Pharmaceutical Formulation

Ingredient	Mg/Capsule
(2RS,12bSR)-Methyl (1,3,4,6,7,12b-hexahydro-2H-benzo[b]furo[2,3-a]quinolizin-2-yl)acetate Hydrochloride	6
starch	87
magnesium stearate	7

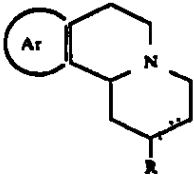
The active ingredient, starch and magnesium stearate are blended together. The mixture is used to fill hard shell capsules of a suitable size at a fill weight of 100 mg per capsule.

EXAMPLE 16

Ingredient	Mg/Capsule
(2RS,12bSR)-1,3,4,6,7,12b-Hexahydro-2-(1-methyl-1-hydroxyethyl)-2H-benzo[b]furo[2,3-a]quinolizine Hydrochloride	6
starch	87
magnesium stearate	7

What is claimed is:

1. A compound of structural formula:



or a pharmaceutically acceptable salt thereof wherein Ar represents an aromatic group selected from X, Y, benzo[b]furo-, X-Y-benzo[b]thieno-, and wherein X and Y are independently:

- (1) hydrogen,
- (2) halo,
- (3) hydroxy,
- (4) C₁₋₃-alkoxy or
- (5) C₁₋₃-alkyl.

R is

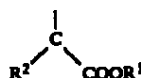
- (1)



wherein R¹ is hydrogen or C₁₋₃ alkyl, either straight or branched chain.

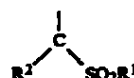
- (2)

23

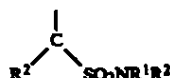
wherein R² is

- (a) hydrogen,
(b) C₁₋₃ alkyl, or
(c) C₁₋₃ alkylidene;

(3)



(4)

wherein R¹ and R² can be joined together to form pyrrolidine or piperidine;

(5)



wherein Q is

- (a) O or
(b) N—OR¹

(6)



wherein Z is

- (a) —OR³ or —SR³
(b) —NR³R³ wherein R³ is

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- (i) H,
(ii) C₁₋₃ alkyl unsubstituted or substituted with
(1) —OH
(2) —COOR¹
(3) —SO₂R²
(4) —N(R²)SO₂R²
(iii) —COOR²
(iv) —SO₂R²
(v) SO₂NR¹R²

10 R⁴ is

- (a) C₁₋₃ alkyl or
(b) C₁₋₃ alkylidene; and

the broken lines represent possible double bonds.

2 The compound of claim 1 wherein Ar is benzo[b-]

15]furo—

3 The compound of claim 2, wherein R is
CH₂CO₂R¹ CH₃CHCO₂R¹ R¹—C=NOR³
R¹(R⁴)C—OH, R¹CHO(CH₂)₂OH, or R¹(R⁴)CO(CH₂)₂OH wherein R¹ R³ and R⁴ are independently C₁₋₃

20 alkyl or H

4 The compound of claim 3 wherein R¹ and R⁴ are methyl and R³ is H.

5 A pharmaceutical composition for the treatment of depression comprising a pharmaceutical carrier and an effective amount of the compound of claim 1

25 6. The composition of claim 5 wherein the Ar is benzo[b]furo—

7 The composition of claim 6, wherein R is —CH₂CO₂R¹ CH₃CHCO₂R¹ R¹—C=NOR³
30 R¹(R⁴)C—OH R¹CH—O(CH₂)₂OH or
R¹(R⁴)C—O(CH₂)₂OH wherein R¹ R³ and R⁴ are independently C₁₋₃alkyl or H.

8 The composition of claim 7 wherein R¹ and R⁴ are methyl and R³ is H

35 9 A method of treating depression which comprises the administration to a patient in need of such treatment of an effective amount of a compound as described in claim 1

10 The method of claim 9 wherein Ar is benzo[b-]

40]furo—

11 The method of claim 10 wherein R is —CH₂CO₂R¹ CH₃CHCO₂R¹ R¹—C=NOR³
R¹(R⁴)C—OH, R¹CHO(CH₂)₂OH, or
R¹(R⁴)C—O(CH₂)₂OH wherein R¹ R³ and R⁴ are in

45 deperently C₁₋₃alkyl or H

12. The method of claim 11 wherein R¹ and R⁴ are methyl and R³ is H

* * * * *

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United States Patent Office

3,492,303

Patented Jan 27, 1970

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3,492,303

1,2,3,4,4a,5,6,8,9,14,14b,14c-DODECAHYDROBENZ-
[h]INDOLO[2,3-a]QUINOLIZINES

John Shavel, Jr., Mendham and Glenn Curtis Morrison,
Dover, N.J., assignors to Warner-Lambert Pharmaceu-
tical Company, Morris Plains, N.J., a corporation of
Delaware

No Drawing Continuation-in-part of application Ser. No.
537,251, Feb. 9, 1966. This application July 28, 1967,
Ser. No. 656,694

Int. Cl. C07d 57/02 39/12 A61k 27/00

U.S. Cl. 260-286

10 Claims

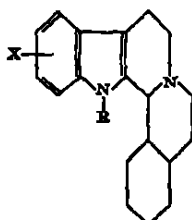
ABSTRACT OF THE DISCLOSURE

The present invention relates to 1,2,3,4,4a,5,6,8,9,14,14b,14c-dodecahydrobenz[h]indolo[2,3-a]quinolizines, in which X is hydrogen and lower alkyl, lower alkoxy halogen, amino, NN disubstituted amino and etherified mercapto and R is hydrogen, lower alkyl, phenyl, lower alkyl, substituted phenyl, lower alkyl and acyl

These compounds are useful as central nervous system depressants

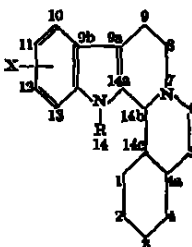
The present application is a continuation in part application of our co pending application Ser. No. 537,251 filed Feb. 9, 1966 now abandoned

This invention relates to new and useful heterocyclic compounds and relates more particularly to new and novel 1,2,3,4,4a,5,6,8,9,14,14b,14c dodecahydrobenz[h]indolo[2,3-a]quinolizines having the formula



wherein X represents hydrogen, lower alkyl such as methyl, ethyl, isobutyl, hexyl and the like, lower alkoxy such as methoxy and ethoxy, halogens such as fluorine, chlorine and bromine, amino, NN disubstituted amino and the like, etherified mercapto such as methylmercapto and ethylmercapto, nitro and hydroxyl, and R represents hydrogen, lower alkyl such as methyl, ethyl, propyl, isobutyl, hexyl and the like, phenyl, lower alkyl such as phenethyl, substituted phenyl, lower alkyl such as halogen substituted benzyl, nitrobenzyl, lower alkoxy substituted benzyl and the acyl residue of a carboxylic acid such as acetyl, benzoyl and the like

The numbering of the compounds of this invention is as follows



2

The use of a dot at ring junctions, as in structure (4) below denotes beta orientation of the hydrogen atom whereas the use of a dotted line denotes alpha orientation of the hydrogen atom. Since all the compounds described in this patent are d, l mixtures the above stereochemical designations are only relative and each structure is to be considered as only one of the two mirror images.

Also embraced within the scope of this invention are the pharmaceutically accepted acid addition salts of the above-described bases, their quaternary ammonium salts and N-oxides

The symbols R and X as used hereinafter have the same meaning described above.

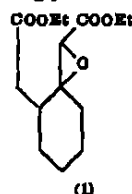
The invention also includes within its scope a new and novel process for preparing the above compounds as well as the intermediates employed for their synthesis

The new and novel compounds of this invention have interesting and significant pharmacological activity and are useful as central nervous system depressants, for mammals

In order to use these compounds or their salts as central nervous system depressants the selected compound from about 1 mg. to 100 mg. is combined with a pharmaceutical carrier such as starch, mannitol or lactone to form dosage forms such as tablets and capsules or with water or vegetable oil to form solutions and suspensions suitable for parenteral administration. They may be administered orally or parenterally at a dosage of about 1 mg. to 100 mg. several times daily to produce the desired depressant effect.

In addition they are valuable intermediates in the production of other compounds of the 1,2,3,4,4a,5,6,8,9,14,14b,14c dodecahydrobenz[h]indolo[2,3-a]quinolizines series.

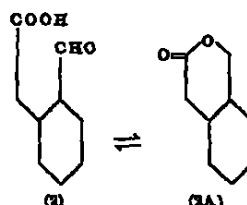
The compounds of this invention are prepared by reacting 2-(carboethoxymethyl)cyclohexanone with ethyl chloracetate to form a glycidic ester of the formula



(I)

This reaction is usually carried out in an alcoholic solvent such as t butanol at below room temperature, particularly at 0-15° C. using an alkali metal salt of the alcohol such as potassium t butoxide as a catalyst.

The ester (I) is converted to its corresponding dicarboxylic acid by treatment first with an alkali metal hydroxide such as sodium hydroxide and then a mineral acid such as hydrochloric acid. The intermediate acid is then heated in the presence of copper powder at an elevated temperature of 150-300° C. more particularly near 250° C. in vacuo. The pyrolysate is a mixture of the acid aldehyde (2) and its enol lactone (2A) having the formulae



(2)

(2A)

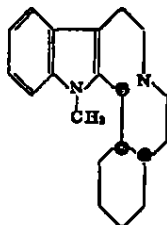
This mixture can be converted to the acid aldehyde by hydrolysis with a dilute acid such as acetic acid. The pure

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EXAMPLE 11

Cis-syn 1 2 3 4 4a 5 6 8 9 14 14b 14c-dodecahydro-14 methylbenz[a]indolo[2 3 h]quinolizine

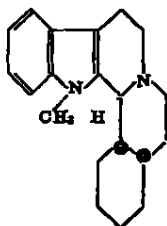


A mixture of 56 g of cis-syn 1 2 3 4 4a 5 6 8 9 14, 14b 14c-dodecahydrobenz[a]indolo[2 3 h]quinolizine, 96 g of sodium hydride dispersion (55% in mineral oil) 34 ml of dimethyl carbonate and 500 ml of tetrahydrofuran is refluxed for 20 hr with stirring. The excess sodium hydride is destroyed by the dropwise addition of water and the solvent removed in vacuo on the steam bath. The residue is treated with 1300 ml of chloroform and 100 ml of water. The chloroform layer is washed with water, dried over sodium sulfate and the solvent is removed. The residue is dissolved in 100 ml of Skelly solve B and the solution filtered. On standing there is deposited 32 g (55%) of cis-syn 1 2 3 4 4a 5 6 8 9 14 14b 14c-dodecahydro-14 methylbenz[a]indolo[2 3 h]quinolizine as a crystalline solid. M.P. 143-148. Recrystallization from methanol gives an analytical sample. M.P. 149-150.

Analysis for $C_{29}H_{35}N_3$ —Calcd C 81.58 H 8.90 N 9.52 Found C 81.52 H 8.87 N 9.38

EXAMPLE 12

Cis-anti 1 2 3 4 4a 5 6 8 9 14 14b 14c-dodecahydrobenz 14 methyl[a]indolo[2 3 h]quinolizine



A mixture of 47 g of cis-anti 1 2 3 4 4a 5 6 8 9 14 14b 14c dodecahydrobenz 14 methyl[a]indolo[2 3 h]quinolizine 96 g of sodium hydride dispersion (55% in mineral oil) 40 ml of dimethyl carbonate and 250 ml of tetrahydrofuran is refluxed for 20 hr. The excess hydride is destroyed by the dropwise addition of water and the solvent is removed in vacuo on the steam bath. The residue is treated with 1 l of chloroform and 50 ml of water. The chloroform layer is washed with water, dried over sodium sulfate and the solvent is removed. The residue is dissolved in 20 ml of Skelly solve B and the solution filtered. On cooling in an icebath there is deposited 18 g (36%) of a crystalline solid, M.P. 109-110. Recrystallization from methanol gives an analytical sample. M.P. 111-112°.

Analysis for $C_{29}H_{35}N_3$ —Calcd C, 81.58 H 8.90 N 9.52 Found C 81.77 H 9.11 N 9.30

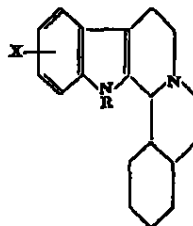
It is understood that the foregoing detailed description is given merely by way of illustration and that many variations may be made therein without departing from the spirit of our invention.

Having described our invention what we desire to secure by Letters Patent is

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We claim

1 A compound selected from the group consisting of the free base of the formula



wherein X is a member selected from the group consisting of hydrogen, lower alkyl, lower alkoxy, halogen, amino, etherified mercapto, nitro and hydroxyl and R is a member selected from the group consisting of hydrogen, lower alkyl, phenyl, lower alkyl, and acyl of a lower alkanic acid and benzoic acid, the pharmaceutically acceptable acid addition salts and the quaternary ammonium salts thereof.

2 The compound of claim 1 which is trans-anti 1 2 3 4 4a 5 6 8 9 14, 14b, 14c dodecahydrobenz[a]indolo[2 3 h]quinolizine.

3 The compound of claim 1 which is trans-syn 1 2 3 4 4a 5 6 8 9 14 14b 14c dodecahydrobenz[a]indolo[2 3 h]quinolizine.

4 The compound of claim 1 which is 2 3 4 4a 5 6 8 9 14 14c decahydro 1H benz[a]indolo[2 3 h]quinolizinium chloride.

5 The compound of claim 1 which is cis-syn 1 2 3 4, 4a, 5 6 8 9 14 14b 14c dodecahydrobenz[a]indolo[2 3 h]quinolizine.

6 The compound of claim 1 which is cis-anti 1 2 3 4 4a 5 6 8 9 14 14b 14c dodecahydrobenz[a]indolo[2 3 h]quinolizine.

7 The compound of claim 1 which is trans-anti 1, 2, 3, 4a 5 6 8 9 14 14b 14c-dodecahydro 14 methylbenz[a]indolo[2 3 h]quinolizine.

8 The compound of claim 1 which is trans-syn 1 2 3 4, 4a, 5 6 8 9 14 14b 14c dodecahydro 14 methylbenz[a]indolo[2 3 h]quinolizine.

9 The compound of claim 1 which is cis-syn 1 2 3 4, 4a 5 6 8 9 14, 14b 14c dodecahydro 14 methylbenz[a]indolo[2 3 h]quinolizine.

10 The compound of claim 1 which is cis-anti 1, 2 3 4 4a 5 6 8 9 14, 14b 14c dodecahydrobenz 14 methyl[a]indolo[2 3 h]quinolizine.

References Cited

UNITED STATES PATENTS

3 022 309	2/1962	Muller	260-287
3 087 930	4/1963	Schut	260-288
3 103 513	10/1963	Nauta	260-289 X
3 219 661	11/1965	Shavel et al.	260-288 X
3 240 782	3/1966	Brossi et al.	260-286
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DONALD G. DAUS, Primary Examiner

U S C I X R

260-288 348 468 487 521 343 5 376 15 687

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

2020

Bogotá, D C , 12 de julio de 2007

Abogado
EMILIO FERRERO
(Apoderado)

Solicitante Onon Corporation

ASUNTO	Radicación	04110419
	Trámite	002
	Evento	001
	Actuar ión	430
	Oficio	6950
	Folios	014

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

1 Documentos estudiados

- | | |
|-----------------------------|--|
| 1 1 <u>Descripción</u> | (Folios 251 a 364) |
| 1 2 <u>Reivindicaciones</u> | 1 a 35 (Folios 365 a 403), modificadas 1 a 37 (Folios 410 a 449) |
| 1 3 <u>Proridad</u> | Folios 4 a 219 (03 de abril de 2002 FL y US y 20020642 y 60/369347, respectivamente) |

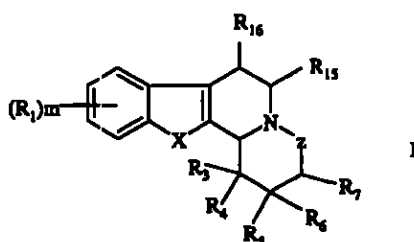
2 Objeto de la invención

La presente solicitud se titula "Compuestos policíclicos como potentes antagonistas del adreno-receptor alfa-2"

El objeto de la presente solicitud se refiere a derivados de aniquinolizina farmacológicamente activos y compuestos relacionados y con sus sales farmacéuticamente aceptables y ésteres de los mismos así como también, con las composiciones farmacéuticas que los contienen y con su utilización como antagonistas alfa-2

Los receptores alfa adrenergicos se pueden dividir en una base farmacológica en adreno-receptores alfa-1 y alfa-2 ambos a su vez se pueden dividir en subtipos en seres humanos se han descubierto tres subtipos codificados genéticamente, a saber adreno-receptores alfa-2 A alfa-2B y alfa-2C Los adreno-receptores alfa-2 A se expresan ampliamente en diversos tejidos, los adreno-receptores alfa-2C se concentran en el SNC y parecen desempeñar una función en la modulación del comportamiento específico provocado por el SNC y las respuestas fisiológicas

Reivindicaciones 1 a 14 (folios 410 a 417) Un uso de un compuesto de la fórmula I, que son dervados de aniquinolizina



Reivindicaciones 15 a 34 y 36 (folios 417 a 448, 449) un compuesto derivado de anquilolizina de fórmula IA, IB, IC, ID, IE

Reivindicacion 35 (folios 448 y 449) Una composición farmacéutica caracterizada porque comprende al menos un compuesto de las reivindicaciones 15 a 32 (derivado de anquilolizina de fórmula IA)

Reivindicacion 37 (folio 449) Un método para el tratamiento de una enfermedad o condición en donde se indica que será útil un antagonista de los adreno-receptores alfa-2

El problema planteado en esta solicitud es la necesidad de compuestos que se puedan utilizar para el tratamiento de una amplia variedad de enfermedades y condiciones del sistema periférico y el sistema nervioso central (SNC)

La solución propuesta por la presente es solicitud consiste en derivados de anquilolizina antagonistas del adreno-receptor alfa-2

El objeto de la solicitud definido anteriormente se clasificó en la IPC A61K 31/55, 31/4375

3 De la solicitud de Patente

3 1 Reivindicaciones (artículo 30 D 486)

De acuerdo con lo revelado en el capítulo reivindicatorio, los compuestos de fórmula IA, IB, IC, ID, IE de las reivindicaciones 15 a 33 y dependientes, tienen grupos sustituyentes que son demasiado amplios resultando un número elevado de compuestos por lo cual tales reivindicaciones no son concisas

4 Unidad de Invención (artículo 25 D 486)

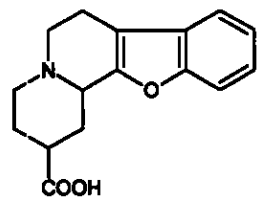
Según lo anterior la (s) reivindicación (es) 34 (folios 445 a 448) tal como está presentada, que se refiere(n) a un compuesto que es 2beta-metoxi-1,2,3,4,6,7,12balfa-octahidro-indolo[2,3-alfa]quinolizina y otros compuestos más, no guarda(n) unidad de invención con la reivindicación 1 y sus dependientes, que se relacionan con un compuesto derivado de anquilolizina

5 Excepciones de Patentabilidad (artículo 20 D486 literal a)-d))

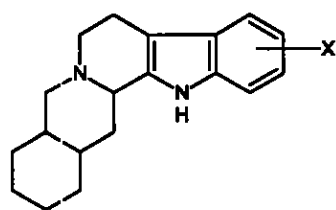
De acuerdo con lo anterior, la(s) reivindicación(es) 37 (Folio 449), que se refiere(n) a un método para el tratamiento de una enfermedad en donde se indica que será útil un antagonista de los adreno-receptores alfa-2, no es (son) patentable(s) porque se refiere a un método de tratamiento el cual se considera exceptuado de patentabilidad

- R₁₅ puede ser hidrógeno, alquilo C₁₋₆, alqueno C₂₋₆, hidroxi-alquilo C₁₋₆, alcoxi C₁₋₆-alquilo C₁₋₆, entre otros
- R₁₆ puede ser hidrógeno, alquilo C₁₋₆
- m es 0 a 2 y n es 0 o 1

La antenorndad US 4686226 D1 (folios 471 a 477) menciona compuestos derivados de benzo[b]furo- y benzo[b]tienc quinolizinas que son antagonistas del adreno-receptor alfa-2 y pueden tener la siguiente formula estructural



El documento US 3492303 D2 (folios 478 y 479) menciona compuestos de 1,2,3,4,4a,5,6,8,9,14,14b,14c-dodecahidrobenzo[h]indol[2,3-a]-quinolizinas que tienen actividad sobre el SNC



Donde X puede ser hidrógeno, alquilo inferior, alcoxi, halogeno, NH₂, NO₂, OH, etc

El problema técnico planteado en esta solicitud la necesidad de compuestos que se puedan utilizar para el tratamiento de una amplia vanedad de enfermedades y condiciones del sistema penférico y el sistema nervioso central (SNC) se habia resuelto previamente mediante compuestos derivados de anliquinolizina ya conocidos(as) Por esta razón se considera que las sustituciones al anliquinazolina reivindicadas en la presente solicitud son evidentes para una persona medianamente versada en la materia

Ademas, puesto que tanto D1 y D2 divulgaban previamente derivados de anliquinolizina (folios 471 a 479) con actividad antagonista del adreno-receptor alfa-2 y empleados para el tratamiento de enfermedades del SNC, una persona conocedora de la matena motivada por tal sugerencia lograria el objeto de esta solicitud compuestos de fórmula I, derivados de anliquinolizina y que son antagonistas del adreno-receptor alfa-2 con actividad sobre el SNC, de manera que para una persona medianamente versada en la matena seria obvio combinar estos dos documentos Por lo cual puede no haber Nivel Inventivo

9 Conclusion

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

Nº	Documento Nº	Reivindicaciones afectadas	Requisito que afecta
D1	US 4686226	15 a 36	Nivel Inventivo
D2	US 3492303	15 a 36	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 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 N° 10 de 2001.



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

El anterior requerimiento fue notificado por fijación en lista, de fecha 27 JUL 2007

CONCEPTO TÉCNICO No 1052	EXAMINADOR TÉCNICO Código No 202005
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EXAMEN TÉCNICO DE FONDO			
Nº Radicación	04110419	Fecha de presentación	3-04 2002
Nº Prioridad	FI20020642 US60/369347	Fecha de Prioridad	3-04-2002

Palabras clave	
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CLASIFICACIONES INTERNACIONALES DE BUSQUEDA
A61K 31/55 A61K 31/4375

DOCUMENTOS CORRESPONDIENTES EN OTROS PAÍSES	
WO 03/082866	9-10 2003
Patente Original	

BASES DE DATOS CONSULTADAS
EPOLINE ESPACENET

INFORMES DE EXÁMENES EN OTRAS OFICINAS			
Oficina		Fecha	Reivindicaciones
EUROPEA			

ANTERIORIDADES ENCONTRADAS			
Documento		Relevancia	Reivindicaciones afectadas
US 4686226		Nivel Inventivo	15 a 36
US 3492303		Nivel Inventivo	15 a 36
EP 0130823		—	—

LITERATURA NO PATENTES			
Documento no Patentes		Relevancia	Reiv afectadas

Observaciones	
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Fecha del examen	Art 45 12-07-07
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