



No. 05-112548-00006-0000

Fecha: 2009-03-25 16:18:40 Dep. 2020 NULCREACIONE
Tra. 11 PATENTELIYII Eve: 379 FASENACIONALII
Act. 444 RESPUESTAREQUL Folios: 7

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Señores

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

DIVISIÓN DE NUEVAS CREACIONES

E. _____ S. _____ D. _____

Ref: Expediente No. 05.112.548

**Solicitud de patente de invención titulada: "DERIVADOS DE AMINA CICLICA,
PROCESOS PARA SU PREPARACIÓN Y COMPOSICIONES
FARMACÉUTICAS QUE CONTIENEN LOS MISMOS"**

Solicitante: GLAXO GROUP LIMITED.

Nuestra Ref.: P2005/0000150

RESPUESTA AL OFICIO No.14558 NOTIFICADO POR FIJACIÓN EN LISTA No. 370,
DE FECHA 14 DE NOVIEMBRE DE 2008
(EXAMEN DE FONDO)

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

1. En primer lugar y con el ánimo de brindar mayor claridad a la materia reivindicada, me permito presentar un **Capítulo Reivindicatorio Modificado**, que reemplaza en su totalidad al Capítulo Reivindicatorio presentado al momento de radicar esta solicitud. Para tal efecto, adjunto un recibo de pago que cubre la tasa de modificación correspondiente.

Así entonces, el Capítulo Reivindicatorio Modificado contiene las siguientes modificaciones:

Reivindicación original	Modificaciones
1	Se limita al compuesto del Ejemplo 98 o la sal del mismo.
2	Se limita a la sal clorhidrato del Ejemplo 99.
13, 14 y 15	Eliminadas.

Valga anotar que las modificaciones efectuadas al Capítulo Reivindicatorio cumplen a cabalidad con lo estipulado en el Artículo 34 de la Decisión 486, ya que éstas de ninguna manera implican una ampliación de la protección correspondiente a la divulgación contenida en la solicitud inicial. Por el contrario, éstas constituyen una franca limitación a la protección originalmente pretendida.

2. a- El Examinador argumenta que las Reivindicaciones 13, 14 y 15 no son patentables porque reclaman usos y métodos de tratamiento.

b- Con el ánimo de superar la anterior objeción, las Reivindicaciones 13, 14 y 15 han sido retiradas del Capítulo Reivindicatorio Modificado.

3. a- El Examinador argumenta que las patentes WO99/25685 (D1) y WO02/083134 (D2) afectan el nivel inventivo de la presente invención.

El Examinador argumenta que la única diferencia entre los compuestos de la invención y D1, es que los compuestos de la presente invención comprenden sustituyentes sobre el nitrógeno del anillo de piperidina no divulgados en D1. Sin embargo, el Examinador anota que dichas sustituciones son similares a aquellas reveladas en D2.

El Examinador señala que los sustituyentes sobre el anillo de piperidina de la presente invención resultan obvios a la luz de D1, así como los sustituyentes del extremo carboxamido de la molécula, que resultan derivados de D2.

Por lo tanto, el Examinador concluye que para una persona medianamente versada en la materia resultaría evidente combinar las enseñanzas de D1 y D2, para obtener los compuestos de la presente invención.

b- i) En primer lugar, es importante resaltar que la presente solicitud se refiere a derivados de piperidina sustituidos en la posición 4 por un grupo carboxamida o acetamida y por

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un grupo arilo, que además presentan un grupo alquilo C_1-C_4 sustituyendo el nitrógeno de la posición 1, y son activos como inhibidores de la recaptación de serotonina. De manera preferente, la presente invención ahora se dirige únicamente al compuesto N-[1-(3-cloro-1-naftalenil)etil]-2-[4-(4-fluorofenil)-1-metil-4-piperidinil]-N-metilacetamida.

ii) En cuanto al arte previo citado, debo señalar que D1 se refiere a derivados de 4-(alquil, alquenil/Cy)-4-carboxamido piperidinas N-sustituidas, con actividad como agonistas de VLA-4 y/o $\alpha 4\beta 7$, útiles para inhibir o prevenir las patologías asociadas a la adhesión celular. De acuerdo con esto, las enseñanzas de D1 conducen inequívocamente al desarrollo de compuestos en los que el nitrógeno de la piperidina no se encuentra directamente sustituido por un grupo alquilo (metilo, en el caso del compuesto específicamente reivindicado). Por el contrario, los compuestos de D1 comprenden un grupo L unido directamente al nitrógeno del ciclo de piperidina, el cual puede ser: $-C(O)-$, $O-C(O)-$; $NR^e-C(O)-$; $-S(O)_2-$, $-P(O)(OR_4)-$ ó $-C(O)C(O)-$.

Adicionalmente, los compuestos de D1 son útiles en la inhibición y prevención de desordenes asociados a la adhesión de leucocitos. Nada en D1 siquiera sugiere que las piperidinas que presentan un grupo carboxamida en la posición 4 (acetamida, en el caso del compuesto de la Reivindicación 1), serían útiles como antagonistas NK1 y como inhibidores de recaptación de serotonina.

iii) En cuanto a D2, esta referencia revela 4-aminometil-piperidininas N-sustituidas. Nada en D2 enseña o siquiera sugiere estructuras que comprendan un grupo carboxamida o acetamida en la posición 4 del anillo de piperidina.

Adicionalmente, D2 enseña que las 4-aminometil-piperidinas N-sustituidas son antagonistas del receptor MCH. D2 no enseña que las 4-aminometil-piperidinas N-sustituidas serían útiles como antagonistas del receptor NK1 y/o inhibidoras de la recaptación selectiva de serotonina.

iv) Así las cosas, debo subrayar que la persona medianamente versada en la materia, a partir de las enseñanzas de D1 y/o D2, no se inclinaría hacia la producción de piperidinas que comprendan específicamente: (i) un grupo alquilo C_{1-4} (e.g. metilo) directamente unido al átomo de nitrógeno del ciclo (a diferencia de D1) y (ii) una carboxamida (e.g. acetamida) en la posición 4 (a diferencia de D2).

Adicionalmente, nada en D1 y/o D2, independientemente o en combinación, sugiere que las 4-carboxi-piperidinas N-sustituidas, y aún más específicamente el Compuesto de la Reivindicación 1, serían útiles como inhibidores de la recaptación de la serotonina.

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De hecho, una persona versada en la materia, tomando en cuenta la información divulgada en D1 y/o D2, a lo sumo intentaría obtener 4-carboxamida-piperidinas N- sustituidas, esperando obtener agentes útiles como agonistas de VLA-4 y/o $\alpha 4\beta 7$ (de acuerdo con D1), o 4-aminometil-piperidinas N-sustituidas como antagonistas del receptor MCH.

En ese sentido, me permito subrayar que la evaluación de nivel inventivo en el análisis de patentes debe realizarse sobre la base de qué hubiera sido obvio para una persona versada en el arte. Claramente, la búsqueda del estado de la técnica de anterioridades, basada únicamente en la estructura molecular, sin considerar también los diferentes mecanismos de acción, no es representativa de la práctica realizada en el ámbito de la investigación farmacéutica. La persona versada en la técnica con la tarea de desarrollar fármacos como antagonistas del receptor NK1 y/o como inhibidores de recaptación de la serotonina, evidentemente enfocaría su investigación en el estudio estructural de agentes en el estado de la técnica con ese mecanismo de acción particular. Por esta razón, la persona versada en la técnica jamás consideraría relevantes enseñanzas previas de cómo diseñar agentes con un mecanismo de acción diferente, como ocurre en el presente caso respecto de la materia revelada en D1 y/o D2, que enseñan compuestos con actividad completamente diferente.

4. Por todo lo anterior, considero que las objeciones presentadas por el Examinador en su examen de fondo No. 3081 han sido resueltas y por consiguiente solicito respetuosamente se tengan por cumplidos los requisitos de patentabilidad, en tanto no se logró desvirtuar ninguno de ellos por parte del Despacho, y se proceda con la concesión de la patente.

Atentamente,

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

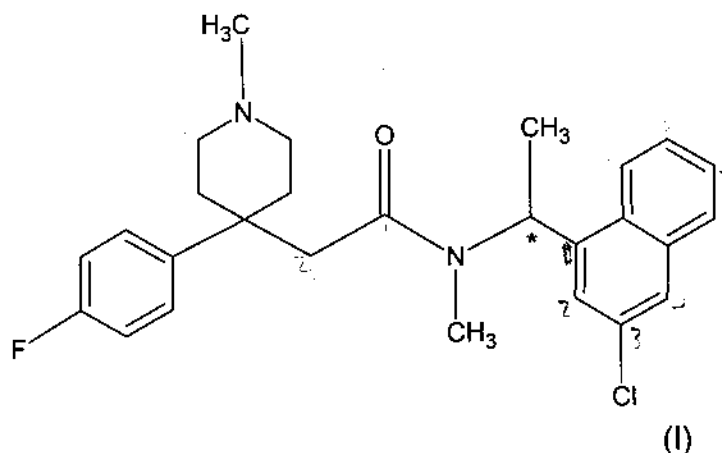
Anexos:

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

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CAPÍTULO REIVINDICATORIO MODIFICADO
(EXAMEN DE FONDO)

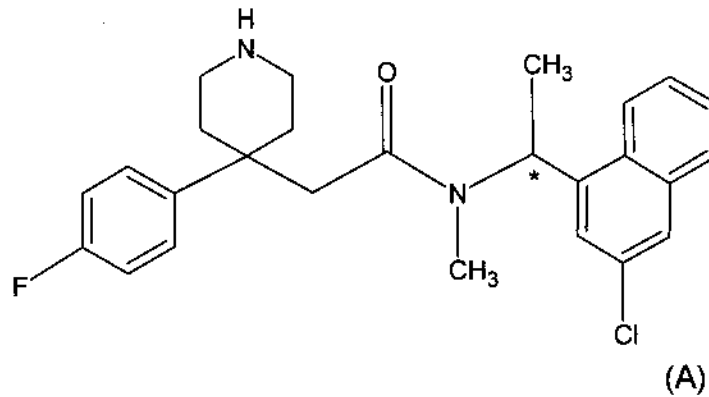
1. N-[1-(3-cloro-1-naftalenil)etil]-2-[4-(4-fluorofenil)-1-metil-4-piperidinil]-N-metilacetamida ó una sal farmacéuticamente aceptable del mismo.
2. Una sal del compuesto que se reivindicó en la Reivindicación 1 el cual es clorhidrato de N-[1-(3-cloro-1-naftalenil)etil]-2-[4-(4-fluorofenil)-1-metil-4-piperidinil]-N-metilacetamida.
3. Un enantiómero del compuesto que se reivindicó en la Reivindicación 1 ó 2.
4. Un enantiómero del compuesto que se reivindicó en la Reivindicación 1 ó 2 que tiene la formula (I)



cuya estereoquímica absoluta en el estereocentro indicado en la formula (I) como * es el mismo que para (-)-[3-cloro-1-naftalenil)etil]amina.

5. Un enantiómero del compuesto que se reivindicó en la Reivindicación 1 producido a partir del compuesto N-[1-(3-cloro-1-naftalenil)etil]-2-[4-(4-fluorofenil)-4-piperidinil]-N-metilacetamida (ejemplo 98).
6. Un enantiómero del compuesto que se reivindicó en la Reivindicación 2 producido a partir del compuesto N-[1-(3-cloro-1-naftalenil)etil]-2-[4-(4-fluorofenil)-1-metil-4-piperidinil]-N-metilacetamida (ejemplo 99).
7. Un proceso para la preparación de un compuesto que se reivindicó en la Reivindicación 1 el cual comprende hacer reaccionar un compuesto de fórmula (A), cuya estereoquímica absoluta en el estereocentro indicado en la

formula (A) como * es el mismo que para (-)-[3-cloro-1-naftalenil]etilamina.
con una solución de formaldehído en agua y triacetoxiborohidruro de sodio.

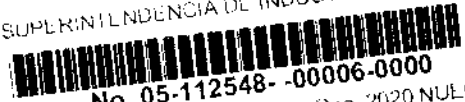


8. Una composición farmacéutica que comprende un compuesto que se reivindicó en las Reivindicaciones 1 ó 2 mezclado con uno ó más vehículos ó excipientes farmacéuticamente aceptables.

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 05-112548- -00006-0000

Fecha 2009-03-25 16:18:40 Dep. 2020 NULCREACIONE
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Act 444 RESPUESTA REQUE Folios: 7

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 900176089-2

RECIBO OFICIAL DE CAJA : 09 - 22,739
FECHA : MARZO 24 DE 2009

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CLARTE RAISBEK	CONSIGNACION	BANCO DE BOGOTA	062754367	110361134	20/03/2009	3,684,000.00

***** CONCEPTO *****

CANT.	DETALLE	CONCEPTO	TOTAL CONCEPTO
1	50005-01-03 CAMBIO DE MODALIDAD Y MODIFICA	12 MARCAS Y LEMAS COMERCIALES	111,000.00
TOTAL :			111,000.00

SON: CIENTO ONCE MIL PESOS

RESPONSABLE :

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RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

Description

This invention concerns novel substituted 1,2-ethanediamine derivatives which antagonize the pharmacological actions of the endogenous neuropeptide tachykinins known as neurokinins, particularly at the neurokinin 1 (NK1) and the neurokinin 2 (NK2) receptors. The novel 1,2-ethanediamine derivatives are useful whenever such antagonism is desired. Thus, such compounds may be of value in the treatment of those diseases in which the NK1 and/or NK2 receptor is implicated, for example, in the treatment of asthma and related conditions. The invention also provides pharmaceutical compositions containing the novel 1,2-ethanediamine derivatives for use in such treatment, methods for their use, and processes and intermediates for the manufacture of the novel 1,2-ethanediamine derivatives.

The mammalian neurokinins comprise a class of peptide neurotransmitters which are found in the peripheral and central nervous systems. The three principal neurokinins are SP (SP), Neurokinin A (NKA) and Neurokinin B (NKB). There are also N-terminally extended forms of at least NKA. At least three receptor types are known for the three principal neurokinins. Based upon their relative selectivities favoring the neurokinin agonists SP, NKA and NKB, the receptors are classified as neurokinin 1 (NK1), neurokinin 2 (NK2) and neurokinin 3 (NK3) receptors, respectively. In the periphery, SP and NKA are localized in C-afferent sensory neurons, which neurons are characterized by non-myelinated nerve endings known as C-fibers, and are released by selective depolarization of these neurons, or selective stimulation of the C-fibers. C-Fibers are located in the airway epithelium, and the tachykinins are known to cause profound effects which clearly parallel many of the symptoms observed in asthmatics. The effects of release or introduction of tachykinins in mammalian airways include bronchoconstriction, increased microvascular permeability, vasodilation, increased mucus secretion, neurogenic inflammation and activation of mast cells. Thus, the tachykinins are implicated in the pathophysiology and airway hyperresponsiveness observed in asthmatics; and blockade of the action of released tachykinins may be useful in the treatment of asthma and related conditions. A cyclopeptide antagonist (FK-224) selective for both NK1 and NK2 receptors has demonstrated clinical efficacy in human patients suffering from asthma and chronic bronchitis. M. Ichinose, et al., *Lancet*, 1992, 340, 1248. Nonpeptidic tachykinin antagonists have been reported, for example in European Patent Application, Publication Number (EPA) 428434, EPA 474561, EPA 512901, EPA 512902, EPA 515240 and EPA 559538, as well as in WO 94/10146.

K. Nagarajan, et al., *Proc. Indian Acad. Sci. (Chem. Sci.)*, 1992, 104, 383-397 (Nagarajan), discloses the synthesis of 1,2-ethanediamine derivatives of formula I (formula set out hereinbelow following the Examples, together with other formulae denoted by Roman numerals) wherein Q¹ is a pyrrolidino or piperidino radical of formula Id and Q⁴ is phenyl, 3,4-dimethoxyphenyl, 3,4-(methylenedioxy)phenyl, 3-methoxyphenyl, or 2-thienyl. The compounds disclosed in Nagarajan have been excluded from the definition of the compounds of the invention hereinbelow. Nagarajan does not disclose pharmaceutical compositions containing the compounds disclosed therein, nor does Nagarajan disclose a pharmaceutical utility for the compounds.

We have discovered a series of non-peptidic antagonists of the NK1 and NK2 receptors, and this is the basis for our invention.

According to the invention, there is provided a Compound of the invention which is a compound of formula I, wherein

Q¹ is a radical selected from the group of radicals of formulae Ia, Ib, Ic, Id, Ie, If, Ig, Ih, Ij, Ik and Im, wherein for a radical of formula Ia, Z^a is nitrogen or a group CR^{ad} in which R^{ad} is hydrogen or R^{ad} together with R^{ac} and the existing carbon to carbon bond forms a double bond; R^{aa} is Ar or Het; R^{ab} is hydrogen and R^{ac} is hydrogen or hydroxy or R^{ac} together with R^{ad} and the existing carbon to carbon bond forms a double bond, or R^{ac} and R^{ad} together form a diradical -(CH₂)_j- in which j is an integer from 1 to 5, or R^{ab} and R^{ac} together form a diradical -(CH₂)_k- in which k is an integer from 2 to 6, or R^{ab} and R^{ac} together are oxo or dialkylaminoalkoxyimino of formula -N-O-(CH₂)_q-NR^{ae}R^{af} in which q is the integer 2 or 3 and R^{ae} and R^{af} are independently hydrogen or (1-4C)alkyl, or the radical NR^{ae}R^{af} is pyrrolidino, piperidino or morpholino; for a radical of formula Ib, Z^b is a substituted imino group R^{ba}N or R^{ba}CH₂N in which R^{ba} is (3-7C)cycloalkyl, Ar or Het, or Z^b is a disubstituted methylene group R^{bb}(CH₂)_p-C-R^{bc} in which R^{bb} is Ar or Het, p is the integer 0 or 1; and R^{bc} is hydrogen, hydroxy, (1-4C)alkoxy, (1-4C)alkanoyloxy, COOR^{bd} (wherein R^{bd} is hydrogen or (1-3C)alkyl), cyano, NR^{be}R^{bf} or SR^{be} in which R^{be} and R^{bf} are independently hydrogen, (1-4C)alkyl, (1-4C)hydroxyalkyl or (1-4C)alkanoyl, or the radical NR^{be}R^{bf} is pyrrolidino, piperidino or morpholino; and R^{ba} is hydrogen or (1-4C)alkyl, or R^{bc} forms a double bond with the carbon atom to which it is bonded and with the adjacent carbon atom in the piperidine ring; or Z^b is a disubstituted methylene group R^{bb}CR^{bi} which forms a spirocyclic ring wherein R^{bb} is phenyl which is joined by an ortho-substituent diradical X^b to R^{bi} in which the phenyl R^{bb} may bear a further substituent selected from halo, (1-3C)alkyl, (1-3C)alkoxy, hydroxy, (1-3C)alkylthio, (1-3C)alkylsulfinyl and (1-3C)alkylsulfonyl; the diradical X^b is methylene, carbonyl or sulfonyl; and R^{bi} is oxy or imino of formula -NR^{bi}, in which R^{bi} is hydrogen or (1-3C)alkyl; for a radical of formula Ic, R^{ca} is Ar or Het; and Z^c is oxo, thio, sulfinyl, sulfonyl or imino of formula -NR^{cb}, in which R^{cb} is (1-3C)alkyl or R^{cc}R^{cd}N-(CH₂)_q- in which q is the integer 2 or 3 and in which R^{cc} and R^{cd} are independently

hydrogen or (1-3C)alkyl or the radical $R^{cd}R^{ed}N$ is pyrrolidino, piperidino or morpholino;

for a radical of formula Id, R^{da} is 1, 2 or 3;

for a radical of formula Ie, J^e is oxygen, sulfur or NR^{ea} in which R^{ea} is hydrogen or (1-3C)alkyl; R^{eb} is hydrogen, (1-6C)alkyl which may bear a hydroxy substituent and/or one to three fluoro substituents, (3-6C)alkenyl (in which a vinyl carbon is not bound to nitrogen), 2-hydroxyethyl, (3-7C)cycloalkyl, Ar or Het; R^{ec} is hydrogen, (1-6C)alkyl which may bear a hydroxy substituent and/or one to three fluoro substituents, (3-6C)cycloalkyl, (1-5C)alkoxy (only when J^e is oxygen), (3-6C)cycloalkoxy (only when J^e is oxygen), or an amino group of formula $NR^{ed}R^{ee}$ containing zero to seven carbon atoms in which each of R^{ed} and R^{ee} is independently hydrogen, (1-5C)alkyl or (3-6C)cycloalkyl, or the radical $R^{ed}R^{ee}$ is pyrrolidino, piperidino, morpholino, thiomorpholino (or its S-oxide) or piper-

az nyl (which piperazinyl group may bear a (1-3C)alkyl substituent at the 4-position); for a radical of formula If, J^f is oxygen, sulfur or NR^{fa} in which R^{fa} is hydrogen or (1-3C)alkyl; L^f is a divalent hydrocarbon group in which the 1-position is bound to the carbon bearing the group J^f , the divalent group L^f being selected from trimethylene, cis-propenylene, tetramethylene, cis-butenylene, cis-but-3-enylene, cis,cis-butadienylene, pentamethylene and cis-pentenylene which divalent group L^f itself may bear one or two methyl substituents;

for a radical of formula Ig, Z^g is (1-8C)alkyl or (3-8C)cycloalkyl which may bear one or more substituents selected from the group consisting of halo, (3-6C)cycloalkyl, cyano, nitro, hydroxy, (1-4C)alkoxy, (1-5C)alkanoyloxy, aroyl, heteroaroyl, oxo, imino (which may bear a (1-6C)alkyl, (3-6C)cycloalkyl, (1-5C)alkanoyl or aroyl substituent), hydroxyimino (which hydroxyimino may bear a (1-4C)alkyl or a phenyl substituent on the oxygen), an amino group of formula $NR^{ga}R^{gb}$, an amino group of formula $NR^{gc}R^{gd}$, an amidino group of formula $C(=NR^{ge})NR^{gf}R^{gf}$ and a carbamoyl group of formula $CON(OR^{gh})R^{gi}$, but excluding any radical wherein a hydroxy and an oxo substituent together form a carboxy group, wherein an amino group of formula $NR^{ga}R^{gb}$ contains zero to seven carbon atoms and each of R^{ga} and R^{gb} is independently hydrogen, (1-5C)alkyl or (3-6C)cycloalkyl, or the radical $NR^{ga}R^{gb}$ is pyrrolidino, piperidino, morpholino, thiomorpholino (or its S-oxide) or piperazinyl (which piperazinyl may bear a (1-3C)alkyl substituent group at the 4-position); and wherein R^{gc} is hydrogen or (1-3C)alkyl and R^{gd} is (1-5C)alkanoyl, aroyl or heteroaroyl; or R^{gd} is a group of formula $C(=J^g)NR^{ge}R^{gf}$ in which J^g is oxygen, sulfur, NR^{ge} or CH_2R^{gi} ; and wherein the amino group $NR^{ge}R^{gf}$ contains zero to seven carbon atoms and each of R^{ge} and R^{gf} is independently hydrogen, (1-5C)alkyl or (3-6C)cycloalkyl, or the radical $NR^{ge}R^{gf}$ is pyrrolidino, piperidino, morpholino, thiomorpholino (or its S-oxide) or piperazinyl (which piperazinyl may bear a (1-3C)alkyl substituent at the 4-position) or R^{ge} is hydrogen or (1-4C)alkyl and R^{gf} together with R^{ge} forms an ethylene or trimethylene group; R^{ge} is hydrogen, (1-4C)alkyl or together with R^{gf} forms an ethylene or trimethylene group; R^{gi} is cyano, nitro or SO_2R^{gk} and R^{gk} is (1-4C)alkyl or phenyl; R^{gh} and R^{gi} are independently (1-3C)alkyl; and in which a cyclic group which is a substituent on Z^g or formed by substitution on Z^g may bear one or more (1-3C)alkyl groups on carbon as further substituents; and in which any aryl or heteroaryl group which is a part of the group Z^g may bear one or more halo, (1-4C)alkyl, (1-4C)alkoxy, cyano, trifluoromethyl or nitro substituents;

for a radical of formula Ih, G^h denotes a single bond, a double bond or a divalent hydrocarbon radical; J^h denotes a radical joined to the ring by a single bond if G^h denotes a double bond or, otherwise, a radical joined by a double bond; M^h denotes a heteroatom, a substituted heteroatom, or a single bond; and L^h denotes a hydrocarbon radical in which the 1-position is attached to M^h ; wherein the values of G^h , J^h , M^h and L^h are selected from

(a) G^h is a single bond; J^h is oxo or thioxo; M^h is oxy, thio or NR^{ha} ; and L^h is L^{ha} ;

(c) G^h is a single bond; J^h is NR^{hb} ; M^h is NR^{ha} ; and L^h is L^{ha} ;

(c) G^h is a double bond; J^h is OR^{ha} , SR^{ha} or $NR^{ha}R^{hd}$; M^h is nitrogen; and L^h is L^{ha} ;

(d) G^h is methylene which may bear one or two methyl substituents; J^h is oxo, thioxo or NR^{he} ; M^h is oxy, thio, sulfinyl, sulfonyl or NR^{ha} ; and L^h is L^{hb} ;

(e) G^h is a single bond; J^h is oxo, thioxo or NR^{he} ; M^h is nitrogen; and L^h is L^{he} ;

(f) G^h is methine, which may bear a (1-3C)alkyl substituent; J^h is oxo, thioxo or NR^{he} ; M^h is nitrogen; and L^h is L^{he} ;

(g) G^h is cis-vinylene, which may bear one or two methyl substituents; J^h is oxo, thioxo, or NR^{he} ; M^h is nitrogen; and L^h is L^{he} ; and

(h) G^h is a single bond; J^h is oxo or thioxo; M^h is a single bond; and L^h is L^{hf} ; wherein

R^{ha} is hydrogen or (1-3C)alkyl; R^{hb} is hydrogen, (1-3C)alkyl, cyano, (1-3C)alkylsulfonyl or nitro; R^{hc} and R^{hd} are independently hydrogen or (1-3C)alkyl or the radical $NR^{he}R^{hd}$ is pyrrolidino, piperidino, morpholino, thiomorpholino (or its S-oxide) or piperazinyl (which piperazinyl may bear a (1-3C)alkyl substituent at the 4-position); R^{he} is hydrogen or (1-3C)alkyl; L^{ha} is ethylene, cis-vinylene, trimethylene or tetramethylene which radical L^{ha} itself may bear one or two methyl substituents; L^{hb} is ethylene or trimethylene which radical L^{hb} itself may bear one or two methyl substituents; L^{he} is prop-2-en-1-yliden-3-yl, which radical L^{he} itself may bear one or two methyl substituents; L^{hf} is cis-vinylene, which radical L^{hf} itself may bear one or two methyl substituents;

L^{he} is methine, which radical L^{he} itself may bear a (1-3C)alkyl substituent; and L^{hf} is 4-oxabutan-1,4-diyl;

for a radical of formula Ij, X^j is (1-6C)alkyl, $-CH_2OR^{ja}$, $-CH_2SR^{ja}$, $-CH_2S(O)R^{ja}$, $-CH_2S(O)_2R^{ja}$, $-COR^{ja}$, $-COOR^{ja}$, $-C(=J^{ja})NR^{jb}R^{jc}$, $-C(R^{ja})(OR^{jd})(OR^{je})$, $-CH_2N(R^{ja})C(=J^{ja})R^{jf}$, $-CH_2N(R^{ja})COOR^{ja}$ or $-CH_2N(R^{ja})C(=J^{ja})NR^{jb}R^{jc}$;

B^j is a direct bond and U^j is a hydrocarbon chain in which the 1-position is bound to B^j and U^j is selected from trimethylene, tetramethylene, cis-1-butenylene and cis,cis-butadienylene; or B^j is $N(R^{jh})$ and U^j is a hydrocarbon chain selected from ethylene, trimethylene and cis-vinylene; or B^j is N and U^j is a hydrocarbon chain in which the 1-position is bound to B^j and U^j is cis,cis-prop-2-en-1-ylidin-3-yl; J^j and J^{ja} are independently oxygen or sulfur; R^{ja} , R^{jf} and R^{jh} are independently hydrogen or (1-6C)alkyl; R^{jb} and R^{jc} are independently hydrogen or (1-6C)alkyl; or the radical $NR^{jb}R^{jc}$ is pyrrolidino, piperidino, morpholino, thiomorpholino (or its S-oxide) or piperazinyl (which piperazinyl may bear a (1-3C)alkyl substituent at the 4-position); R^{jd} and R^{je} are independently (1-3C)alkyl or together form a divalent hydrocarbon chain selected from ethylene and trimethylene; R^{ja} is (1-6C)alkyl; and

for a radical of formula Ik, Z^k is a nitrogen linked radical of formula II wherein E^1 , E^2 , E^3 and E^4 form a divalent four membered chain $(-E^1-E^2-E^3-E^4-)$ in which each of E^1 , E^2 , E^3 and E^4 is methine; or in which one or two of E^1 , E^2 , E^3 and E^4 is nitrogen and the remaining E^1 , E^2 , E^3 and E^4 are methine; and further wherein one or more of E^1 , E^2 , E^3 and E^4 which is methine may bear a halo, (1-3C)alkyl, hydroxy, (1-3C)alkoxy, (1-3C)alkylthio, (1-3C)alkylsulfonyl or (1-3C)alkylsulfonyle substituent; and wherein the radicals F^k , G^k , and $I^k(X^k)$ are selected from

(a) G^k is a direct bond, $I^k(X^k)$ is a radical having the formula $=C(Z^k)-$ and F^k is a radical selected from $-CH=$ and $-N=$;

(b) G^k is a direct bond, $I^k(X^k)$ is a radical having the formula $-C(=J^k)-$ and F^k is a radical selected from $-N(R^{kf})-$, $-CH_2-CH_2-$, $-CH=CH-$, $-CH_2-N(R^{kf})-$ and $-CH=N-$;

(c) G^k is a radical having the formula $-CH_2-I^k(X^k)$ is a radical having formula $-C(=J^k)-$ and F^k is selected from $-CH_2-$ and $-N(R^{kf})-$; and

(d) G^k is selected from $-CH_2-$, $-CH_2-CH_2-$, $-CH=CH-$ and $-N=CH-$, $I^k(X^k)$ is a radical having the formula $-C(=J^k)-$ and F^k is a direct bond; wherein

J^k is oxygen or sulfur; Z^k is $-OR^{ka}$, $-SR^{ka}$, $-COR^{ka}$, $-COOR^{ka}$, $-C(=J^{ka})NR^{kb}R^{kc}$ or $-C(R^{ka})(OR^{kd})(OR^{ke})$; J^{ka} is oxygen or sulfur; R^{ka} and R^{kf} are independently hydrogen or (1-6C)alkyl; R^{kb} and R^{kc} are independently hydrogen or (1-6C)alkyl; or the radical $NR^{kb}R^{kc}$ is pyrrolidino, piperidino, morpholino, thiomorpholino (or its S-oxide) or piperazinyl (which piperazinyl may bear a (1-3C)alkyl substituent at the 4-position); R^{kd} and R^{ke} are independently (1-3C)alkyl or R^{kd} and R^{ke} together form ethylene or trimethylene; or Z^k is an imido radical selected from phthalimido, succinimido, maleimido, glutarimido, and 3-oxa-, 3-thia- and 3-azaglutarimido, in which the imido radical may bear one or more (1-3C)alkyl substituents and, in addition, the aromatic portion of the phthalimido may bear one or more halo, hydroxy or (1-3C)alkoxy substituents;

for a radical of formula Im, R^{ma} is 1 or 2; and wherein

for a radical Q1, Ar is a phenyl radical or an ortho-fused bicyclic carbocyclic radical of nine or ten ring atoms in which at least one ring is aromatic, which radical Ar may be unsubstituted or may bear one or more substituents selected from halo, cyano, trifluoromethyl, (1-4C)alkyl, (1-4C)alkoxy, methylenedioxy, hydroxy, mercapto, $-S(O)_nR^{xa}$, (1-5C)alkanoyl, (1-5C)alkanoyloxy, nitro, $NR^{xb}R^{xc}$, $NR^{xd}R^{xe}$, $C(=NR^{xf})NR^{xg}R^{xh}$, $CONR^{xb}R^{xc}$ and $COOR^{xi}$ wherein n is the integer 0, 1, or 2; R^{xa} is (1-6C)alkyl, (3-6C)cycloalkyl or phenyl (which phenyl may bear a halo, trifluoromethyl, (1-3C)alkyl or (1-3C)alkoxy substituent); the radical $NR^{xb}R^{xc}$ contains zero to seven carbons and each of R^{xb} and R^{xc} is independently hydrogen, (1-5C)alkyl or (3-6C)cycloalkyl, or the radical $NR^{xb}R^{xc}$ is pyrrolidino, piperidino, morpholino, thiomorpholino (or its S-oxide) or piperazinyl (which piperazinyl may bear a (1-3C)alkyl substituent at the 4-position) and wherein R^{xd} is hydrogen or (1-4C)alkyl and R^{xe} is (1-5C)alkanoyl, benzoyl; or a group of formula $C(=J^x)NR^{xg}R^{xh}$ in which J^x is oxygen, sulfur, NR^{xf} or CHR^{xi} ; R^{xf} is hydrogen, (1-5C)alkyl; or together with R^{xg} forms an ethylene or trimethylene diradical, the radical $NR^{xg}R^{xh}$ contains zero to 7 carbons and each of R^{xg} and R^{xh} is independently hydrogen, (1-5C)alkyl or (3-6C)cycloalkyl, or the radical $NR^{xg}R^{xh}$ is pyrrolidino, piperidino, morpholino, thiomorpholino (or its S-oxide) or piperazinyl (which piperazinyl may bear a (1-3C)alkyl substituent at the 4-position); or R^{xg} together with R^{xf} forms an ethylene or trimethylene diradical and R^{xh} is hydrogen or (1-5C)alkyl; R^{xi} is cyano, nitro, (1-5C)alkylsulfonyl or phenylsulfonyl; and R^{xi} is hydrogen, (1-5C)alkyl or benzyl; and Het is a radical (or stable N-oxide thereof) attached via a ring carbon of a monocyclic aromatic ring containing five or six ring atoms consisting of carbon and one to four heteroatoms selected from oxygen, sulfur and nitrogen, or an ortho-fused bicyclic heterocycle derived therefrom by fusing a propenylene, trimethylene, tetramethylene or benz-diradical, which radical Het may be unsubstituted or may be substituted on carbon by one

or more of the substituents defined above for Ar and may be substituted on nitrogen by (1-3C)alkyl;

Q² and Q³ are independently hydrogen or (1-3C)alkyl;

Q⁴ is phenyl; which may bear one or two substituents independently selected from halo, trifluoromethyl, hydroxy, (1-3C)alkoxy, (1-3C)alkyl and methylenedioxy; or Q⁴ is thienyl, imidazolyl, benzo[b]thiophenyl or naphthyl any of which may bear a halo substituent; or Q⁴ is biphenyl; or Q⁴ is carbon-linked indolyl which may bear a benzyl substituent at the 1-position; and

Q⁵ is formyl, 4-imidazolidinyl, 3-pyrrolidinyl (wherein the nitrogen may optionally be substituted by a substituent selected from (1-3C)alkyl, acyl, and benzyloxycarbonylaminoacetyl), (3-6C)cycloalkyl, trifluoromethyl, 4-piperidino (wherein the nitrogen may optionally be substituted by a substituent selected from (1-3C)alkyl, and acyl), aryl, heteroaryl, pyrid-1-ylmethyl, fluorenyl, β -styryl, a radical of formula XII-XXII or xanthenyl; or Q⁵ is (1-8C)alkyl which may be substituted by 0-3 substituents selected from aryl, heteroaryl, (aryl)oxy, aryl(1-3C)-alkyl, heteroaryl(1-3C)-alkyl, (1-6C)alkyl, (heteroaryl)oxy, benzyloxy, (3-6C)cycloalkyl, adamantyl, norbornanyl, β -styryl, cyano, trifluoromethyl, oxo, hydroxy, (1-4C)alkoxy, -NR^aR^b, -NC(=O)NR^cR^d, -NC(=O)OR^e, -C(=O)OR^f, -S(O)R^g, -S(O)₂R^h, -NRⁱ, SR^j, and the radicals of formulae XII-XXII;

R^a-R^b are independently selected from hydrogen, acyl, formyl, and (1-4C)alkyl, or the group NR^aR^b may form a cyclic group selected from pyrrolidino, piperidino, morpholino, thiomorpholino (or its S-oxide) or piperazinyl (which piperazinyl may bear a (1-3C)alkyl substituent at the 4-position);

R^c-R^d and R^e are independently selected from hydrogen, phenyl, benzyl, phenethyl and (1-4C)alkyl;

R^g and R^h are independently selected from hydrogen, phenyl, benzyl, phenethyl, β -styryl and (1-4C)alkyl;

Rⁱ is hydrogen, (1-4C)alkyl, acyl or (1-4C)alkoxy;

wherein any aryl or heteroaryl in, or any aryl or heteroaryl portion of, Q⁵, or any aryl or heteroaryl portion of R^a-Rⁱ, may be unsubstituted or may bear 1-5 substituents selected from halo, cyano, trifluoromethyl, (1-4C)alkyl, (1-4C)alkoxy, methylenedioxy, phenoxy, benzyloxy, NR^kR^m, -NS(O)₂aryl (wherein the aryl group may be substituted by 0-3 (1-3C)alkyl groups), hydroxy, -SRⁿ, and nitro; and wherein any β -styryl may optionally be substituted at the β -position by a substituent selected from (1-3C)alkoxy;

wherein R^k-R^m are independently selected from hydrogen, acyl, formyl and (1-4C)alkyl, or the group NR^kR^m may form a cyclic group selected from pyrrolidino, piperidino, morpholino, thiomorpholino (or its S-oxide) or piperazinyl (which piperazinyl may bear a (1-3C)alkyl substituent at the 4-position); and

Rⁿ is hydrogen or (1-3C)alkyl;

or the N-oxide of a piperidino nitrogen in Q¹ indicated by Δ in formulae Ia-I m (or of either basic piperazinyl nitrogen of Q¹ when Z^a is nitrogen);

or a pharmaceutically acceptable salt thereof;

or a quaternary ammonium salt thereof in which the piperidino nitrogen in Q¹ indicated by Δ in formulae Ia-I m (or either basic piperazinyl nitrogen of Q¹ when Z^a is nitrogen) is a quadricovalent ammonium nitrogen wherein the fourth radical on the nitrogen R¹ is (1-4C)alkyl or benzyl and the associated counterion A is a pharmaceutically acceptable anion;

provided that when Q¹ is a pyrrolidino or piperidino radical of formula Id; Q⁴ is not phenyl, 3,4-dimethoxyphenyl, 3,4-(methylenedioxy)phenyl, 3-methoxyphenyl, or 2-thienyl.

A preferred sub-group of compounds of the invention are compounds of formula I as defined above, wherein Q⁵ is aryl, or heteroaryl; or Q⁵ is a radical of formula III wherein: a) R¹ is aryl, heteroaryl, aryl(1-3C)alkyl or heteroaryl(1-3C)alkyl; and R² and R³ are independently hydrogen, aryl, heteroaryl, aryl(1-3C)alkyl, heteroaryl(1-3C)alkyl, (1-6C)alkyl or (3-6C)cycloalkyl; or b) R¹ and R² together with the carbon to which they are attached form a (3-6C)cycloalkyl and R³ is hydrogen or (1-6C)alkyl; wherein any aryl or heteroaryl ring in Q⁵ may be unsubstituted or may bear one or more substituents selected from halo, cyano, trifluoromethyl, (1-4C)alkyl, (1-4C)alkoxy, methylenedioxy, hydroxy and nitro;

or the N-oxide of a piperidino nitrogen in Q¹ indicated by Δ in formulae Ia-I m (or of either basic piperazinyl nitrogen of Q¹ when Z^a is nitrogen);

or a pharmaceutically acceptable salt thereof;

or a quaternary ammonium salt thereof in which the piperidino nitrogen in Q¹ indicated by Δ in formulae Ia-I m (or either basic piperazinyl nitrogen of Q¹ when Z^a is nitrogen) is a quadricovalent ammonium nitrogen wherein the fourth radical on the nitrogen R¹ is (1-4C)alkyl or benzyl and the associated counterion A is a pharmaceutically acceptable anion.

It will be appreciated that a compound of formula I may contain one or more asymmetrically substituted carbon atoms and that such a compound may be isolated in optically active, racemic and/or diastereomeric forms. A compound may exhibit polymorphism. It is to be understood that the present invention encompasses any racemic, optically active, diastereomeric, polymorphic or stereoisomeric form, or mixture thereof, which form possesses NK1 and NK2 antagonist

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properties, it being well known in the art how to prepare optically-active forms (for example, by resolution of the racemic form or by synthesis from optically-active starting materials) and how to determine the NK1 and NK2 antagonist properties by the standard tests known in the art and those described hereinafter.

In this specification R^a , R^b , R^1 , R^2 , et cetera stand for generic radicals and have no other significance. It is to be understood that the generic terms "(1-3C)alkyl" and "(1-6C)alkyl" include both straight and branched chain alkyl radicals but references to individual alkyl radicals such as "propyl" embrace only the straight chain ("normal") radical, branched chain isomers such as "isopropyl" being referred to specifically. A similar convention applies to other generic groups, for example, alkoxy, alkanoyl, et cetera. Halo is fluoro, chloro, bromo or iodo. Aryl denotes a phenyl radical or an ortho-fused bicyclic carbocyclic radical having about nine to ten ring atoms in which at least one ring is aromatic. Heteroaryl encompasses a radical attached via a ring carbon of a monocyclic aromatic ring containing five ring atoms consisting of carbon and one to four heteroatoms selected from oxygen, sulfur and nitrogen or containing six ring atoms consisting of carbon and one or two nitrogens, as well as a radical of an ortho-fused bicyclic heterocycle of about eight to ten atoms derived therefrom, particularly a benz-derivative or one derived by fusing a propenylene, trimethylene or tetramethylene diradical thereto, as well as a stable N-oxide thereof.

Particular values are listed below for radicals, substituents and ranges for a compound of formula I as described above for illustration only and they do not exclude other defined values or other values within defined ranges for the radicals and substituents.

A particular value for Ar is phenyl which may be unsubstituted or may bear a chloro, methyl, methoxy, hydroxy or methylsulfinyl substituent. A particular value for Het is furyl, thienyl, 2-imidazolyl, 1,3,4-oxadiazol-2-yl, pyridyl or pyrimidinyl which ring may be unsubstituted or may bear a chloro, methyl, methoxy, hydroxy, methylsulfinyl, methoxycarbonyl or ethoxycarbonyl substituent. A particular value for aryl is phenyl. A particular value for heteroaryl is furyl, pyridyl or pyrimidinyl. A particular value for halo is chloro or bromo. A particular value for (1-3C)alkyl is methyl, ethyl, propyl or isopropyl; for (1-4C)alkyl is methyl, ethyl, propyl, isopropyl, butyl, isobutyl or t-butyl; for (1-5C)alkyl is methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl or isopentyl; for (1-6C)alkyl is methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, isopentyl, hexyl or isohexyl; and for (1-8C)alkyl is methyl, ethyl, propyl, isopropyl, isopentyl, 1-ethylpropyl, hexyl, isohexyl, 1-propylbutyl, or octyl. A particular value for (3-6C)cycloalkyl is cyclopropyl, cyclopentyl or cyclohexyl; for (3-7C)cycloalkyl is cyclopropyl, cyclopentyl, cyclohexyl or cycloheptyl; and for (3-8C)cycloalkyl is cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl. A particular value for (3-6C)alkenyl is allyl, 2-butenyl or 3-methyl-2-butenyl. A particular value for (1-4C)alkanoyl is formyl, acetyl, propionyl, butyryl or isobutyryl; and for (1-5C)alkanoyl is formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl or pivaloyl.

A more particular value for Ar is phenyl which may be unsubstituted or may bear a methoxy, hydroxy or methylsulfinyl substituent. A more particular value for Het is pyridyl or pyrimidinyl which ring may be unsubstituted or may bear a methoxy, hydroxy or methylsulfinyl substituent. A more particular value for heteroaryl is pyridyl. A more particular value for halo is chloro. A more particular value for (1-3C)alkyl is methyl; for (1-4C)alkyl is methyl or ethyl; for (1-5C)alkyl is methyl, ethyl, propyl or isopropyl; for (1-6C)alkyl is methyl, ethyl, propyl, isopropyl, butyl, isobutyl or t-butyl; and for (1-8C)alkyl is methyl, ethyl, propyl, isopropyl, 1-ethylpropyl or 1-propylbutyl. A more particular value for (3-6C)cycloalkyl is cyclopropyl or cyclopentyl; for (3-7C)cycloalkyl is cyclopropyl or cyclopentyl; and for (3-8C)cycloalkyl is cyclopropyl, cyclopentyl, cyclohexyl or cycloheptyl. A more particular value for (3-6C)alkenyl is allyl. A more particular value for (1-4C)alkanoyl is formyl or acetyl; and for (1-5C)alkanoyl is formyl, acetyl, propionyl, butyryl or isobutyryl.

A particular value for Q^1 is 4-hydroxy-4-phenylpiperidino, 4-acetamido-4-phenylpiperidino, 4-(benzylsulfinyl)-4-methoxypiperidino, 4-(2-methylsulfinylphenyl)piperidino, or 4-(2-oxoperhydropyrimidin-1-yl)piperidino; Q^2 is methyl, ethyl or propyl; for Q^3 is hydrogen; for Q^4 is 3,4-dichlorophenyl or 3,4-methylenedioxyphenyl; and for Q^5 is phenyl, benzy, 2-methoxyphenyl, 3,5-bis(trifluoro-methyl)benzyl, 2-isopropoxybenzyl and 3,5-bis(trifluoromethyl)phenyl.

A particular group of compounds of formula I are compounds wherein Q^1 is a radical selected from the group of radicals of formulae Ia, Ib, Ic, Id, Ig, Ih, Ij, Ik and Im,

A particular group of compounds of formula I are compounds wherein Q^1 is selected from radicals of formulae Ie, If, Ig, Ih, Ij, Ik and Im.

A particular group of compounds of formula I are compounds of formula VIII wherein, Q^1 is 4-hydroxy-4-phenylpiperidino, 4-acetamido-4-phenylpiperidino, 4-(benzylsulfinyl)-4-methoxypiperidino, or 4-(2-oxoperhydropyrimidin-1-yl)piperidino; Q^2 is (1-3C)alkyl; and Q^5 is phenyl, benzyl, 2-methoxyphenyl, 2-methoxybenzyl, 3,5-bis(trifluoromethyl)phenyl, 3,5-bis(trifluoro-methyl)benzyl, 3,5-dimethylphenyl, 3,5-dimethylbenzyl, 3,5-dichlorophenyl, 3,5-dichlorobenzyl, 3,5-dimethoxyphenyl, or 3,5-dimethoxybenzyl.

A particular group of compounds of formula I are compounds wherein Q^5 is formyl, 4-imidazolidinyl, 3-pyrrolidinyl (wherein the nitrogen may optionally be substituted by a substituent selected from (1-3C)alkyl, acyl, and benzyloxy-carbonylaminoacetyl), (3-6C)cycloalkyl, trifluoromethyl, 4-piperidino (wherein the nitrogen may optionally be substituted by a substituent selected from (1-3C)alkyl, and acyl), aryl, heteroaryl, pyrid-1-ylmethyl, fluorenyl, β -styryl, a radical of formula XI-XXII or xanthenyl; or Q^5 is (1-6C)alkyl which may be substituted by one substituent selected from aryl, heteroaryl, (aryloxy, (heteroaryl)oxy, benzyloxy, (3-6C)cycloalkyl, adamantyl, norbornanyl, β -styryl, cyano, trifluorome-

thesis of known, structurally similar compounds and techniques which are analogous to the above described procedures or the procedures described in the Examples. The starting materials and the procedures for their preparation are additional aspects of the invention.

A convenient intermediate for the preparation of a compound of formula I is an amine of formula IV, which can be prepared as shown in Scheme I, from a piperidine of formula Q¹-H, wherein Q¹ is selected from formulae Ia-I m. Coupling of an aldehyde of formula VI with trimethylsilyl cyanide and a piperidine of formula Q¹-H in the presence of catalytic zinc iodide gives a nitrile of formula VII. Reduction of the nitrile yields an amine of formula IV, wherein Q² is hydrogen.

Piperidines of formula Q¹-H can be prepared from readily available starting materials using known synthetic methods. For example, the preparation of piperidines of formula Q¹-H is disclosed in European Patent Application, Publication Number (EPA) 428434, EPA 474561, EPA 512901, EPA 512902, EPA 515240 and EPA 559538, as well as in WO 94/10146. As will be clear to one skilled in the art, a variety of sequences are available for preparation of the starting materials, and the sequences leading to the starting materials and products of the invention may be altered if appropriate considerations regarding the synthetic methods and radicals present are followed.

The utility of a compound of the invention or a pharmaceutically acceptable salt thereof (hereinafter, collectively referred to as a "Compound") may be demonstrated by standard tests and clinical studies, including those disclosed in the EPA publications noted above, and those described below.

SP Receptor Binding Assay (Test A)

The ability of a Compound of the invention to antagonize the binding of SP at the NK1 receptor may be demonstrated using an assay using the human NK1 receptor expressed in Mouse Erythroleukemia (MEL) cells. The human NK1 receptor was isolated and characterized as described in: B. Hopkins, et al. "Isolation and characterization of the human lung NK1 receptor cDNA" *Biochem. Biophys. Res. Comm.*, 1991, **180**, 1110-1117; and the NK1 receptor was expressed in Mouse Erythroleukemia (MEL) cells using a procedure similar to that described in Test B below.

In general, the Compounds of the invention which were tested demonstrated statistically significant binding activity in Test A with a K_i of 1 μM or much less typically being measured.

Neurokinin A (NKA) Receptor Binding Assay (Test B)

The ability of a Compound of the invention to antagonize the binding of NKA at the NK2 receptor may be demonstrated using an assay using the human NK2 receptor expressed in Mouse Erythroleukemia (MEL) cells, as described in: Aharony, D. et al. "Isolation and Pharmacological Characterization of a Hamster Neurokinin A Receptor cDNA" *Molecular Pharmacology*, 1994, **45**, 9-19. In an initial use of this assay, the IC₅₀ measured for the standard compound L-659,877 was found to be 30 nM versus ³H-NKA binding to MELM.

The selectivity of a Compound for binding at the NK1 and the NK2 receptors may be shown by determining its binding at other receptors using standard assays, for example, one using a tritiated derivative of NKB in a tissue preparation selective for NK3 receptors. In general, the Compounds of the invention which were tested demonstrated statistically significant binding activity in Test B with a K_i of 10 μM or less typically being measured.

Rabbit Pulmonary Artery: NK1 in vitro functional assay (Test C)

The ability of a Compound of the invention to antagonize the action of the agonist, Ac-[Arg⁶, Sar⁹, Met(O₂)¹¹]SP (6-11) (designated ASMSP) in a pulmonary tissue may be demonstrated using a functional assay which is carried out under conditions similar to those described in: Ermonds-Ait, X., et al. "In vitro and in vivo biological activities of Sr 140333, a novel potent non-peptide tachykinin NK₁ receptor antagonist" *Eur. J. Pharmacol.*, 1993, **250**, 403-413; and which is carried out as follows.

Male New Zealand white rabbits are killed by lethal injection (Nembutal, 60 mg/kg into a cannulated ear vein). Heparin, 0.0025 ml/kg of a 1000 U/ml solution, is injected into the ear vein prior to nembutal in order to decrease blood coagulation. The left and right branches of the pulmonary artery are isolated from the rest of the lung tissue and cut in half to provide four ring segments from each animal. The segments, with intact endothelium, are suspended between stainless steel stirrups and placed in water-jacketed (37.0°C) tissue baths containing physiological salt solution of the following composition (mM): NaCl, 119.0; KCl 4.6; CaCl₂, 1.8; MgCl₂, 0.5; NaH₂PO₄, 1.0; NaHCO₃, 25.0; glucose 11.0; indomethacin 0.005 (to inhibit cyclooxygenase); and dl-propranolol, 0.001 (to inhibit β-adrenergic receptors); gassed continuously with 95% O₂-5% CO₂. Initial tension placed on each tissue is 2 grams, which is maintained throughout a 0.5 hour equilibration period. Changes in tension are measured on a Grass polygraph via Grass FT-03 force transducers.

Thiorphan, 1 X 10⁻⁶M (to inhibit E.C.3.4.24.11), and a selective NK2 antagonist (to inhibit NK₂ receptors) such as for example, an antagonist described in WO 94/148,184, EPA 0625509, EPA 0630887, or the antagonist SR48968 (3

X 10⁻⁸M), are added to the tissue baths along with the test compound or its vehicle 90 minutes before the NK₁ receptor agonist, Ac-[Arg⁶, Sar⁹, Met (O₂)¹¹]SP(6-11) (designated ASMSP). Phenylephrine, 3 X 10⁻⁶M, is added in order to induce tone in the tissue. One hour after introducing phenylephrine, cumulative concentration response effects of ASMSP are obtained and papaverine, 1 X 10⁻³M, is added at the end of each experiment to determine the maximum magnitude of relaxation (defined as 100%).

Potencies of the compounds are determined by calculating the apparent dissociation constants (K_B) for each concentration tested using the standard equation:

$$K_B = [\text{antagonist}] / (\text{dose ratio} - 1)$$

where dose ratio = antilog[(agonist-log molar EC₅₀ without compound) - (agonist-log molar EC₅₀ with compound)]. The K_B values are converted to the negative logarithms and expressed as -log molar K_B (i.e. pK_B). The potency of the agonist is determined at 50% of its own maximum relaxation in each curve. The EC₅₀ values are converted to negative logarithms and expressed as -log molar EC₅₀. Maximum relaxation responses to ASMSP are determined by expressing the maximum response to the agonist as a percentage of the relaxation caused by papaverine.

Guinea Pig Trachea Assay: NK₂ in vitro functional assay (Test D)

The ability of a Compound of the invention to antagonize the action of the agonist, [β-Ala⁸]-Neurokinin A(4-10) (designated BANK), in a pulmonary tissue may be demonstrated using a functional assay in guinea pig trachea which is carried out under conditions similar to those described in: Ellis, J.L., et al., "Pharmacological examination of receptors mediating contractile responses to tachykinins in airways isolated from human, guinea pig and hamster" J. Pharmacol. Exp. Ther., 1993, 267, 95-101; and which is carried out as follows.

Male guinea pigs are killed by a sharp blow to the back of the head followed by exsanguination. The trachea are removed, trimmed of excess tissue (including removal of epithelium) and cut in spiral fashion. Each longitudinally cut tracheal segment is suspended as a strip in a water-jacketed (37.5°C) tissue bath containing a physiological salt solution of the following composition (mM): NaCl, 119; KCl 4.6; CaCl₂, 1.8; MgCl₂, 0.5; NaH₂PO₄, 1; NaHCO₃, 25; glucose, 11; and indomethacin, 0.005 (to inhibit cyclooxygenase); gassed continuously with 95% O₂-5% CO₂. Initial tension placed on each tissue is 5 g, which is maintained throughout a 0.5 hour equilibration period before addition of other drugs. Contractile responses are measured on a Grass polygraph via Grass FT-03 force transducers.

Tissues are challenged once with a single concentration of capsaicin (1 X 10⁻⁶M) and washed extensively before addition of a selective NK₁ antagonist, such as for example (±)-CP96345 (3 X 10⁻⁷ M) (to block NK₁ receptors) and thiophan, 1 X 10⁻⁶M (to block E.C.3.4.24.11). Cumulative addition of the NK₂ agonist [β-Ala⁸]-Neurokinin A(4-10) (designated BANK) is begun 35 minutes after addition of thiophan. Test compound is added 120 min before BANK.

Potencies of the compounds are evaluated by calculating apparent dissociation constants (K_B) for each concentration tested using the standard equation:

$$K_B = [\text{antagonist}] / (\text{dose ratio} - 1)$$

where dose ratio = antilog[(agonist -log molar EC₅₀ without compound) - (agonist -log molar EC₅₀ with compound)]. The K_B values are converted to the negative logarithms and expressed as -log molar K_B (i.e. pK_B). The potency of BANK is determined at 50% of its own maximum response level in each curve. The EC₅₀ values are converted to the negative logarithms and expressed as -log molar EC₅₀. Maximum contractile responses to BANK are determined by expressing the maximum response to BANK as a percentage of the initial contraction caused by capsaicin.

In general, the Compounds of the invention which were tested demonstrated functional activity in Tests C and D, with a pK_B of 5 or greater typically being measured in each test. For Example, the compound of Example 2 demonstrated a pK_B of 6.2 in Test C.

Guinea Pig Labored Abdominal Breathing (Dyspnea) Assay: NK₁ and NK₂ in vivo functional assay (Test E)

The activity of a compound as an antagonist of NK₁ or NK₂ receptors also may be demonstrated in vivo in laboratory animals, for example by adapting a routine guinea pig aerosol test described for evaluation of leukotriene antagonists in: Snyder, et al. "Conscious guinea-pig aerosol model for evaluation of peptide leukotriene antagonists" J. Pharmacol. Meth., 1985, 19, 219; which is carried out as follows.

Using the clear plastic chamber described previously by Snyder et al. to secure guinea pigs for a head-only aerosol exposure to bronchoconstrictor agonists, agonist is administered by aerosol to six conscious guinea pigs simultaneously during each maneuver. The tachykinin NK₁-selective agonist ASMSP or the tachykinin NK₂-selective agonist, BANK, 3 X 10⁻⁶M of either, is aerosolized from a Devilbiss Model 25 ultrasonic nebulizer into an air stream entering the chamber at a rate of 2 L/minute.

Guinea pigs (275 - 400 g) are fasted for approximately 16 hours prior to experimentation. Compounds to be evaluated for blockade of effects of ASMSP or BANK or their vehicle (10% PEG400 in saline) are given by p.o., i.v. or

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIRECCION DE NUEVAS CREACIONES

2020
Bogotá, D.C.

Abogado
CARLOS R. OLARTE

ASUNTO	Radicación	05112548
	Trámite	011
	Evento	379
	Actuación	411
	Oficio	209243
	Folios	012

Patente de Invención	☒	Patente de Modelo de Utilidad	☐
Vía Nacional	☐		
Vía PCT (fase nacional)	☒	Cap. I	☐ Cap. II ☒
No. Sol. Internacional	PCT/EP2004/005005		
Fecha de Presentación Internal.	Mayo 7 de 2004.		

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: 133 a 262 | como se radicó inicialmente |
| 1.2 | <u>Reivindicaciones:</u> | Folios: 263 a 267
Folios: 309 a 310 | como se radicó inicialmente
radicado 2009/03/25. |
| 1.3 | <u>Prioridad:</u> | Mayo 9 de 2003; GB; 0310724.0 | |
| 1.4 | Respuesta del solicitante Folios: 305 a 310. | | |

2. Objeto de la invención

Título de la invención: Derivados de amina cíclica, procesos para su preparación y composiciones farmacéuticas que contienen los mismos.

Problema Técnico Planteado: Necesidad de nuevos compuestos útiles como antagonistas de receptores de taquiquininas(NK1) y como inhibidores selectivos de la reabsorción de serotonina (SSRIs).

Solución: Compuesto de la reivindicación 1 ó una sal farmacéuticamente aceptable del mismo.

IPC: C07D211/34, 405/12,405/04, A61K31/445,31/445,31/4465, A61P25/22,25/00

3. De la solicitud de Patente

3.1. Reivindicaciones (artículo 30 D 486)

La reivindicación 2, esta comprendida en la reivindicación 1, dado que en esta, ya se reclama una sal del compuesto N-[1-(3-cloro-1-naftalenil)etil]-2-[4-(4-fluorofenil)-1-metil-4-piperidinil]-N-metilacetamida, estaría incluida la sal de clorhidrato.

Las reivindicaciones 5 y 6 que son de un compuesto se deben definir por sus características estructurales y no en términos de su proceso de obtención.

4. Determinación del Estado de la Técnica

La fecha que se ha tenido en cuenta para determinar el Estado de la Técnica es:

Fecha de presentación de la solicitud prioritaria: Mayo 9 de 2003.

Teniendo en cuenta la fecha indicada se realizó la búsqueda en el estado de la técnica de documentos relacionados con la solicitud encontrándose los siguientes documentos más relevantes:

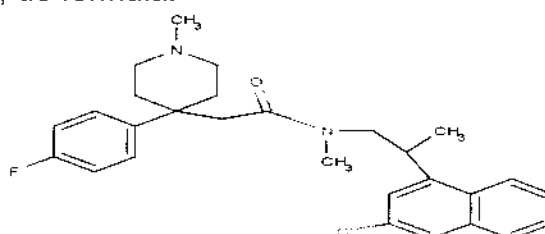
Nº	Documento	Título	Fecha de publicación*
D3	EP0709375	Therapeutic heterocycles	01/05/1996

D3 (folios: 312-319)

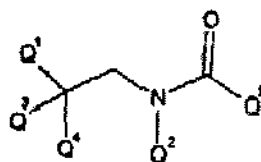
5. Análisis de patentabilidad (artículo 14 D486)

5.2 Nivel inventivo (artículo 18 D486)

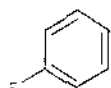
La reivindicación 1 consiste en el compuesto: N-[1-(3-cloro-1-naftalenil)etil]-2-[4-(4-fluorofenil)-1-metil-4-piperidinil]-N-metilacetamida ó una sal farmacéuticamente aceptable del mismo, de formula:



El Estado de la Técnica más cercano es D3 (EP 0709375) que da a conocer compuestos heterociclos de formula (I), derivados de aminas ciclicas, así como sus sales farmacéuticamente aceptables y sus enantiómeros (abstract, folio 312, folios 313-319, pgs 2-9), como antagonistas de receptores de taquiquininas (NK1)



El compuesto objeto de esta solicitud se diferencia de los compuestos de D3, en que en el primero, existe un H en el radical equivalente a Q1 en D3 y el flurofenilo



sustituyendo el piperidino.

Sin embargo introducir un H, en el radical equivalente a Q1, en los compuestos que se daban a conocer en D3, causa que el compuesto reclamado tenga la misma actividad: como antagonista de receptores de taquiquininas (NK1); como la que presentan los compuestos de la anterioridad citada.

El Problema Técnico Objetivo era cómo obtener el compuesto. N-[1-(3-cloro-1-naftalenil) etil]-2-[4-(4-fluorofenil)-1-metil-4-piperidinil]-N-metilacetamida ó una sal farmacéuticamente aceptable del mismo, derivado de amina cíclica, con actividad como antagonista del receptor de taquiquininas(NK1) y como inhibidor selectivo de la reabsorción de serotonina (SSRIs).

Dado que el compuesto reclamado muestra actividad como antagonista de receptores de taquiquininas(NK1), al igual que los compuestos de la anterioridad (folios: 318-319, pgs 8-9), pero, que no existe evidencia de que el compuesto reivindicado sea, además, un inhibidor selectivo de la reabsorción de serotonina (SSRIs), como los compuestos divulgados en D3; por lo tanto el compuesto reclamado no muestra una ventaja, sobre los ya divulgados, convirtiéndose en una alternativa, sin presentar algún paso inventivo.

Por lo anterior las reivindicaciones 1 y sus dependientes 2-8, no presentan altura inventiva.

6. Conclusión:

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

Nº	Documento Nº	Reivindicaciones afectadas	Requisito que afecta
D3	EP0709375	1-8	Nivel Inventivo

7. Respuesta a los argumentos del solicitante:

-El solicitante argumenta que el documentos D1 no afecta el nivel inventivo de la presente solicitud ya que " se refiere a derivados de 4(alquil, alquenil/Cy)-4-carboxamido piperidinas N- sustituidas, con actividad como agonistas de VLA-4 y/o $\alpha 4\beta 7$, útiles para inhibir o prevenir las patologías asociadas a la dehensión celular... nada en D1 sugiere piperidinas que presenten un grupo carboxamida en la posición 4 (acetamida, en el caso del compuesto dela reivindicación 1), serían útiles como antagonistas NK1 y como inhibidores de la recaptación de la serotonina "

Al respecto se aclara que la diferencia estructural, en el compuesto reclamado, en donde existe un grupo CH_3 unido al N de la piperidina; es relevante en cuanto a la actividad farmacológica distinta del compuesto de la solicitud con respecto a los de esta anterioridad, ó sea que se acepta el argumento en cuanto a que D1 no sugiere que el compuesto reclamado sea útil como antagonista NK1 y como inhibidor de la recaptación de la serotonina, no afectando el nivel inventivo de la presente solicitud.

-El solicitante argumenta que el documento D2 no afecta el nivel inventivo de la presente solicitud ya que " las 4-aminometil-piperidinas N sustituidas son antagonistas de MCH y no serían útiles como antagonistas del receptor NK1 y como inhibidores de la recaptación de la serotonina... así las cosas una persona medianamente versada en la materia no se inclinaría hacia la producción de piperidinas que comprenden específicamente un metilo directamente unido al átomo de N del ciclo (a diferencia de D1) y una carboxamida en la posición 4 (a diferencia de D2).

Al respecto se aclara que la diferencia estructural, en el compuesto reclamado, en donde existe un grupo CH_3 unido al N de la piperidina y un grupo carboxamida o acetamida en la posición 4 del anillo de la piperidina; se ve reflejada en cuanto a la actividad farmacológica del compuesto de la solicitud, distinta a los compuestos de D2; así mismo, se acepta el argumento en cuanto a que D2 no sugiere que el compuesto reclamado sea útil como antagonista NK1 y como inhibidor de la recaptación de la serotonina, por lo cual no se ve afectado el nivel inventivo de la presente solicitud.

Por lo anterior se tomo en cuenta el nuevo capítulo reivindicatorio para realizar el presente análisis de patentabilidad, con un nuevo documento D3.

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 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

Directora de Nuevas Creaciones (C)

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

23 JUL. 2010