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SEÑOR

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

E. S. D.

Prostano Ximena Basco

REF: Expediente 09 055.461.

TÍTULO SOLICITADO: MÉTODOS PARA EL TRATAMIENTO DEL ABUSO,
ADICCIÓN Y DEPENDENCIA DEL ALCOHOL.

PUBLICACIÓN: Gaceta 619 de 19/08/2010, N° de publicación 520.

PRIORIDAD: US 60/861.375 de 28/11/2006.

SOLICITANTE: JANSSEN PHARMACEUTICA N.V.

APODERADO: DILIA MARÍA RODRÍGUEZ D'ALEMAN.

TRÁMITE: SUSTENTACION DE OPOSICIÓN

JOSÉ LUIS REYES VILLAMIZAR, mayor de edad y vecino de Bogotá, identificado como aparece al pie de mi firma, abogado en ejercicio, titular de la tarjeta profesional número 44655 del Consejo Superior de la Judicatura, actuando en nombre y representación de **LEGRAND S.A.**, sociedad constituida y vigente de conformidad con las leyes colombianas, con domicilio en Bogotá, en los términos y para los efectos del poder y del certificado de existencia y representación legal adjuntos, y estando dentro del plazo establecido por el artículo 42 de la Decisión 486 de 2000, muy respetuosamente me permito sustentar la oposición presentada oportunamente ante ese Despacho, en los siguientes términos:

I. RATIFICACION.

Comendidamente me permito presentar los argumentos planteados en la oposición respectiva, los cuales, como se dijo en su momento, demuestran que la solicitud

de la referencia incumple los requisitos de patentabilidad establecidos por los artículos 14, 16, 18 y 20 literal d) de la Decisión 486 de 2000, y que por ello no merece recibir el beneficio patentario.

II. COMPLEMENTO DE INFORMACIÓN

En primer lugar, la Decisión 486 de la Comunidad Andina de Naciones en su aparte d) del artículo 20 del capítulo I, acerca de los requisitos de patentabilidad, menciona que *“no serán patentables los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnóstico aplicados a los seres humanos o a animales”*, y si tenemos en cuenta que la solicitud en cuestión reivindica un método de tratamiento del abuso, adicción o dependencia del alcohol, tal como lo señala en sus reivindicaciones 1 a 23, queda claramente expuesta la improcedencia directa para otorgar el privilegio de patente de invención a esta solicitud.

En otro aspecto, y esta vez refiriéndonos a la combinación entre los compuestos de fórmula I y I-A con otros fármacos útiles en el tratamiento de adicciones, es relevante mencionar el concepto de la Doctora en Bioquímica Silvia Susana Giarcovich¹ en su opinión escrita a cerca de “Asociaciones y Patentes” en donde afirma que las asociaciones farmacológicas están restringidas por ciertos principios y lineamientos preestablecidos por varias entidades, puesto que dichas combinaciones deben estar bajo el precepto de eficacia, seguridad y eficiencia terapéutica, veamos:

“3.3.2. Lineamientos FDA:

A continuación se mencionarán lineamientos que la agencia sanitaria de EEUU ha establecido para el caso de los llamados “*Combination Drug Products*”:

3.3.2.1. CFR

El CFR establece la política en relación a las combinaciones de drogas a dosis fija para humanos en 21CFR300.50. Allí se establece que dos o más drogas pueden ser combinadas en una única unidad posológica cuando cada componente hace una contribución al efecto propuesto y la dosis de cada componente es tal que la

¹ Profesora Regular Adjunta del Departamento de Farmacología de la Facultad de Farmacia y Bioquímica de la UBA y Directora Técnica y Gerente de Estudios Clínicos de DIFFUCAP-EURAND SACIFI

combinación es segura y efectiva (se consideran casos especiales cuando se busca aumentar la seguridad y eficacia del principal componente o minimizar su potencial abuso).

**3.3.2.2. Guía "OTC Combination of Drug Products"
[Docket No. 78D-0322]²:**

Esta guía establece en detalle la política de la agencia para combinar dos o más ingredientes activos OTC, seguros y eficaces y caracteriza diferentes tipos de asociaciones de OTC:

- Ingredientes activos de diferentes categorías terapéuticas para tratar distintos síntomas simultáneamente: Sólo se acepta esta asociación si cada ingrediente está presente dentro de su rango de seguridad y eficacia.
- Ingredientes activos de la misma categoría terapéutica que tienen distintos mecanismos de acción para tratar los mismos síntomas o condición: Sólo se acepta esta asociación si es mejor o igual que cada ingrediente solo en su dosis terapéutica y también pueden usarse a dosis subterapéuticas si corresponde.
- Ingredientes activos de la misma categoría terapéutica que tienen el mismo mecanismo de acción: Estos no deberían ser combinados a menos que haya alguna ventaja con respecto a los ingredientes simples (mayor eficacia, seguridad, aceptación del paciente o calidad de la formulación).
- Ingredientes considerados adyuvantes, que aumenten o alteren el efecto de otro ingrediente activo, serán, considerados ingredientes activos.

3.3.2.3. Guía Draft "Current GMP for Combination Products":

Este documento provee una guía para la industria y para el *staff* de la FDA acerca de la aplicabilidad de la cGMP para las asociaciones (*combination products*) y define a un *combination product*, de acuerdo al CFR (21CFR3.2(e)), de forma que no sólo involucra drogas sino *devices*:

Un producto combinado es un producto compuesto de cualquier combinación de una droga y un dispositivo; un producto biológico y un dispositivo; una droga y un producto biológico; o una droga, dispositivo, y un producto biológico. Bajo 21 CFR 3.2 (e), un producto de combinación incluye:

² Anunciada en el Federal Register (1978), Vol. 43, No. 229.

1. *Un producto que comprende dos o más componentes regulados (i.e., droga/dispositivo, biológico/dispositivo, droga/biológico, o droga/dispositivo/biológico) que son combinados físicamente, químicamente, o de otra forma, o mezclados y producidos como una entidad única;*
2. *Dos o más productos separados, empaquetados juntos en un solo paquete, o como una unidad comprendiendo droga y productos del dispositivo, dispositivo y productos biológicos, o biológico y productos de droga;*
3. *Una droga, dispositivo, o producto biológico empaquetado separadamente que, de acuerdo a su plan de investigación o el etiquetado propuesto, es destinado para utilizarse únicamente con una droga, dispositivo, o producto biológico aprobada especificada individualmente, dónde al mismo tiempo ambos son deben estar aceptados para la indicación o efecto y donde, luego de la aprobación del producto propuesto, el etiquetado del producto aprobado necesitaría ser cambiado (e.g., para reflejar un cambio en la indicación, forma farmacéutica, dosis, ruta de administración, cambio significativo en la posología); ó*
4. *Cualquier droga en investigación, dispositivo, o producto biológico empaquetado separadamente que, de acuerdo al etiquetado propuesto es para utilizarse únicamente con otra droga en investigación especificada, dispositivo, o producto biológico, dónde a la vez se requiere que ambos sean aceptados para la misma indicación, uso y efecto.*

Además, dentro de esta guía es muy interesante el concepto de "parte constitutiva de un *combination product*" porque especifica su identidad regulatoria como droga, *device* o producto biológico.

3.3.2.4. Guía Draft "Combination Products Timeliness of Premarket Reviews":

Esta guía provee información a un postulante a reclamar la resolución de una disputa acerca de la duración de la revisión de una postulación referida a un producto combinado. Es una guía referida simplemente a un problema administrativo que demuestra cuán regulado se halla este ámbito que tiene una oficina destinada, la Office of Combination Products.

3.3.3. Lineamientos EMEA: Guía "Fixed Combination Medicinal Products":

Esta guía propone evaluar las potenciales ventajas de la asociación en cuanto a mejoramiento de la relación riesgo/beneficio y a simplificación de la terapia. Asimismo, establece criterios a respetar y requisitos a cumplimentar, tanto generales como particulares. Dentro de los particulares hace especial referencia a:

- La indicación.
- Los estudios farmacodinámicos y farmacocinéticos.
- Eficacia y Seguridad: En este caso diferencia dos escenarios concretos:

a) Cuando la combinación fija corresponde exactamente a combinaciones que están ya en uso difundido, un análisis de los datos bibliográficos bien fundamentados debería ser presentado. Con tal que los datos estén bien documentados, este análisis puede ser útil en reducir la cantidad de ensayos clínicos a ser realizada y podría facilitar la selección de dosis para cada sustancia y el rango de dosis propuesto en la combinación fija.

b) Cuando la combinación fija es esencialmente nueva (las sustancias activas no son usualmente combinadas, la composición cuantitativa es inusual entre sustancias usualmente combinadas o una sustancia enteramente nueva), los datos necesarios son similares a los de una nueva entidad química en la situación donde la combinación fija será propuesta (primero línea o segunda de la línea de terapia). La existencia de experiencia con las sustancias debería ser tenida en cuenta.

y especifica Régimen de dosis y Composición, Ensayos Terapéuticos y Aspectos de Seguridad.

- Paquetes combinados de diferentes productos medicinales para administración simultánea o secuencial.

Conclusión:

Las diferentes agencias sanitarias a nivel internacional han regulado fuertemente el registro de asociaciones de forma de garantizar la seguridad y eficacia de las mismas y la buena calidad en su elaboración. Todo estudio, investigación o análisis derivados de estos requisitos representan procedimientos de rutina y no originales ideas llevadas a la práctica."

Además, se puede considerar que todo efecto sinérgico o terapéutico entre fármacos no se refiere propiamente a una invención, sino que corresponde mejor a la categoría de un descubrimiento, dado que dicho efecto sinérgico o terapéutico conseguido mediante la combinación de fármacos ocurre dentro del organismo y se hace evidente a través de los respectivos ensayos preclínicos y/o clínicos por los que todo fármaco o combinación de fármacos se deben evaluar. Así mismo es importante volver a enfatizar en que la combinación de fármacos para tratar ciertas

patologías, hace parte de las actividades de la profesión médica, y no de las actividades industriales.

También podemos hacer evidente la ausencia de nivel inventivo de la solicitud colombiana, a través de algunos documentos que revelan información acerca de los mismos compuestos reivindicados por la solicitud en cuestión, veamos:

La publicación internacional WO/2000/006545 publicada el 10 de febrero de 2000 revela:

The nociceptin receptor ORL-1 has been shown to be involved with modulation of pain in animal models. ORL-1 (the nociceptin receptor) was discovered as an "orphan opioid-like receptor" i.e. a receptor whose ligand was unknown. The nociceptin receptor is a G protein coupled receptor. While highly related in structure to the three classical opioid receptors, i.e. the targets for traditional opioid analgesics, it is not activated by endogenous opioids. Similarly, endogenous opioids fail to activate the nociceptin receptor. Like the classical opioid receptors, the nociceptin receptor has a broad distribution in the central nervous system.

(...)

In other words, the invention relates to the use of compounds of claim 1 in the treatment of pain, anxiety, cough, asthma, alcohol abuse or depression, and to the use of a nociceptin receptor ORL-1 agonist, alone or in combination with a second agent for treating cough, allergy or asthma symptoms.

(...)

Como se puede apreciar, en esta anterioridad se revela la utilidad de los agonistas del receptor nociceptivo ORL-1 en el tratamiento de trastornos relacionados al abuso de alcohol, teniendo este tipo de agonistas el mismo mecanismo de acción que los compuestos revelados en la solicitud colombiana en trámite.

La publicación internacional WO/2004/022558 publicada el 14 de marzo de 2004 revela:

(57) Abstract: The present invention is directed to novel hydroxy alkyl substituted 1, 3, 8-triazaspiro[4.5]decan-4-one derivatives of the general formula: wherein all variables are as defined herein, useful in the treatment of disorders and conditions mediated by the ORL-1 G-protein coupled receptor. More particularly, the compounds of the present invention are useful in the treatment of disorders and conditions such as anxiety, depression, panic, dementia, mania, bipolar disorder, substance abuse, neuropathic pain, acute pain, chronic pain migraine, asthma, cough, psychosis, schizophrenia, epilepsy, hypertension, obesity, eating disorders, cravings, diabetes, cardiac arrhythmia, irritable bowel syndrome, Crohn's disease, urinary incontinence, adrenal disorders, attention deficit disorder (ADD), attention deficit hyperactivity disorder (ADHD), Alzheimer's disease, for improved cognition or memory and for mood stabilization.

(...)

Tulshian et al. in PCT publication WO00/06545 disclose high affinity ligands for the nociceptin receptor ORL-1 and the use of said compounds as nociceptin receptor inhibitors useful in the treatment of pain, anxiety, cough, asthma, depression and alcohol abuse

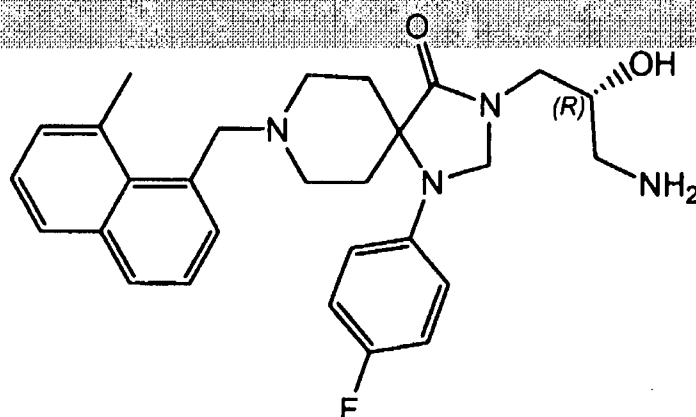
(...)

We now describe novel small molecule modulators of the ORL-1 receptor, useful for the treatment of disorders and conditions mediated by the ORL-1 receptor, such as anxiety, depression, panic, dementia, mania, bipolar disorder, substance abuse, neuropathic pain, acute pain, chronic pain, migraine, asthma, cough, psychosis, schizophrenia, epilepsy, hypertension, obesity, eating disorders, cravings, diabetes, cardiac arrhythmia, irritable bowel syndrome, Crohn's disease, urinary incontinence, adrenal disorders, attention deficit disorder (ADD), attention deficit hyperactivity disorders (ADHD), Alzheimer's disease, for improved cognition or memory and for mood stabilization.

(...)

Example 34

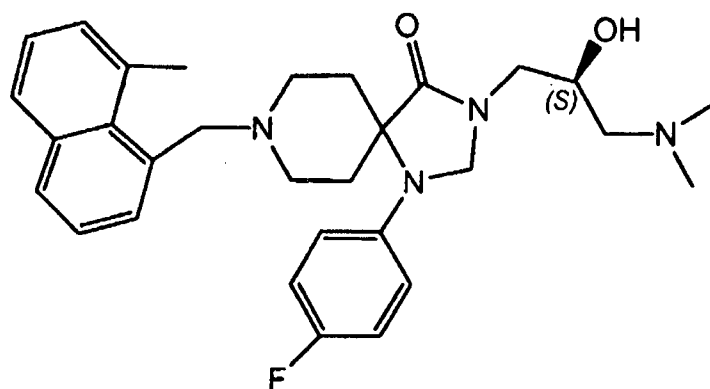
3-(3-Amino-2-(R)-hydroxy-propyl)-1-(4-fluoro-phenyl)-8-(8-methyl-naphthalen-1-ylmethyl)-1,3,8-triaza-spiro[4.5]decan-4-one Compound#438



(...)

Example 46

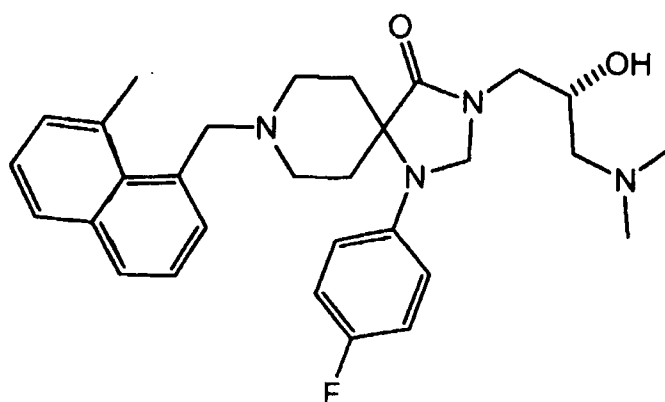
3-[3-(Ethyl-methyl-amino)-2-hydroxy-(S)-propyl]-1-(4-fluoro-phenyl)-8-(8-methyl-naphthalen-1-ylmethyl)-1,3,8-triaza-spiro[4.5]decan-4-one Compound #440



(...)

Example 50

3-(3-Dimethylamino-2-(R)-hydroxy-propyl)-1-(4-fluoro-phenyl)-8-(8-methyl-naphthalen-1-ylmethyl)-1,3,8-triaza-spiro[4.5]decan-4-one Compound #441

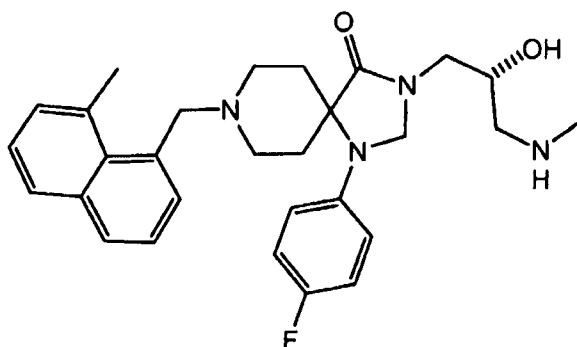


(...)

Example 51

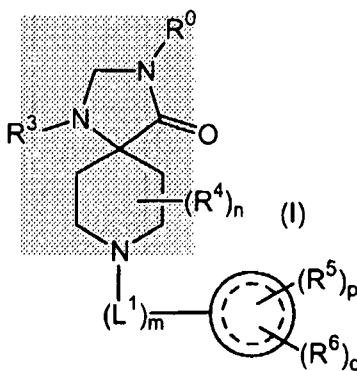
1-(4-Fluoro-phenyl)-3-(2-(R)-hydroxy-3-methylamino-propyl)-8-(8-methyl-naphthalen-1-ylmethyl)-1,3,8-triaza-spiro[4.5]decan-4-one

Compound #660



(...)

1. A compound of the formula (I)



(...)

14. A method of treating a disorder mediated by the ORL-1 receptor, in a subject in need thereof comprising administering to the subject a therapeutically effective amount of the compound of Claim 1.

(...)

15. The method of Claim 14, wherein the disorder mediated by the ORL-1 receptor is selected from the group consisting of anxiety, depression, panic, mania, dementia, bipolar disorder, substance abuse, neuropathic pain, acute pain, chronic pain, migraine, asthma, cough, psychosis, schizophrenia, epilepsy, hypertension, obesity, eating disorders, cravings, diabetes, cardiac arrhythmia, irritable bowel syndrome, Crohn's disease, urinary incontinence, adrenal disorders, attention deficit disorder (ADD), attention deficit hyperactivity disorder (ADHD), Alzheimer's disease, improved cognition, improved memory and mood stabilization.

Como se puede apreciar, en esta anterioridad no solo se revela nuevamente la utilidad del mismo grupo farmacológico de los compuestos revelados en la solicitud colombiana en cuestión (agonistas de receptor ORL-1), sino que además revela compuestos cuya estructura esta estrechamente relacionada a los reivindicados por la solicitud colombiana en trámite, e inclusive revela algunos de los mismos compuestos, como es el caso de los ejemplos de la anterioridad expuestos aquí.

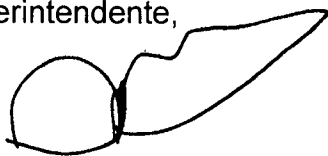
En conclusión, la solicitud colombiana en tramite carece de todos los requisitos fundamentales para poder otorgársele el privilegio de patente de invención, en primer lugar porque incurre en una improcedencia directa de la patentabilidad cuando reivindica un métodos de tratamiento, así como combinaciones farmacológicas que no pueden considerarse una invención, y finalmente porque carece de nivel inventivo al utilizar compuestos que con anterioridad ya se habian relacionado en el tratamiento de los mismos tipos de trastornos.

Por todo lo anterior, ruego se analicen los argumentos expuestos con el rigor y detenimiento habituales, y que en consecuencia el Despacho decrete, además de la negación de la solicitud en comento, el archivo del expediente que lo contiene.

III. ANEXOS.

- ❖ Todas las publicaciones y páginas de Internet mencionadas y citadas en el acápite de Complemento de información.

Señor Superintendente,



JOSE LUIS REYES VILLAMIZAR

C.C. 79.152.473 de Usaquén
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(US). MIDDLETON, Steve, A. [US/US]; 2 Gateshead
Drive, Flemington, NJ 08822 (US). ORSINI, Michael
[US/US]; 24 Nepote Place, Somersct, NJ 08873 (US).

(21) International Application Number:
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(74) Agents: JOHNSON, Philip, S. et al.; Johnson & Johnson,
One Johnson & Johnson Plaza, New Brunswick, NJ 08933
(US).

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(71) Applicant (for all designated States except US):
JANSSEN PHARMACEUTICA, N.V. [BE/BE]; Turn-
houtseweg 30, B-2340 Beerse (BE).

(72) Inventors; and

(75) Inventors/Applicants (for US only): BATTISTA, Kath-
leen [US/US]; 1016 Scenic Drive, Ewing, NJ 08628 (US).
BIGNAN, Gilles [FR/US]; 4 Burr Street, Bridgewater, NJ
08807 (US). CONNOLLY, Peter, J. [US/US]; 74 Delwick
Lane, New Providence, NJ 07974 (US). REITZ, Allen, B.
[US/US]; 109 Greenbriar Road, Lansdale, PA 19466-1519
(US). MORGAN ROSS, Tina [US/US]; 101 Rosemont
Lane, Royerford, PA 19468 (US). SCOTT, Malcolm
[US/US]; 850 Keller Creamery Road, Telford, PA 18969

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AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,
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LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,
MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC,
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UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

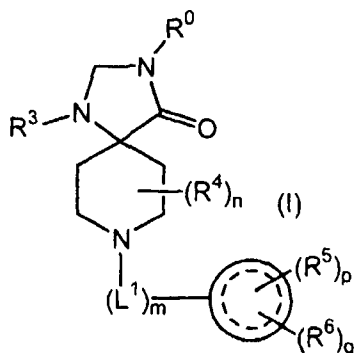
(84) Designated States (regional): ARIPO patent (GH, GM,
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European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,
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— without international search report and to be republished
upon receipt of that report

For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: HYDROXY ALKYL SUBSTITUTED 1,3,8-TRIAZASPIRO[4.5]DECAN-4-ONE DERIVATIVES USEFUL FOR THE
TREATMENT OF ORL-1 RECEPTOR MEDIATED DISORDERS



(57) Abstract: The present invention is directed to novel hydroxy alkyl substituted 1, 3, 8-triazaspiro[4.5]decan-4-one derivatives of the general formula: wherein all variables are as defined herein, useful in the treatment of disorders and conditions mediated by the ORL-1 G-protein coupled receptor. More particularly, the compounds of the present invention are useful in the treatment of disorders and conditions such as anxiety, depression, panic, dementia, mania, bipolar disorder, substance abuse, neuropathic pain, acute pain, chronic pain, migraine, asthma, cough, psychosis, schizophrenia, epilepsy, hypertension, obesity, eating disorders, cravings, diabetes, cardiac arrhythmia, irritable bowel syndrome, Crohn's disease, urinary incontinence, adrenal disorders, attention deficit disorder (ADD), attention deficit hyperactivity disorder (ADHD), Alzheimer's disease, for improved cognition or memory and for mood stabilization.

Tulshian et al. in PCT publication WO00/06545 disclose high affinity ligands for the nociceptin receptor ORL-1 and the use of said compounds as nociceptin receptor inhibitors useful in the treatment of pain, anxiety, cough, asthma, depression and alcohol abuse.

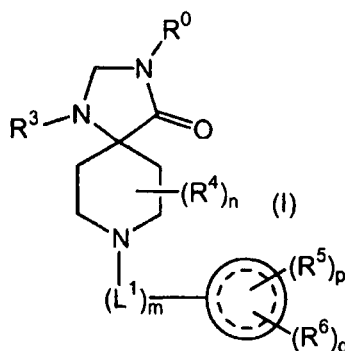
Higgins, et.al., in European Forum of Neuroscience 2000, Brighton, U.K., June 24-28, 2000, Poster 077.22 disclosed, 8-[(1R,3aS)-2,3,3a,4,5,6-hexahydro-1H-phenalen-1-yl]-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one useful as cognition enhancers.

We now describe novel small molecule modulators of the ORL-1 receptor, useful for the treatment of disorders and conditions mediated by the ORL-1 receptor, such as anxiety, depression, panic, dementia, mania, bipolar disorder, substance abuse, neuropathic pain, acute pain, chronic pain, migraine, asthma, cough, psychosis, schizophrenia, epilepsy, hypertension, obesity, eating disorders, cravings, diabetes, cardiac arrhythmia, irritable bowel syndrome, Crohn's disease, urinary incontinence, adrenal disorders, attention deficit disorder (ADD), attention deficit hyperactivity disorders (ADHD), Alzheimer's disease, for improved cognition or memory and for mood stabilization.

SUMMARY OF THE INVENTION

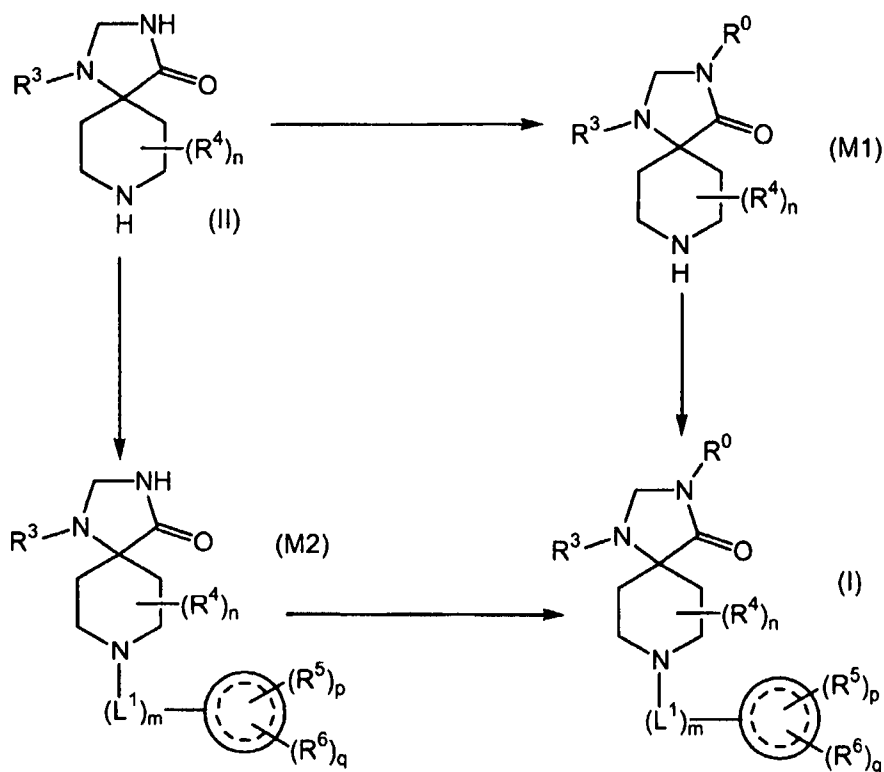
The present invention is directed to compounds of the general formula

(I)



mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, N-methylglucamine ammonium salt, oleate, pamoate (embonate), palmitate, pantothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, sulfate, subacetate, succinate, tannate, tartrate, tosylate, triethiodide and valerate.

The compounds of formula (I) of the present invention may be prepared according to the processes described in more detail herein. More particularly, the compounds of formula (I) may be prepared through intermediates of formula (M1) or (M2), as outlined in Scheme 1.

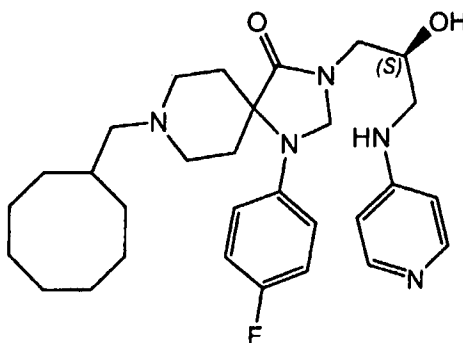


Scheme 1

More particularly, a suitably substituted compound of formula (II), a known compound or compound prepared by known methods, is reacted to yield the compound of formula (M1), which is then further reacted to yield the corresponding compound of formula (I).

Example 33

8-Cyclooctylmethyl-1-(4-fluoro-phenyl)-3-[2-(S)-hydroxy-3-(pyridin-4-ylamino)-propyl]-1,3,8-triaza-spiro[4.5]decan-4-one Compound #36



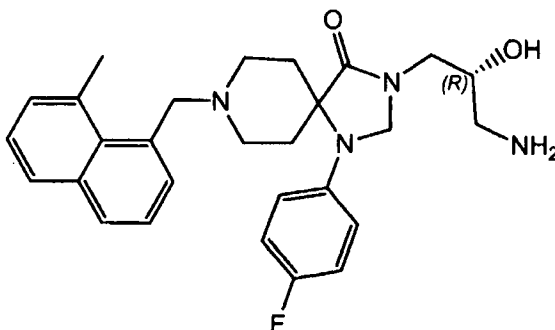
- 5 Cyclooctylmethyl-1-(4-fluoro-phenyl)-3-(R)-oxiranylmethyl-1,3,8-triaza-spiro[4.5]decan-4-one (0.5 g, 1.16 mmol) was dissolved in absolute ethanol (1 mL), mixed with 4-Aminopyridine (0.5 mL, 5.3 mmol) and heated at reflux overnight. The solvent was evaporated and the resulting residue was purified by reverse phase column chromatography (Acetonitrile/water) to yield the title
10 compound as an oil.

^1H NMR (300 MHz, CD_3OD) δ 1.35 (m, 2H), 1.5-1.7 (m, 13 H), 1.9 (s, 9H), 1.95 (m, 1H), 2.4 (m, 2H), 3.1 (d, 2H), 3.2 (m, 2H), 3.4 (m, 2H), 3.55 (d, 2H), 4.0 (m, 1H), 4.15 (m, 1H), 4.3 (m, 1H), 6.8 (d, 2H), 7.1(m, 4H), 8.1(d, 2H).

15

Example 34

3-(3-Amino-2-(R)-hydroxy-propyl)-1-(4-fluoro-phenyl)-8-(8-methyl-naphthalen-1-ylmethyl)-1,3,8-triaza-spiro[4.5]decan-4-one Compound#438

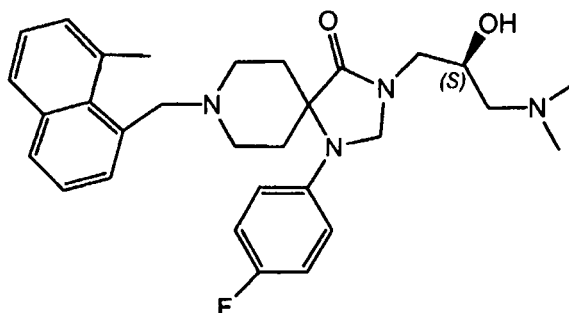


- 1-(4-Fluoro-phenyl)-8-(8-methyl-naphthalen-1-ylmethyl)-3-(S)-oxiranylmethyl-1,3,8-triaza-spiro[4.5]decan-4-one (0.06 g, 0.13 mmol) was
20

Example 46

3-[3-(Ethyl-methyl-amino)-2-hydroxy-(S)-propyl]-1-(4-fluoro-phenyl)-8-(8-methyl-naphthalen-1-ylmethyl)-1,3,8-triaza-spiro[4.5]decan-4-one Compound

#440



5

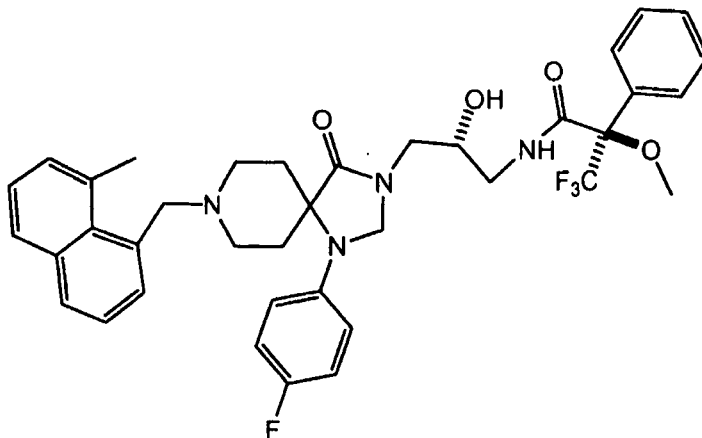
1-(4-Fluoro-phenyl)-8-(8-methyl-naphthalen-1-ylmethyl)-3-(*R*)-oxiranylmethyl-1,3,8-triaza-spiro[4.5]decan-4-one (0.02 g, 0.043 mmol) was dissolved in ethyl alcohol (2 mL). To the solution was then added N-methylethylamine (0.2 mL) and the reaction mixture was stirred at 40°C for 3 hrs in a pressure flask. The solvent was then evaporated *in vacuo* to yield a crude oil. The crude oil was purified via flash chromatography (5.0% ammonia, 2.0 M in methanol /dichloromethane) to yield the title compound as an oil.

10

¹H NMR (400 MHz, CDCl₃) δ 7.77-7.75 (1H, m), 7.71-7.68 (1H, m), 7.38-7.30 (4H, m), 6.96-6.91 (2H, m), 6.88-6.84 (2H, m), 4.82-4.75 (2H, m), 4.08-3.98 (3H, m), 3.61-3.57 (1H, m), 3.34-3.29 (1H, m), 3.11 (3H, s), 2.83-2.54 (8H, m), 2.44 (3H, s), 2.32-2.23 (2H, m), 1.68-1.63 (2H, m); 1.15 (3H, t, *J* = 7.2 Hz)

15

MS (ES⁺) *m/z* 519.3 (M + H)⁺.



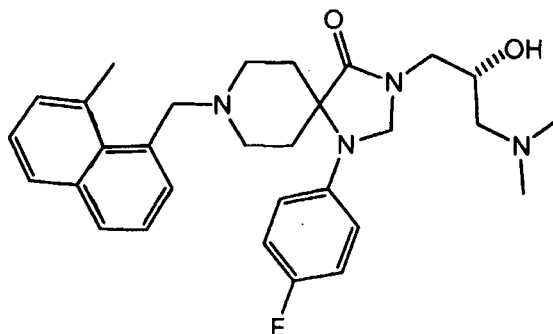
3-(3-Amino-2-(R)-hydroxy-propyl)-1-(4-fluoro-phenyl)-8-(8-methyl-naphthalen-1-ylmethyl)-1,3,8-triaza-spiro[4.5]decan-4-one (0.0118 g, 0.024 mmol) was dissolved in dichloromethane (1.0 mL) and pyridine (0.15 mL). To
 5 the reaction mixture was then added at 0°C (S)-(+)-α-methoxy-α-(trifluoromethyl)phenyl acetyl chloride (8.7 mg, 0.034 mmol) under nitrogen atmosphere. The reaction mixture was stirred at 0°C for one hour, then the solvent was evaporated *in vacuo* to yield a crude foam. The crude foam was dissolved in ethyl acetate and successively washed twice with aqueous 0.5N
 10 HCl, twice with aqueous NaHCO₃, brine, dried with Na₂SO₄, filtered and the solvent evaporated *in vacuo* to yield a white foam.

¹H NMR (300 MHz, CDCl₃) δ 7.78-7.75 (1H, m), 7.71-7.68 (1H, m), 7.64-7.61 (1H, m), 7.56-7.54 (2H, m), 7.42-7.40 (3H, m), 7.39-7.30 (3H, m), 6.97-6.93 (2H, m), 6.87-6.83 (2H, m), 4.70 (1H, d, *J* = 4.9 Hz), 4.64 (1H, d, *J* = 4.9
 15 Hz), 3.99 (3H, s), 4.01 (1H, s), 3.60-3.54 (1H, m), 3.45-3.32 (5H, m), 3.1 (3H, s), 2.82-2.74 (4H, m), 2.24-2.20 (2H, m), 1.70-1.63 (4H, m)

MS (ES⁺) *m/z* 693.0 (M + H)⁺.

Example 50

20 3-(3-Dimethylamino-2-(R)-hydroxy-propyl)-1-(4-fluoro-phenyl)-8-(8-methyl-naphthalen-1-ylmethyl)-1,3,8-triaza-spiro[4.5]decan-4-one Compound #441



1-(4-Fluoro-phenyl)-8-(8-methyl-naphthalen-1-ylmethyl)-3-(S)-oxiranylmethyl-1,3,8-triaza-spiro[4.5]decan-4-one (0.035 g, 0.07 mmol) was dissolved in ethyl alcohol (2 mL). To the solution was then added a 2.0M solution of dimethylamine in methanol (1.0 mL, 2.0 mmol) and the reaction mixture was stirred at 45°C for 3 hrs in a pressure flask. The solvent was then evaporated *in vacuo* to yield a crude oil. The crude oil was purified via flash chromatography (5.0% ammonia 2.0 M in methanol /dichloromethane) to yield the title compound as a foam.

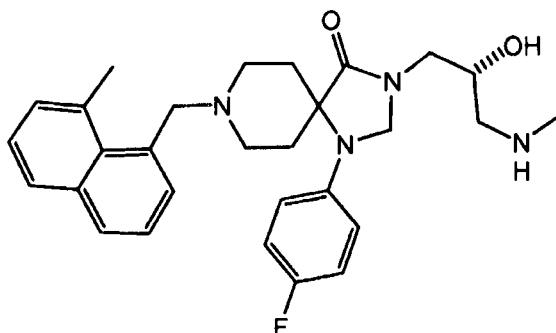
¹H NMR (400 MHz, CDCl₃) δ 7.78-7.75 (1H, m), 7.71-7.68 (1H, m), 7.38-7.31 (4H, m), 6.96-6.91 (2H, m), 6.88-6.84 (2H, m), 4.80 (1H, d, *J* = 5.1 Hz), 4.77 (1H, d, *J* = 5.1 Hz), 4.01 (2H, m), 3.95-3.87 (1H, m), 3.62-3.58 (1H, m), 3.31-3.26 (1H, m), 3.11 (3H, s), 2.86-2.78 (6H, m), 2.36-2.22 (9H, m), 1.68-1.63 (2H, m)

MS (ES⁺) *m/z* 505.4 (M + H)⁺.

Example 51

1-(4-Fluoro-phenyl)-3-(2-(R)-hydroxy-3-methylamino-propyl)-8-(8-methylnaphthalen-1-ylmethyl)-1,3,8-triaza-spiro[4.5]decan-4-one

Compound #660



1-(4-Fluoro-phenyl)-8-(8-methyl-naphthalen-1-ylmethyl)-3-(S)-oxiranylmethyl-1,3,8-triaza-spiro[4.5]decan-4-one (0.05 g, 0.109 mmol) was dissolved in methanol (3 mL). To the solution was then added a 2.0M solution of methylamine in methanol (1.0 mL, 2.0 mmol) and the reaction mixture was stirred at 40°C for 3 hrs in a pressure flask. The solvent was then evaporated *in vacuo* to yield a crude oil. The crude oil was purified via flash chromatography (5.0% ammonia 2.0 M in methanol /dichloromethane) to yield the title compound as a foam.

¹H NMR (400 MHz, CDCl₃) δ 7.78-7.75 (1H, m), 7.71-7.68 (1H, m), 7.38-7.31 (4H, m), 6.96-6.91 (2H, m), 6.88-6.84 (2H, m), 4.80 (1H, d, J = 5.1 Hz), 4.77 (1H, d, J = 5.1 Hz), 4.00 (2H, m), 3.97-3.86 (1H, m), 3.58-3.53 (1H, m), 3.43-3.35 (1H, m), 3.12 (3H, s), 2.84-2.69 (7H, m), 2.56-2.49 (1H, m), 2.44 (3H, s), 2.31-2.24 (2H, m), 1.67-1.64 (2H, m)

MS (ES⁺) *m/z* 491.1 (M + H)⁺.

Example 52

1-(4-Fluoro-phenyl)-3-[2-(R)-hydroxy-3-(3-methylamino-propylamino)-propyl]-8-(8-methyl-naphthalen-1-ylmethyl)-1,3,8-triaza-spiro[4.5]decan-4-one

20

Compound #656

Distinct colonies appeared in approximately 3 weeks. One week later, 48 out of approximately 100 colonies per dish were subcultured to 1 well each of two 24 well plates containing 1 ml of selective medium per well.

Confluent wells were expanded to 6 well plates, then T25 flasks and T75 flasks. Cell lines showing poor growth patterns were eliminated. Membranes were prepared from each cell line and receptor activity determined by a receptor binding assay.

EXAMPLE 67

10 Method for measuring affinity for the ORL-1 receptor

The nociceptin receptor binding assay measures the binding of ^{125}I -Tyr ^{14} -nociceptin (2200 Ci/mmol, New England Nuclear) to human nociceptin receptor (ORL-1) on HEK293 cell membranes.

HEK293 cell membrane (prepared as described in Pulito, V.L. *et al.*, 15 2000, *J. Pharmacol. Exp. Ther.* **294**, 224-229), with the exception that the buffer used was a mixture of 50 mM Tris-HCl pH7.8, 5 mM MgCl $_2$ and 1 mM EGTA), was added to PEI treated WGA FlashPlates (New England Nuclear) at 1 μg /well in binding buffer of 50 mM Tris-HCl pH 7.8, 5 mM MgCl $_2$ and 1 mM EGTA. ^{125}I -Tyr ^{14} -nociceptin was added at a final concentration of 0.5 nM and 20 the volume adjusted to 50 μl with binding buffer. The plate was incubated for two hours at room temperature, the reactions were aspirated and the wells washed two times with 200 μl binding buffer and then filled with 200 μl binding buffer. The plates were then sealed and counted on a Packard Top Count to determine radioactivity bound to the membranes.

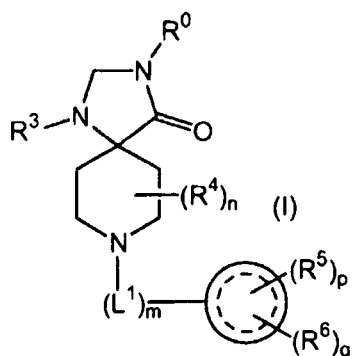
25

For each test compound, the total binding (%Inh) was measured at several concentrations and the IC $_{50}$ (the concentration at which 50% of the binding is inhibited) was determined from the graphical display of X = logarithm of concentration versus Y = response, using the following calculation:

30
$$Y = \frac{(\text{Minimum}) + (\text{Maximum-Minimum})}{(1+10^{\log(\text{EC}_{50}^{-X})})}$$

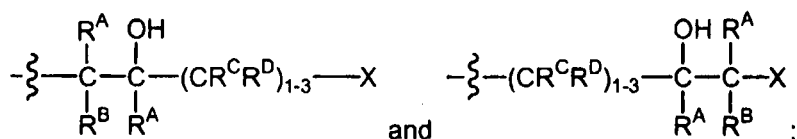
What is claimed is:

1. A compound of the formula (I)



- 5 wherein

R^0 is selected from the group consisting of



each R^A and R^B is independently selected from the group consisting of hydrogen and C_{1-4} alkyl;

- 10 each R^C and R^D is independently selected from the group consisting of hydrogen, hydroxy, carboxy, C_{1-4} alkyl, C_{1-4} alkoxy, nitro, cyano, $N(R^E)_2$, aryl, ar C_{1-4} alkyl, heteroaryl or heterocycloalkyl; wherein the aryl, ar C_{1-4} alkyl, heteroaryl or heterocycloalkyl substituent is optionally substituted with one or more substituents independently selected from hydroxy, carboxy, C_{1-4} alkyl, C_{1-4} alkoxy, nitro, cyano or $N(R^E)_2$;

15 each R^E is independently selected from the group consisting of hydrogen and C_{1-4} alkyl;

- X is selected from the group consisting of $-NR^1R^2$, $-C(O)-NR^1R^2$, $-NR^1-C(O)-R^2$, $-OR^1$, $-SR^1$, $-SOR^1$, $-SO_2R^1$, $-S-(C_{2-4}alkyl)-NR^1R^2$, $-S-(C_{2-4}alkyl)-C(O)O-C(CH_3)_3$, $-SO-(C_{1-4}alkyl)-NR^1R^2$ and $-SO_2-(C_{1-4}alkyl)-NR^1R^2$; wherein the alkyl portion of the $-S-(C_{2-4}alkyl)-NR^1R^2$, $-SO-(C_{1-4}alkyl)-NR^1R^2$ or $-SO_2-(C_{1-4}alkyl)-NR^1R^2$ group is optionally substituted with one or more substituents independently selected from carboxy, hydroxy, hydroxy C_{1-4} alkyl, C_{1-4} alkyl, C_{1-4} alkoxycarbonyl or $-CONR^1R^2$;

each R^1 and R^2 is independently selected from the group consisting of hydrogen, C_{1-8} alkyl, C_{1-8} alkoxy, C_{1-8} alkoxycarbonyl, cycloalkyl, cycloalkyl- C_{1-4} alkyl, partially unsaturated carbocyclyl, partially unsaturated carbocyclyl- C_{1-4} alkyl, aryl, arC_{1-4} alkyl, arC_{1-4} alkoxy, heteroaryl, heteroaryl- C_{1-4} alkyl, heterocycloalkyl, heterocycloalkyl- C_{1-4} alkyl, -C(O)- C_{1-6} alkyl, -C(O)-aryl, -C(O)- arC_{1-4} alkyl, -C(O)-heteroaryl, -C(O)-heterocycloalkyl, -C(O)O-cycloalkyl and -C(O)O-aryl, -C(O)O- arC_{1-4} alkyl, -C(O)O-(partially unsaturated carbocyclyl), -C(O)O-heteroaryl, -C(O)O-heterocycloalkyl; wherein the C_{1-8} alkyl, cycloalkyl, partially unsaturated carbocyclyl, aryl, arC_{1-8} alkyl, heteroaryl or heterocycloalkyl group, whether alone or part of a substituent group, is optionally substituted with one or more substituents independently selected from halogen, hydroxy, carboxy, C_{1-4} alkyl, C_{1-4} alkoxy, trifluoromethyl, trifluoromethoxy, nitro, cyano, -C(O)- C_{1-4} alkyl, C_{1-4} alkoxycarbonyl, $N(R^E)_2$, $N(R^E)_2$ - C_{1-4} alkyl, $N(R^E)$ -C(O)C(CH₃)₃, - C_{1-4} alkyl- $N(R^E)$ -C(O)O- C_{1-4} alkyl and - $N(R^E)$ -C(O)O- C_{1-4} alkyl, aryl, aryloxy, cycloalkyl, heteroaryl, aryl substituted heteroarylamino sulfonyl or C_{1-6} alkylthio;

alternatively when R^1 and R^2 are both bound to the same nitrogen atom, R^1 and R^2 are taken together with the nitrogen atom to which they are bound to form a heteroaryl or heterocycloalkyl group; wherein the heteroaryl or heterocycloalkyl group is optionally substituted with one or more substituents independently selected from halogen, hydroxy, carboxy, C_{1-4} alkyl, hydroxy substituted C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkoxycarbonyl, trifluoromethyl, trifluoromethoxy, nitro, cyano, $N(R^E)_2$, aryl, arC_{1-4} alkyl, heteroaryl, heterocycloalkyl, di(C_{1-6})alkylamino-carbonyl, C_{1-4} alkoxycarbonyl- $N(R^E)$ - or arylamino- C_{1-4} alkyl; wherein the aryl, arC_{1-4} alkyl, heteroaryl or heterocycloalkyl substituent is optionally further substituted with one or more substituents independently selected from halogen, hydroxy, carboxy, C_{1-4} alkyl, C_{1-4} alkoxy, trifluoromethyl, trifluoromethoxy, nitro, cyano, $N(R^E)_2$, phenyl or substituted phenyl; wherein the substituents on the phenyl are one or more independently selected from halogen, hydroxy, carboxy, C_{1-4} alkyl, C_{1-4} alkoxy, trifluoromethyl, trifluoromethoxy, nitro, cyano or $N(R^E)_2$;

R^3 is selected from the group consisting of aryl, arC_{1-6} alkyl and heteroaryl; wherein the aryl, arC_{1-6} alkyl or heteroaryl group is optionally

substituted with one or more substituents independently selected from halogen, hydroxy, carboxy, C₁₋₄alkyl, C₁₋₄alkoxy, trifluoromethyl, trifluoromethoxy, nitro, cyano or N(R^E)₂;

n is an integer from 0 to 2;

- 5 R⁴ is selected from the group consisting of hydroxy, C₁₋₄alkyl and hydroxy substituted C₁₋₄alkyl;

m is an integer from 0 to 1;

L¹ is selected from the group consisting of C₁₋₆alkyl and C₃₋₆alkenyl;

- wherein the double bond of the C₃₋₆alkenyl group is at least one carbon atom removed from the attachment point to the N atom; and wherein the C₁₋₆alkyl or C₃₋₆alkenyl group is optionally substituted with one to two substituents independently selected from hydroxy, fluoro, C₁₋₆alkyl, fluorinated C₁₋₆alkyl or C₁₋₆alkoxy;



- 15 is selected from the group consisting of cycloalkyl, partially unsaturated carbocyclyl, aryl, heteroaryl and heterocycloalkyl;

p is an integer from 0 to 5;

- R⁵ is selected from the group consisting of hydroxy, carboxy, halogen, C₁₋₆alkyl, hydroxy substituted C₁₋₆alkyl, C₁₋₆alkoxy, nitro, cyano, NR¹R², trifluoromethyl, trifluoromethoxy, C₁₋₄alkoxycarbonyl, -SO-NR¹R², -SO₂-NR¹R² and -C(O)-NR¹R²;

q is an integer from 0 to 1;

R⁶ is selected from the group consisting of -(L²)₀₋₁-R⁷;

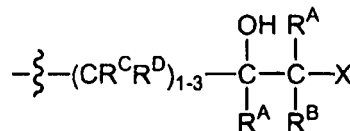
- L² is selected from the group consisting of -C₁₋₆alkyl-, -C₂₋₄alkenyl-, -C₂₋₆alkynyl-, -O-, -S-, -NH-, -N(C₁₋₄alkyl)-, -C₁₋₆alkyl-O-, -C₁₋₆alkyl-S-, -O-C₁₋₆alkyl-, -S-C₁₋₆alkyl-, -O-C₂₋₆alkyl-O-, -S-C₂₋₆alkyl-S-, -SO₂-, -SO₂NH-, -SO₂N(C₁₋₄alkyl)-, -NH-SO₂-, -N(C₁₋₄alkyl)-SO₂-, -C(O)-O- and -O-C(O)-;

- R⁷ is selected from the group consisting of aryl, partially unsaturated carbocyclyl, cycloalkyl, heteroaryl and heterocycloalkyl; wherein the aryl, partially unsaturated carbocyclyl, cycloalkyl, heteroaryl or heterocycloalkyl group is optionally substituted with one or more substituents independently selected from hydroxy, carboxy, halogen, C₁₋₆alkyl, C₁₋₆alkoxy, nitro, cyano,

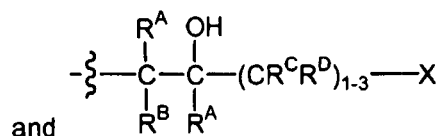
$N(R^E)_2$, trifluoromethyl, trifluoromethoxy, C_{1-4} alkoxycarbonyl, $-SO_2-N(R^E)_2$ and $-C(O)-N(R^E)_2$;

or a pharmaceutically acceptable salt thereof.

- 5 2. A compound as in Claim 1 wherein



R^0 is selected from the group consisting of



- each R^C and R^D is independently selected from hydrogen, C_{1-4} alkyl, C_{1-4} alkoxy, hydroxy, carboxy or aryl; wherein the aryl is optionally substituted with
 10 one to two substituents independently selected from hydroxy, carboxy, C_{1-4} alkyl, C_{1-4} alkoxy, nitro, cyano or $N(R^E)_2$;

- X is selected from the group consisting of $-NR^1R^2$, $-C(O)-NR^1R^2$, $-NR^1-C(O)-R^2$, $-OR^1$, $-SR^1$, $-SO-R^1$, $-SO_2-R^1$, $-S-(C_{2-4}alkyl)-NR^1R^2$, $-S-(C_{2-4}alkyl)-NR^1-C(O)OC(CH_3)_3$, $-SO-(C_{1-4}alkyl)-NR^1R^2$ and $-SO_2-(C_{1-4}alkyl)-NR^1R^2$; wherein the
 15 alkyl portion of the $-S-(C_{2-4}alkyl)-NR^1R^2$, $-SO-(C_{1-4}alkyl)-NR^1R^2$ or $-SO_2-(C_{1-4}alkyl)-NR^1R^2$ group is optionally substituted with one to two substituents independently selected from C_{1-4} alkyl, hydroxy C_{1-4} alkyl, C_{1-4} alkoxycarbonyl or carboxy;

- R^1 is selected from the group consisting of hydrogen, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkoxycarbonyl, aryl, $arC_{1-4}alkyl$, $arC_{1-4}alkyloxy$, heteroaryl, heteroaryl-alkyl, heterocycloalkyl, heterocycloalkyl-alkyl, cycloalkyl-alkyl, $C(O)-C_{1-4}alkyl$ and $-C(O)-heteroaryl$;

- wherein the $C_{1-4}alkyl$, aryl, $arC_{1-4}alkyl$, heteroaryl, heterocycloalkyl or cycloalkyl group, whether alone or part of a substituent group, is optionally
 25 substituted with one to three substituents independently selected from halogen, hydroxy, carboxy, $C_{1-4}alkyl$, $C_{1-4}alkoxy$, $C_{1-4}alkoxycarbonyl$, $N(R^E)_2$, $N(R^E)_2-C_{1-4}alkyl$, $N(R^E)-C(O)OC(CH_3)_3$, nitro, trifluoromethyl, trifluoromethoxy, phenyl,

phenoxy, heteroaryl, cycloalkyl, 1-phenyl-pyrazol-2-yl-aminosulfonyl or C₁₋₄alkylthio;

R² is selected from the group consisting of hydrogen, C₁₋₄alkyl, C₁₋₄alkoxy, cycloalkyl, cycloalkyl-C₁₋₄alkyl, aryl, arC₁₋₄alkyl, arC₁₋₄alkyloxy, partially
 5 unsaturated carbocyclyl, partially unsaturated carbocyclyl-C₁₋₄alkyl, heteroaryl, heteroaryl-C₁₋₄alkyl, heterocycloalkyl, heterocycloalkyl-C₁₋₄alkyl, -C(O)-C₁₋₄alkyl, -C(O)-aryl, -C(O)-arC₁₋₄alkyl, -C(O)-heteroaryl, -C(O)-heterocycloalkyl, -C(O)O-cycloalkyl and -C(OO)-C₁₋₄alkyl;

wherein the C₁₋₄alkyl, aryl, arC₁₋₄alkyl, partially unsaturated carbocyclyl,
 10 heteroaryl, heterocycloalkyl or cycloalkyl group, whether alone or part of a substituent group, is optionally substituted with one to three substituents independently selected from halogen, hydroxy, carboxy, C₁₋₄alkyl, C₁₋₄alkoxy, C₁₋₄alkoxycarbonyl, N(R^E)₂, N(R^E)₂-C₁₋₄alkyl, (CH₃)₃COC(O)-N(R^E)-C₁₋₄alkyl, nitro, cyano, trifluoromethyl, trifluoromethoxy, phenyl, phenoxy, heteroaryl,
 15 cycloalkyl, 1-phenyl substituted heteroaryl-aminosulfonyl, -C(O)-C₁₋₄alkyl or C₁₋₄alkylthio;

alternatively when R¹ and R² are both bound to the same nitrogen atom, R¹ and R² are taken together with the nitrogen atom to which they are bound to
 20 form a heteroaryl or heterocycloalkyl group;

wherein the heteroaryl or heterocycloalkyl is optionally substituted with one to three substituents independently selected from halogen, hydroxy, carboxy, C₁₋₄alkyl, hydroxy substituted C₁₋₄alkyl, C₁₋₄alkoxy, C₁₋₄alkoxycarbonyl, trifluoromethyl, trifluoromethoxy, nitro, cyano, N(R^E)₂, phenyl, arC₁₋₄alkyl,
 25 heterocycloalkyl, di(C₁₋₄alkyl)amino-carbonyl, C₁₋₄alkoxycarbonylamino or phenylamino-C₁₋₄alkyl;

wherein the phenyl or arC₁₋₄alkyl substituent on the heteroaryl or heterocycloalkyl group is optionally substituted with one or two substituents independently selected from halogen, hydroxy, carboxy, C₁₋₄alkyl, C₁₋₄alkoxy,
 30 trifluoromethyl, trifluoromethoxy, nitro, cyano, N(R^E)₂ or substituted phenyl;
 wherein the substituents on the phenyl are one to three independently selected from halogen;

R^3 is selected from the group consisting of aryl and arC₁₋₄alkyl; wherein the aryl or arC₁₋₄alkyl group is optionally substituted with one to three substituents independently selected from halogen, hydroxy, carboxy, C₁₋₄alkyl, C₁₋₄alkoxy, trifluoromethyl, trifluoromethoxy, nitro, cyano or N(R^E)₂;

5 n is an integer from 0 to 1;

L^1 is C₁₋₄alkyl; wherein the C₁₋₄alkyl group is optionally substituted with one to two substituents independently selected from hydroxy, fluoro, C₁₋₄alkyl, fluorinated C₁₋₄alkyl or C₁₋₄alkoxy;

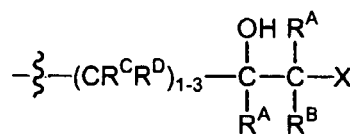
10 R^5 is selected from the group consisting of hydroxy, carboxy, halogen, C₁₋₄alkyl, C₁₋₄alkoxy, nitro, cyano, N(R^E)₂, trifluoromethyl, trifluoromethoxy, C₁₋₄alkoxycarbonyl, -SO- N(R^E)₂, -SO₂- N(R^E)₂ and -C(O)- N(R^E)₂;

L^2 is selected from the group consisting of -C₁₋₄alkyl-, -O-, -S-, -N(R^E)-, -C(O)O- and -O-C(O)-;

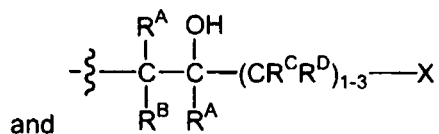
15 R^7 is selected from the group consisting of cycloalkyl, aryl, heteroaryl and heterocycloalkyl; wherein the aryl, heteroaryl or heterocycloalkyl group is optionally substituted with one to two substituents independently selected from hydroxy, carboxy, halogen, C₁₋₄alkyl, C₁₋₄alkoxy, nitro, cyano, N(R^E)₂, trifluoromethyl, trifluoromethoxy or C₁₋₄alkoxycarbonyl; or a pharmaceutically acceptable salt thereof.

20

3. A compound as in Claim 2 wherein



R^0 is selected from the group consisting of



each R^A, R^B, R^C and R^D is hydrogen;

25 X is selected from the group consisting of -NR¹R², -OR¹, -SR¹, -S-(C₂₋₄alkyl)-NR¹R² and -S-(C₂₋₄alkyl)-NR¹-C(O)O-C(CH₃)₃; wherein the alkyl portion of the -S-(C₂₋₄alkyl)-NR¹R² or -S-(C₁₋₄alkyl)-NR¹-C(O)O-C(CH₃)₃ group is optionally substituted with a carboxy or C₁₋₄alkoxycarbonyl group;

R¹ is selected from the group consisting of hydrogen, C₁₋₄alkyl, C₁₋₄alkoxycarbonyl, arC₁₋₄alkyl and C(O)-C₁₋₄alkyl;

wherein the C₁₋₄alkyl or aryl group, whether alone or part of a substituent group, is optionally substituted with one to two substituents independently
 5 selected from carboxy, C₁₋₄alkyl, C₁₋₄alkoxy, C₁₋₄alkoxycarbonyl, N(R^E)₂ or N(R^E)-C(O)OC(CH₃)₃;

R² is selected from the group consisting of hydrogen, C₁₋₄alkyl, C₁₋₄alkoxy, cycloalkyl, aryl, arC₁₋₄alkyl, arC₁₋₄alkyloxy, partially unsaturated carbocyclyl, partially unsaturated carbocyclyl-C₁₋₄alkyl, heteroaryl, heteroaryl-
 10 C₁₋₄alkyl, heterocycloalkyl, heterocycloalkyl-C₁₋₄alkyl, cycloalkyl-C₁₋₄alkyl, -C(O)arC₁₋₄alkyl, -C(O)-heteroaryl, -C(OO)-cycloalkyl and -C(O)O-C₁₋₄alkyl;

wherein the C₁₋₄alkyl, aryl, arC₁₋₄alkyl, partially unsaturated carbocyclyl, heteroaryl, heterocycloalkyl or cycloalkyl group, whether alone or part of a substituent group, is optionally substituted with one to three substituents
 15 independently selected from halogen, hydroxy, carboxy, C₁₋₄alkyl, C₁₋₄alkoxy, C₁₋₄alkoxycarbonyl, N(R^E)₂, N(R^E)₂-C₁₋₄alkyl, (CH₃)₃CO-C(O)-N(R^E)-C₁₋₄alkyl, nitro, trifluoromethyl, trifluoromethoxy, phenyl, phenoxy, heteroaryl, cycloalkyl, 1-phenyl-pyrazol-2-yl-aminosulfonyl or C₁₋₄alkylthio;

20 alternatively when R¹ and R² are both bound to the same nitrogen atom, R¹ and R² are taken together with the nitrogen atom to which they are bound to form a group selected from heterocycloalkyl and heteroaryl;

wherein the heteroaryl or heterocycloalkyl is optionally substituted with one or more substituents independently selected from hydroxy, carboxy, C₁₋₄alkyl, hydroxy substituted C₁₋₄alkyl, C₁₋₄alkoxy, phenyl, arC₁₋₄alkyl, heterocycloalkyl, C₁₋₄alkoxycarbonyl, amino, C₁₋₄alkylamino, di(C₁₋₄alkyl)amino, di(C₁₋₄alkyl)amino-carbonyl, t-butoxycarbonylamino or phenylamino-C₁₋₄alkyl;
 25

wherein the phenyl or arC₁₋₄alkyl substituent is optionally substituted with one or two substituents independently selected from chloro, trifluoromethyl or chlorophenyl;
 30

R³ is aryl; wherein the aryl group is optionally substituted with one or more substituents independently selected from halogen;

n is 0;

27

L^1 is C_{1-4} alkyl;

R^5 is selected from the group consisting of halogen, C_{1-4} alkyl and trifluoromethyl;

R^6 is $-(L^2)_0-R^7$;

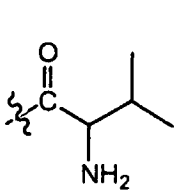
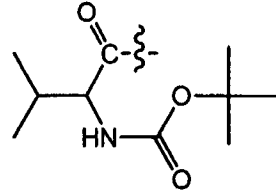
- 5 R^7 is selected from the group consisting of aryl and heteroaryl; or a pharmaceutically acceptable salt thereof.

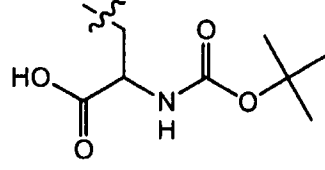
4. A compound as in Claim 3 wherein

- R^0 is selected from the group consisting of $-\text{CH}_2-\text{CH}(\text{OH})-\text{CH}_2-\text{X}$ and $-\text{CH}_2-\text{CH}_2-\text{CH}(\text{OH})-\text{CH}_2-\text{X}$;

X is selected from the group consisting of $-\text{NR}^1\text{R}^2$, $-\text{OR}^1$, $-\text{SR}^1$, $-\text{S}-\text{CH}_2\text{CH}(\text{CO}_2\text{H})-\text{NH}-\text{C}(\text{O})-\text{CH}_3$ and $-\text{S}-\text{CH}_2\text{CH}(\text{CO}_2\text{H})-\text{NH}-\text{C}(\text{O})\text{O}(\text{C}(\text{CH}_3)_3)$;

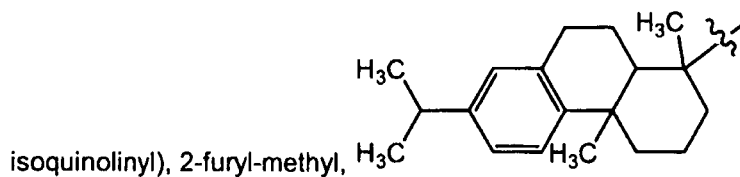
R^1 is selected from the group consisting of hydrogen, methyl, ethyl, n-propyl, n-butyl, t-butyl, amino-n-propyl, dimethylaminoethyl, benzyl,

- 15 phenylethyl, 4-methyl-benzyl, , , 2-(3,4-dimethoxy-phenyl)ethyl, 3-methyl-phenyl, ethoxy-carbonyl-methyl, 2-amino-2-

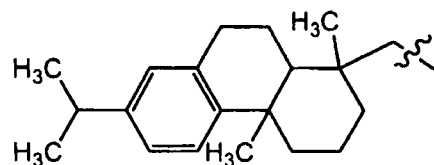
 methoxycarbonyl-ethyl, t-butoxycarbonyl and

- R^2 is selected from the group consisting of hydrogen, methyl, methoxy, ethyl, carboxy-methyl, ethoxycarbonylmethyl, 2,2,2-trifluoroethyl, ethoxy, 20 dimethylaminoethyl, t-butoxycarbonylamino-ethyl, n-butyl, t-butyl, n-propyl, 3-hydroxy-n-propyl, 3-methoxy-n-propyl, methylamino-n-propyl, dimethylamino-n-propyl, di(n-butyl)amino-n-propyl, t-butoxycarbonylamino-n-propyl, 3-phenyl-n-propyl, 3-(2-pyridyl)-n-propyl, t-butoxycarbonyl, cyclopropyl, phenyl, 4-fluorophenyl, 4-methylphenyl, 3,4-dimethoxyphenyl, 2-aminophenyl, 4-biphenyl, 25 2-ethoxyphenyl, 4-((1-phenyl-pyrazol-2-yl)-aminosulfonyl)-phenyl, 4-cyclohexylphenyl, 4-(aminoethyl)phenyl, 4-(t-butoxycarbonylamino-ethyl)-

- phenyl, -CH(CH₃)-phenyl, benzyl, benzyloxy, 2-methylbenzyl, 3-methylbenzyl, 4-methylbenzyl, 2-methoxybenzyl, 3-methoxybenzyl, 4-methoxybenzyl, 2-ethoxybenzyl, 3-ethoxybenzyl, 2-bromobenzyl, 3-bromobenzyl, 4-bromobenzyl, 3-chlorobenzyl, 4-chlorobenzyl, 3-iodobenzyl, 2-fluorobenzyl, 3-fluorobenzyl, 4-fluorobenzyl, 2-trifluoromethylbenzyl, 3-trifluoromethylbenzyl, 4-trifluoromethylbenzyl, 4-trifluoromethoxybenzyl, 4-methoxycarbonylbenzyl, 2,3-dimethoxybenzyl, 2,4-dichlorobenzyl, 3,4-dichlorobenzyl, 2,4-difluorobenzyl, 2,5-difluorobenzyl, 3,4-difluorobenzyl, 3,4,5-trimethoxybenzyl, 2,4,6-trimethoxybenzyl, 4-carboxybenzyl, 3-nitrobenzyl, 4-nitrobenzyl, 2,4-dimethoxybenzyl, 3,4-dimethoxybenzyl, 3,5-dimethoxybenzyl, 3,4-difluorobenzyl, 3,5-di(trifluoromethyl)benzyl, 4-(dimethylamino)benzyl, 2-phenylethyl, 2-(4-bromophenyl)ethyl, 2-(3-methoxyphenyl)ethyl, 2-(4-methoxyphenyl)ethyl, 2-(3,4-dimethoxyphenyl)ethyl, 2-(2-nitro-4,5-dimethoxyphenyl)ethyl, 3-(4-morpholinyl)-n-propyl, 2-(4-morpholinyl)ethyl, 2-(4-imidazolyl)ethyl, 1-adamantanyl, 1-adamantanyl-methyl, (2,5-dimethoxy-2,5-dihydro-fur-2-yl)methyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyridyl-methyl, 3-pyridyl-methyl, 4-pyridyl-methyl, 2-(3,4-dimethyl-pyridyl), 2-(5-bromopyridyl), 2-(4,6-dimethyl-pyridyl), 2-(5-methyl-pyridyl), 3-(6-methoxy-pyridyl), 6-methylthio-2-pyridyl-carbonyl, thienyl-methyl, 2-thienylethyl, 4-pyridinyl, 1-naphthyl, 1-naphthyl-methyl, 1-(3,4-methylenedioxyphenyl)methyl, 2-(3,4-methylenedioxyphenyl)ethyl, 1-phenyl-2-(t-butoxycarbonyl)ethyl, -C(O)-C(OCH₃)(CF₃)-phenyl, -C(O)O-(2-isopropyl-5-methyl-cyclohexyl), 1-(4-ethoxycarbonyl-piperidinyl), 2-(3H-imidazol-4-yl)ethyl, 2-(1,2,3,4-tetrahydro-



isoquinolinyl), 2-furyl-methyl, H₃C



25

, 2S-hydroxy-S-cyclopentyl-methyl, 2S-hydroxy-S-cyclohexyl-methyl, 2S-hydroxy-S-cycloheptyl-methyl, 2-phenoxy-ethyl, 2-(2-pyridyl)-ethyl, 2-(6-fluoro-2-indolyl)ethyl and 2-phenyl-cyclopropyl;

alternatively when R¹ and R² are both bound to the same nitrogen atom, R¹ and R² are taken together with the nitrogen atom to which they are bound to form a group selected from 1-morpholinyl, 1-(4-(3-trifluoromethyl-phenyl)-piperazinyl), 1-(4-piperidinyl-piperidinyl), 1-(4-pyrrolidinyl-piperidinyl), 1-(4-phenyl-piperidinyl), 1-(3-hydroxy-piperidinyl), 1-(4-hydroxy-piperidinyl), 1-(3-hydroxymethyl-piperidinyl), 1-(3,5-dimethyl-piperidinyl), 1-(4-dimethylamino-piperidinyl), 1-(4-(3,4-methylenedioxyphenylmethyl)-piperazinyl), 1-(3-(diethylaminocarbonyl)-piperidinyl), 1-(4-t-butoxycarbonylamino-piperidinyl), 1-(2,3-dihydro-1H-pyrrolyl), 1-(4-[(4-chlorophenyl)-phenyl-methyl]-piperazinyl), 2-(1,2,3,4-tetrahydro-isoquinolinyl), 1-(4-t-butoxycarbonyl-piperazinyl), 2-(1,2,3,4-tetrahydro-6,7-dimethoxy-isoquinolinyl), 4-(2,6-dimethyl-morpholinyl), 1-(4-benzyl-piperazinyl), 1-pyrrolidinyl, 1-(2,3-dihydro-pyrrolidinyl), 1-(3-hydroxy-pyrrolidinyl), 1-(3-(S)-hydroxy-pyrrolidinyl), 1-piperidinyl, 1-(3-ethoxycarbonyl-piperidinyl), 1-(4-ethoxycarbonyl-piperidinyl), 1-imidazolyl, 1-(2-(phenylamino-methyl)-N-pyrrolidinyl), 1-(3-(R)-dimethylamino-pyrrolidinyl), 1-(3-(R)-hydroxy-pyrrolidinyl), 1-(3,4-dihydroxy-2,5-bis-hydroxymethyl-pyrrolidinyl), 1-(3-(R)-t-butoxycarbonylamino-pyrrolidinyl), 1-(3-(S)-ethylamino-pyrrolidinyl), 1-(3-(R)-amino-pyrrolidinyl), 1-(3-(S)-amino-pyrrolidinyl), 1-(3-(R)-methylamino-pyrrolidinyl), 1-(3-(S)-methylamino-pyrrolidinyl), 1-(3-(N-methyl-N-t-butoxycarbonyl-amino)-pyrrolidinyl) or 1-(2-(3,5-dichlorophenyl)-3-methyl-5-carboxy-1,2,4-triazolyl);

R³ is selected from the group consisting of phenyl and 4-fluorophenyl;

L¹ is selected from the group consisting of -CH₂-, -CH(CH₃)- and -CH₂CH₂-;



is selected from the group consisting of cyclooctyl, 1-acenaphthenyl, R-1-acenaphthenyl, S-1-acenaphthenyl, cyclohexyl, phenyl, 1-naphthyl, 2-naphthyl, 1,2,3,4-tetrahydro-naphthyl, 2-thienyl, benzothienyl, 4,5,6,7-tetrahydro-benzothienyl, bicyclo[3.1.1]hepten-2-yl, bicyclo[3.1.1]heptyl and (3aS)-2,3,3a,4,5,6-hexahydro-1H-phenalen-1-yl;

R^5 is selected from the group consisting of chloro, methyl, n-propyl and trifluoromethyl;

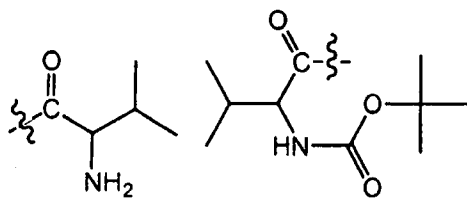
R^7 is selected from the group consisting of phenyl and 2-thienyl;
or a pharmaceutically acceptable salt thereof.

5

5. A compound as in Claim 4 wherein

X is selected from the group consisting of $-NR^1R^2$, $-SR^1$ and $-S-CH_2CH(CO_2H)-NH-C(O)-CH_3$.

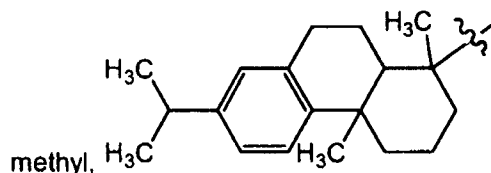
R^1 is selected from the group consisting of hydrogen, methyl, ethyl, n-propyl, n-butyl, t-butyl, dimethylaminoethyl, benzyl, phenylethyl,



, 3-methyl-phenyl, 2-(3,4-dimethoxyphenyl)-ethyl, ethoxycarbonyl-methyl, dimethylamino-ethyl and 2-amino-2-methoxycarbonyl-ethyl;

R^2 is selected from the group consisting of hydrogen, methyl, methoxy, ethyl, ethoxycarbonyl-methyl, 2,2,2-trifluoroethyl, ethoxy, dimethylaminoethyl, n-butyl, t-butyl, n-propyl, di(n-butyl)amino-n-propyl, 3-phenyl-n-propyl, 3-(2-pyridyl)-n-propyl, cyclopropyl, phenyl, 4-fluorophenyl, 4-methylphenyl, 2-aminophenyl, 4-(t-butoxycarbonylamino-ethyl)-phenyl, 3,4-dimethoxyphenyl, 4-biphenyl, 2-ethoxyphenyl, 4-((1-phenyl-pyrazol-2-yl)-aminosulfonyl)-phenyl, 4-(aminoethyl)-phenyl, benzyl, benzyloxy, 2-methylbenzyl, 3-methylbenzyl, 4-methylbenzyl, 2-methoxybenzyl, 3-methoxybenzyl, 4-methoxybenzyl, 2-ethoxybenzyl, 3-ethoxybenzyl, 2-bromobenzyl, 3-bromobenzyl, 4-bromobenzyl, 3-chlorobenzyl, 4-chlorobenzyl, 3-iodobenzyl, 2-fluorobenzyl, 3-fluorobenzyl, 4-fluorobenzyl, 2-trifluoromethylbenzyl, 3-trifluoromethylbenzyl, 4-trifluoromethylbenzyl, 4-trifluoromethoxybenzyl, 4-methoxycarbonyl-benzyl, 2,3-dimethoxybenzyl, 2,4-dichlorobenzyl, 3,4-dichlorobenzyl, 2,4-difluorobenzyl, 2,5-difluorobenzyl, 3,4-difluorobenzyl, 3,4,5-trimethoxybenzyl, 2,4,6-trimethoxybenzyl, 4-carboxybenzyl, 3-nitrobenzyl, 4-nitrobenzyl, 2,4-dimethoxybenzyl, 3,4-dimethoxybenzyl, 3,5-dimethoxybenzyl, 3,4-

- difluorobenzyl, 3,5-di(trifluoromethyl)-benzyl, 2-phenylethyl, 2-(4-bromophenyl)ethyl, 2-(3-methoxyphenyl)ethyl, 2-(4-methoxyphenyl)ethyl, 2-(3,4-dimethoxyphenyl)ethyl, 2-(2-nitro-4,5-dimethoxy-phenyl)ethyl, 3-(4-morpholinyl)-n-propyl, 2-(4-morpholinyl)ethyl, 2-(4-imidazolyl)ethyl,
- 5 adamantanyl, 1-adamantanyl-methyl, 2-(2,5-dimethoxy-2,5-dihydro-furyl)methyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyridyl-methyl, 3-pyridyl-methyl, 4-pyridyl-methyl, 2-(3,4-dimethyl-pyridyl), 2-(5-bromopyridyl), 2-(4,6-dimethyl-pyridyl), 2-(5-methyl-pyridyl), 3-(6-methoxy-pyridyl), thienylmethyl, 2-thienylethyl, 1-naphthyl, 1-naphthyl-methyl, 1-(3,4-
- 10 methylenedioxyphenyl)methyl, 2-(3,4-methylenedioxyphenyl)ethyl, 2-furyl-



methyl, 2S-hydroxy-S-cyclopentyl-methyl, 2S-hydroxy-S-cyclohexyl-methyl, 2S-hydroxy-S-cycloheptyl-methyl, 2-phenoxy-ethyl and 2-(6-fluoro-2-indolyl)-ethyl;

- 15 alternatively when R¹ and R² are both bound to the same nitrogen atom, R¹ and R² are taken together with the nitrogen atom to which they are bound to form a group selected from 1-(4-(3-trifluoromethyl-phenyl)-piperazinyl), 1-(4-phenyl-piperidinyl), 1-(4-piperidinyl-piperidinyl), 1-(4-(3,4-
- methylenedioxyphenyl-methyl)-piperazinyl), 1-(3-(diethylaminocarbonyl)-piperidinyl), 1-(4-[(4-chlorophenyl)-phenylmethyl]-piperazinyl), 2-(1,2,3,4-
- 20 tetrahydro-isoquinoliny), 1-(4-t-butoxycarbonyl-piperazinyl), 2-(1,2,3,4-tetrahydro-6,7-dimethoxy-isoquinoliny), 4-(2,6-dimethyl-morpholinyl), 1-(4-benzyl-piperazinyl), 1-morpholinyl, 1-pyrrolidinyl, 1-(2,3-dihydro-pyrrolidinyl), 1-piperidinyl, 1-(3,5-dimethyl-piperidinyl), 1-(3-hydroxymethyl-piperidinyl), 1-(3-
- 25 ethoxycarbonyl-piperidinyl), 1-(4-(ethoxycarbonyl)-piperidinyl), 1-imidazolyl and 1-(2-(phenylamino-methyl)-N-pyrrolidinyl);

L¹ is selected from the group consisting of -CH₂- and -CH₂-CH₂-;



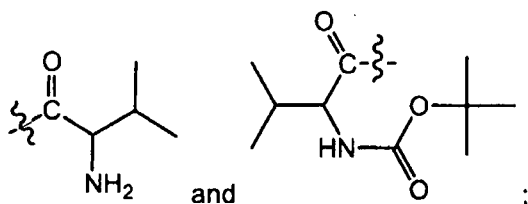
is selected from the group consisting of cyclooctyl, 1-acenaphthenyl, R-1-acenaphthenyl, S-1-acenaphthenyl, cyclohexyl, phenyl, 1-naphthyl and (3a-S)-2,3,3a,4,5,6-hexahydro-1H-phenalen-2-yl;

p is an integer from 0 to 2;

- 5 R^7 is 2-thienyl;
or a pharmaceutically acceptable salt thereof.

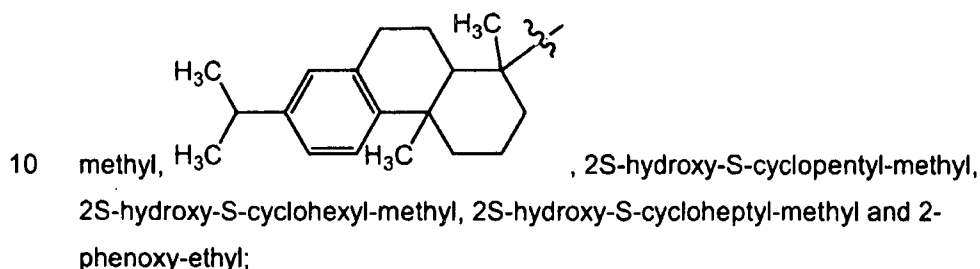
6. A compound as in Claim 5 wherein

- R^1 is selected from the group consisting of hydrogen, methyl, ethyl, n-propyl, n-butyl, t-butyl, dimethylaminoethyl, benzyl, phenylethyl, 2-(3,4-dimethoxyphenyl)-ethyl, dimethylamino-ethyl, ethoxycarbonyl-methyl,



- R^2 is selected from the group consisting of hydrogen, methyl, methoxy, ethyl, ethoxycarbonyl-methyl, ethoxy, dimethylaminoethyl, n-butyl, n-propyl, di(n-butyl)amino-n-propyl, 3-phenyl-n-propyl, 3-(2-pyridyl)-n-propyl, cyclopropyl, phenyl, 4-fluorophenyl, 4-methylphenyl, 2-aminophenyl, 3,4-dimethoxyphenyl, 4-(t-butoxycarbonylamino-ethyl)-phenyl, 4-biphenyl, 2-ethoxyphenyl, 4-((1-phenyl-pyrazol-2-yl)-aminosulfonyl)-phenyl, 4-(aminoethyl)-phenyl, benzyl, benzyloxy, 2-methylbenzyl, 3-methylbenzyl, 4-methylbenzyl, 2-methoxybenzyl, 3-methoxybenzyl, 4-methoxybenzyl, 2-ethoxybenzyl, 3-ethoxybenzyl, 2-bromobenzyl, 3-bromobenzyl, 4-bromobenzyl, 3-chlorobenzyl, 4-chlorobenzyl, 3-iodobenzyl, 2-fluorobenzyl, 3-fluorobenzyl, 4-fluorobenzyl, 2-trifluoromethylbenzyl, 3-trifluoromethylbenzyl, 4-trifluoromethylbenzyl, 4-trifluoromethoxybenzyl, 4-methoxycarbonyl-benzyl, 2,3-dimethoxybenzyl, 2,4-dichlorobenzyl, 3,4-dichlorobenzyl, 2,4-difluorobenzyl, 2,5-difluorobenzyl, 3,4,5-trimethoxybenzyl, 2,4,6-trimethoxybenzyl, 3-nitrobenzyl, 4-nitrobenzyl, 2,4-dimethoxybenzyl, 3,4-dimethoxybenzyl, 3,5-dimethoxybenzyl, 3,4-difluorobenzyl, 3,5-di(trifluoromethyl)-benzyl, 2-phenylethyl, 2-(4-

bromophenyl)ethyl, 2-(3-methoxyphenyl)ethyl, 2-(4-methoxyphenyl)ethyl, 2-(3,4-dimethoxyphenyl)ethyl, 2-(2-nitro-4,5-dimethoxy-phenyl)ethyl, 3-(4-morpholinyl)-n-propyl, 2-(4-morpholinyl)ethyl, 2-(4-imidazolyl)ethyl, 1-adamantanyl, 1-adamantanyl-methyl, 2-(2,5-dimethoxy-2,5-dihydro-furyl)methyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyridyl-methyl, 3-pyridyl-methyl, 4-pyridyl-methyl, 2-(3,4-dimethyl-pyridyl), 2-(5-bromopyridyl), 2-(4,6-dimethyl-pyridyl), 2-(5-methyl-pyridyl), 3-(6-methoxy-pyridyl), thienylmethyl, 2-thienylethyl, 1-naphthyl, 1-naphthyl-methyl, 1-(3,4-methylenedioxyphenyl)methyl, 2-(3,4-methylenedioxyphenyl)ethyl, 2-furyl-



alternatively when R¹ and R² are both bound to the same nitrogen atom,
 15 R¹ and R² are taken together with the nitrogen atom to which they are bound to form a group selected from 1-(4-(3-trifluoromethyl-phenyl)-piperazinyl), 1-(4-phenyl-piperidinyl), 1-(4-piperidinyl-piperidinyl), 1-(4-(3,4-methylenedioxyphenyl-methyl)-piperazinyl), 1-(3-(diethylaminocarbonyl)-piperidinyl), 1-(4-[(4-chlorophenyl)-phenylmethyl]-piperiazinyl), 2-(1,2,3,4-tetrahydro-isoquinolinyl), 1-(4-t-butoxycarbonyl-piperazinyl), 2-(1,2,3,4-
 20 tetrahydro-6,7-dimethoxy-isoquinolinyl), 4-(2,6-dimethyl-morpholinyl), 1-(4-benzyl-piperazinyl), 1-(3,5-dimethyl-piperidinyl), 1-(3-hydroxymethyl-piperidinyl), 1-(3-ethoxycarbonyl-piperidinyl), 1-(4-(ethoxycarbonyl)-piperidinyl), 1-piperidinyl, 1-morpholinyl, 1-pyrrolidinyl, 1-imidazolyl, 1-(2,3-dihydro-pyrrolidinyl), and 1-(2-(phenylamino-methyl)-N-pyrrolidinyl);

p is an integer from 0 to 1;

R⁵ is selected from the group consisting of methyl, n-propyl and trifluoromethyl;

or a pharmaceutically acceptable salt thereof.

30

7. A compound as in Claim 4 wherein

R^0 is $-\text{CH}_2-\text{CH}(\text{OH})-\text{CH}_2-\text{X}$;

X is $-\text{NR}^1\text{R}^2$;

R^1 is selected from the group consisting of hydrogen, 2-(3,4-

5 dimethoxyphenyl)-ethyl, 1-(3,4-dimethoxyphenyl)-n-ethyl and amino-n-propyl;

R^2 is selected from the group consisting of hydrogen, methyl, n-butyl, 3-hydroxy-n-propyl, 3-methoxy-n-propyl, methylamino-n-propyl, dimethylamino-n-propyl, t-butoxycarbonylamino-n-propyl, N-methyl-N-t-butoxycarbonyl-amino-n-ethyl, 3-nitrobenzyl, 4-methoxycarbonyl-benzyl, $-\text{CH}(\text{CH}_3)$ -phenyl, 4-pyridinyl, 1-(4-ethoxycarbonyl-piperidinyl) and 2-(3H-imidazol-4-yl)-ethyl;

alternatively when R^1 and R^2 are both bound to the same nitrogen atom, R^1 and R^2 are taken together with the nitrogen atom to which they are bound to form a group selected from 2-(1,2,3,4-tetrahydro-6,7-dimethoxy-isoquinolinyl), 1-(4-[(4-chlorophenyl)-phenyl-methyl]-piperazinyl), 1-pyrrolidinyl, 1-(3-hydroxy-pyrrolidinyl), 1-(3-(S)-hydroxy-pyrrolidinyl), 1-(3-(R)-hydroxy-pyrrolidinyl), 1-(4-hydroxy-piperidinyl), 1-(3-(R)-dimethylamino-pyrrolidinyl), 1-(4-t-butoxycarbonylamino-pyrrolidinyl), 1-(3-(R)-t-butoxycarbonylamino-pyrrolidinyl), 1-(3-(R)-amino-pyrrolidinyl), 1-(3-(S)-amino-pyrrolidinyl), 1-(3-(R)-methylamino-pyrrolidinyl), 1-(3-(S)-methylamino-pyrrolidinyl), 1-(3-(S)-ethylamino-pyrrolidinyl), 1-(4-dimethylamino-pyrrolidinyl), 1-(3-(N-methyl-N-t-butoxycarbonyl-amino-pyrrolidinyl) or 1-(2-(3,5-dichlorophenyl)-3-methyl-5-carboxy-1,2,4-triazolyl);

R^3 is selected from the group consisting of phenyl and 4-fluorophenyl;

L^1 is selected from the group consisting of $-\text{CH}_2-$ and $-\text{CH}_2\text{CH}_2-$;



25 is selected from the group consisting cyclooctyl, 1-naphthyl, 1-acenaphthenyl, R-1-acenaphthenyl, S-1-acenaphthenyl, bicyclo[3.1.1]hepten-2-yl, bicyclo[3.1.1]heptyl and (3aS)-2,3,3a,4,5,6-hexahydro-1H-phenalen-1-yl.

p is an integer from 0 to 1;

R^5 is methyl;

30 q is 0;

or a pharmaceutically acceptable salt thereof.

8/6

8. A compound as in Claim 7 wherein

R^1 is selected from the group consisting of hydrogen, 1-(3,4-dimethoxyphenyl)-n-ethyl and amino-n-propyl;

5 R^2 is selected from the group consisting of hydrogen, methyl, n-butyl, 3-hydroxy-n-propyl, 3-methoxy-n-propyl, methylamino-n-propyl, dimethylamino-n-propyl, N-methyl-N-t-butoxycarbonyl-amino-n-ethyl, 3-nitrobenzyl, 4-methoxycarbonyl-benzyl, -CH(CH₃)-phenyl, 4-pyridinyl and 2-(3H-imidazol-4-yl)-ethyl;

10 alternatively when R^1 and R^2 are both bound to the same nitrogen atom, R^1 and R^2 are taken together with the nitrogen atom to which they are bound to form a group selected from 2-(1,2,3,4-tetrahydro-6,7-dimethoxy-isoquinolinyl), 1-(4-[(4-chlorophenyl)-phenyl-methyl]-piperazinyl), 1-pyrrolidinyl, 1-(3-hydroxy-pyrrolidinyl), 1-(3-(R)-hydroxy-pyrrolidinyl), 1-(4-hydroxy-piperidinyl), 1-(3-(R)-dimethylamino-pyrrolidinyl), 1-(4-t-butoxycarbonylamino-pyrrolidinyl), 1-(3-(R)-t-butoxycarbonylamino-pyrrolidinyl), 1-(3-(R)-amino-pyrrolidinyl), 1-(3-(S)-amino-pyrrolidinyl), 1-(3-(R)-methylamino-pyrrolidinyl), 1-(3-(S)-methyamino-pyrrolidinyl), 1-(3-(S)-ethylamino-pyrrolidinyl), 1-(4-dimethylamino-pyrrolidinyl), 1-(3-(N-methyl-N-t-butoxycarbonyl-amino-pyrrolidinyl) or 1-(2-(3,5-dichlorophenyl)-3-methyl-5-carboxy-1,2,4-triazolyl);



is selected from the group consisting cyclooctyl, 1-naphthyl, 1-acenaphthenyl, R-1-acenaphthenyl, S-1-acenaphthenyl, bicyclo[3.1.1]hepten-2-yl, bicyclo[3.1.1]heptyl and (3aS)-2,3,3a,4,5,6-hexahydro-1H-phenalen-1-yl. or a pharmaceutically acceptable salt thereof.

25

9. A compound as in Claim 1 selected from the group consisting of

8-(R) acenaphthen-1-yl-3-(3-amino-2-(S)-hydroxy-propyl)-1-(4-fluorophenyl)-1,3,8-triaza-spiro[4.5]decan-4-one;

8-(R) acenaphthen-1-yl-3-(3-amino-2-(R)-hydroxy-propyl)-1-(4-fluorophenyl)-1,3,8-triaza-spiro[4.5]decan-4-one;

30

8-(R)-Acenaphthen-1-yl-3-(3-dimethylamino-2-(R)-hydroxy-propyl)-1-(4-fluoro-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one;

3-(3-Amino-2-(R)-hydroxy-propyl)-1-(4-fluoro-phenyl)-8-(8-methyl-naphthalen-1-ylmethyl)-1,3,8-triaza-spiro[4.5]decan-4-one;

5 3-(3-Dimethylamino-2-(R)-hydroxy-propyl)-1-(4-fluoro-phenyl)-8-(8-methyl-naphthalen-1-ylmethyl)-1,3,8-triaza-spiro[4.5]decan-4-one;

8-(R)-Acenaphthen-1-yl-1-(4-fluoro-phenyl)-3-[2-(R)-hydroxy-3-(3-hydroxymethyl-piperidin-1-yl)-propyl]-1,3,8-triaza-spiro[4.5]decan-4-one;

3-(3-Amino-2-(R)-hydroxy-propyl)-8-cyclooctyl-1-(4-fluoro-phenyl)-1,3,8-
10 triaza-spiro[4.5]decan-4-one;

3-(3-Amino-2-(R)-hydroxy-propyl)-1-(4-fluoro-phenyl)-8-1-(S)-(3aS)-(2,3,3a,4,5,6-hexahydro-1H-phenalen-1-yl)-1,3,8-triaza-spiro[4.5]decan-4-one;

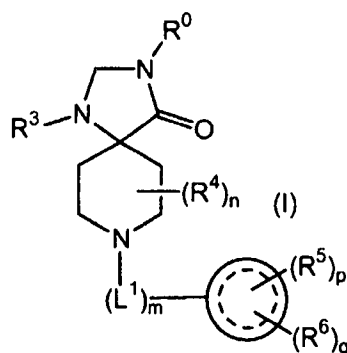
1-(4-Fluoro-phenyl)-3-[2-(R)-hydroxy-3-(3-hydroxy-propylamino)-propyl]-8-(8-methyl-naphthalen-1-ylmethyl)-1,3,8-triaza-spiro[4.5]decan-4-one;

15 1-(4-Fluoro-phenyl)-3-[2-(R)-hydroxy-3-(3-methylamino-propylamino)-propyl]-8-(8-methyl-naphthalen-1-ylmethyl)-1,3,8-triaza-spiro[4.5]decan-4-one;

3-[3-(3-Dimethylamino-propylamino)-2-(R)-hydroxy-propyl]-1-(4-fluoro-phenyl)-8-(8-methyl-naphthalen-1-ylmethyl)-1,3,8-triaza-spiro[4.5]decan-4-one
and pharmaceutically acceptable salts thereof.

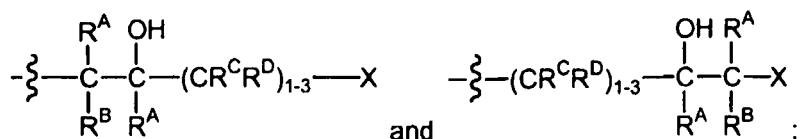
20

10. A compound of the formula (I)



wherein

R^0 is selected from the group consisting of



each R^A and R^B is independently selected from the group consisting of hydrogen and C_{1-4} alkyl;

- 5 each R^C and R^D is independently selected from the group consisting of hydrogen, hydroxy, carboxy, C_{1-4} alkyl, C_{1-4} alkoxy, nitro, cyano, $N(R^E)_2$, aryl, ar C_{1-4} alkyl, heteroaryl or heterocycloalkyl; wherein the aryl, ar C_{1-4} alkyl, heteroaryl or heterocycloalkyl substituent is optionally substituted with one or more substituents independently selected from hydroxy, carboxy, C_{1-4} alkyl, C_{1-4} alkoxy, nitro, cyano or $N(R^E)_2$;

10 each R^E is independently selected from the group consisting of hydrogen and C_{1-4} alkyl;

- X is selected from the group consisting of $-NR^1R^2$, $-C(O)-NR^1R^2$, $-NR^1-C(O)-R^2$, $-OR^1$, $-SR^1$, $-SOR^1$, $-SO_2R^1$, $-S-(C_{2-4}alkyl)-NR^1R^2$, $-S-(C_{2-4}alkyl)-C(O)O-C(CH_3)_3$, $-SO-(C_{1-4}alkyl)-NR^1R^2$ and $-SO_2-(C_{1-4}alkyl)-NR^1R^2$; wherein the alkyl portion of the $-S-(C_{2-4}alkyl)-NR^1R^2$, $-SO-(C_{1-4}alkyl)-NR^1R^2$ or $-SO_2-(C_{1-4}alkyl)-NR^1R^2$ group is optionally substituted with one or more substituents independently selected from carboxy, hydroxy, hydroxy C_{1-4} alkyl, C_{1-4} alkyl, C_{1-4} alkoxycarbonyl or $-CONR^1R^2$;

- 20 each R^1 and R^2 is independently selected from the group consisting of hydrogen, C_{1-8} alkyl, C_{1-8} alkoxy, cycloalkyl, cycloalkyl- C_{1-4} alkyl, partially unsaturated carbocycl, aryl, ar C_{1-4} alkyl, ar C_{1-4} alkoxy, heteroaryl, heteroaryl- C_{1-4} alkyl, heterocycloalkyl, heterocycloalkyl- C_{1-4} alkyl, $-C(O)-C_{1-6}alkyl$, $-C(O)-aryl$, $-C(O)-arC_{1-4}alkyl$, $-C(O)-heteroaryl$ and $-C(O)-heterocycloalkyl$; wherein the C_{1-8} alkyl, cycloalkyl, partially unsaturated carbocycl, aryl, ar C_{1-8} alkyl, heteroaryl or heterocycloalkyl group, whether alone or part of a substituent group, is optionally substituted with one or more substituents independently selected from halogen, hydroxy, carboxy, C_{1-4} alkyl, C_{1-4} alkoxy, trifluoromethyl, trifluoromethoxy, nitro, cyano, $-C(O)-C_{1-4}alkyl$, C_{1-4} alkoxycarbonyl, $N(R^E)_2$, $N(R^E)_2-C_{1-4}alkyl$, $N(R^E)-C(O)C(CH_3)_3$, aryl, aryloxy, cycloalkyl, heteroaryl, aryl substituted heteroarylamino sulfonyl or $C_{1-6}alkylthio$;

- alternatively when R^1 and R^2 are both bound to the same nitrogen atom, R^1 and R^2 are taken together with the nitrogen atom to which they are bound to form a heteroaryl or heterocycloalkyl group; wherein the heteroaryl or heterocycloalkyl group is optionally substituted with one or more substituents
- 5 independently selected from halogen, hydroxy, carboxy, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkoxycarbonyl, trifluoromethyl, trifluoromethoxy, nitro, cyano, $N(R^E)_2$, aryl, ar C_{1-4} alkyl, heteroaryl, heterocycloalkyl, di(C_{1-6})alkylamino-carbonyl, t-butoxycarbonyl or arylamino- C_{1-4} alkyl; wherein the aryl, ar C_{1-4} alkyl, heteroaryl or heterocycloalkyl substituent is optionally further substituted with one or more
- 10 substituents independently selected from halogen, hydroxy, carboxy, C_{1-4} alkyl, C_{1-4} alkoxy, trifluoromethyl, trifluoromethoxy, nitro, cyano, $N(R^E)_2$ or substituted phenyl; wherein the substituents on the phenyl are one or more independently selected from halogen, hydroxy, carboxy, C_{1-4} alkyl, C_{1-4} alkoxy, trifluoromethyl, trifluoromethoxy, nitro, cyano or $N(R^E)_2$;
- 15 R^3 is selected from the group consisting of aryl, ar C_{1-6} alkyl and heteroaryl; wherein the aryl, ar C_{1-6} alkyl or heteroaryl group is optionally substituted with one or more substituents independently selected from halogen, hydroxy, carboxy, C_{1-4} alkyl, C_{1-4} alkoxy, trifluoromethyl, trifluoromethoxy, nitro, cyano or $N(R^E)_2$;
- 20 n is an integer from 0 to 2;
- R^4 is selected from the group consisting of hydroxy, C_{1-4} alkyl and hydroxy substituted C_{1-4} alkyl;
- m is an integer from 0 to 1;
- L^1 is selected from the group consisting of C_{1-6} alkyl and C_{3-6} alkenyl;
- 25 wherein the double bond of the C_{3-6} alkenyl group is at least one carbon atom removed from the attachment point to the N atom; and wherein the C_{1-6} alkyl or C_{3-6} alkenyl group is optionally substituted with one to two substituents independently selected from hydroxy, fluoro, C_{1-6} alkyl, fluorinated C_{1-6} alkyl or C_{1-6} alkoxy;



- 30 is selected from the group consisting of cycloalkyl, partially unsaturated carbocyclyl, aryl, heteroaryl and heterocycloalkyl;

p is an integer from 0 to 5;

R^5 is selected from the group consisting of hydroxy, carboxy, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, nitro, cyano, NR^1R^2 , trifluoromethyl, trifluoromethoxy, C_{1-4} alkoxycarbonyl, $-SO-NR^1R^2$, $-SO_2-NR^1R^2$ and $-C(O)-NR^1R^2$;

5 q is an integer from 0 to 1;

R^6 is selected from the group consisting of $-(L^2)_{0-1}-R^7$;

L^2 is selected from the group consisting of $-C_{1-6}$ alkyl-, $-C_{2-4}$ alkenyl-, $-C_{2-6}$ alkynyl-, $-O-$, $-S-$, $-NH-$, $-N(C_{1-4}alkyl)-$, $-C_{1-6}alkyl-O-$, $-C_{1-6}alkyl-S-$, $-O-C_{1-6}alkyl-$, $-S-C_{1-6}alkyl-$, $-O-C_{2-6}alkyl-O-$, $-S-C_{2-6}alkyl-S-$, $-SO_2-$, $-SO_2NH-$, $-SO_2N(C_{1-4}alkyl)-$, $-NH-SO_2-$, $-N(C_{1-4}alkyl)-SO_2-$, $-C(O)-O-$ and $-O-C(O)-$;

10 R^7 is selected from the group consisting of aryl, partially unsaturated carbocyclyl, cycloalkyl, heteroaryl and heterocycloalkyl; wherein the aryl, partially unsaturated carbocyclyl, cycloalkyl, heteroaryl or heterocycloalkyl group is optionally substituted with one or more substituents independently selected from hydroxy, carboxy, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, nitro, cyano, $N(R^E)_2$, trifluoromethyl, trifluoromethoxy, C_{1-4} alkoxycarbonyl, $-SO_2-N(R^E)_2$ and $-C(O)-N(R^E)_2$;

or a pharmaceutically acceptable salt thereof.

20 11. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of Claim 1.

12. A pharmaceutical composition made by mixing a compound of Claim 1 and a pharmaceutically acceptable carrier.

25

13. A process for making a pharmaceutical composition comprising mixing a compound of Claim 1 and a pharmaceutically acceptable carrier.

14. A method of treating a disorder mediated by the ORL-1 receptor, in a
30 subject in need thereof comprising administering to the subject a therapeutically effective amount of the compound of Claim 1.

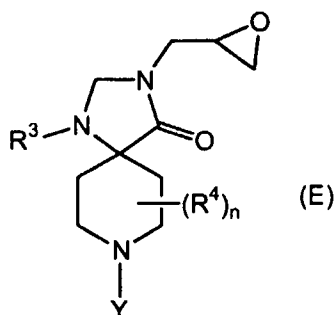
15. The method of Claim 14, wherein the disorder mediated by the ORL-1 receptor is selected from the group consisting of anxiety, depression, panic, mania, dementia, bipolar disorder, substance abuse, neuropathic pain, acute pain, chronic pain, migraine, asthma, cough, psychosis, schizophrenia, epilepsy, hypertension, obesity, eating disorders, cravings, diabetes, cardiac arrhythmia, irritable bowel syndrome, Crohn's disease, urinary incontinence, adrenal disorders, attention deficit disorder (ADD), attention deficit hyperactivity disorder (ADHD), Alzheimer's disease, improved cognition, improved memory and mood stabilization.
16. A method of treating a disorder mediated by the ORL-1 receptor, in a subject in need thereof comprising administering to the subject a therapeutically effective amount of the composition of Claim 11.
17. A method of treating a condition selected from the group consisting of anxiety, depression, panic, mania, dementia, bipolar disorder, substance abuse, neuropathic pain, acute pain, chronic pain, migraine, asthma, cough, psychosis, schizophrenia, epilepsy, hypertension, obesity, eating disorders, cravings, diabetes, cardiac arrhythmia, irritable bowel syndrome, Crohn's disease, urinary incontinence, adrenal disorders, attention deficit disorder (ADD), attention deficit hyperactivity disorder (ADHD), Alzheimer's disease, improved cognition, improved memory and mood stabilization, in a subject in need thereof comprising administering to the subject a therapeutically effective amount of the compound of Claim 1.
18. A method of treating a condition selected from the group consisting of anxiety, depression, panic, mania, dementia, bipolar disorder, substance abuse, neuropathic pain, acute pain, chronic pain, migraine, asthma, cough, psychosis, schizophrenia, epilepsy, hypertension, obesity, eating disorders, cravings, diabetes, cardiac arrhythmia, irritable bowel syndrome, Crohn's disease, urinary incontinence, adrenal disorders, attention deficit disorder (ADD), attention deficit hyperactivity disorder (ADHD), Alzheimer's disease, improved cognition, improved memory and mood stabilization, in a subject in

need thereof comprising administering to the subject a therapeutically effective amount of the composition of Claim 7.

19. The use of a compound as in Claim 1 for the preparation of a medicament for the treatment of (a) anxiety, (b) depression, (c) panic, (d) mania, (e) dementia, (f) bipolar disorder, (g) substance abuse, (h) neuropathic pain, (i) acute pain, (j) chronic pain, (k) migraine, (l) asthma, (m) cough, (n) psychosis, (o) schizophrenia, (p) epilepsy, (q) hypertension, (r) obesity, (s) eating disorders, (t) cravings, (u) diabetes, (v) cardiac arrhythmia, (w) irritable bowel syndrome, (x) Crohn's disease, (y) urinary incontinence, (z) adrenal disorders, (aa) attention deficit disorder (ADD), (bb) attention deficit hyperactivity disorder (ADHD), (cc) Alzheimer's disease, for (dd) improved cognition, (ee) improved memory or (ff) mood stabilization, in a subject in need thereof.

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20. A compound of the formula (E)



wherein

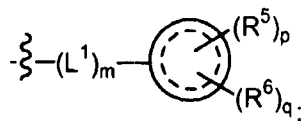
- 20 R^3 is selected from the group consisting of aryl, arC₁₋₆alkyl and heteroaryl; wherein the aryl, arC₁₋₆alkyl or heteroaryl group is optionally substituted with one or more substituents independently selected from halogen, hydroxy, carboxy, C₁₋₄alkyl, C₁₋₄alkoxy, trifluoromethyl, trifluoromethoxy, nitro, cyano or N(R^E)₂;

each R^E is independently selected from hydrogen or C₁₋₄alkyl;

25 n is an integer from 0 to 2;

R^4 is selected from the group consisting of hydroxy, C₁₋₄alkyl and hydroxy substituted C₁₋₄alkyl;

Y is selected from the group consisting of hydrogen, C₁₋₄alkyl, t-



butoxycarbonyl and

m is an integer from 0 to 1;

L¹ is selected from the group consisting of C₁₋₆alkyl and C₃₋₆alkenyl;

- 5 wherein the double bond of the C₃₋₆alkenyl group is at least one carbon atom removed from the attachment point to the N atom; and wherein the C₁₋₆alkyl or C₃₋₆alkenyl group is optionally substituted with one to two substituents independently selected from hydroxy, fluoro, C₁₋₆alkyl, fluorinated C₁₋₆alkyl or C₁₋₆alkoxy;



- 10 is selected from the group consisting of cycloalkyl, partially unsaturated carbocyclyl, aryl, heteroaryl and heterocycloalkyl;

p is an integer from 0 to 5;

R⁵ is selected from the group consisting of hydroxy, carboxy, halogen, C₁₋₆alkyl, hydroxy substituted C₁₋₆alkyl, C₁₋₆alkoxy, nitro, cyano, NR¹R²,

- 15 trifluoromethyl, trifluoromethoxy, C₁₋₄alkoxycarbonyl, -SO-NR¹R², -SO₂-NR¹R² and -C(O)-NR¹R²;

q is an integer from 0 to 1;

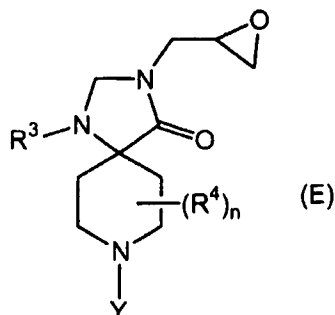
R⁶ is selected from the group consisting of -(L²)₀₋₁-R⁷;

- 20 L² is selected from the group consisting of -C₁₋₆alkyl-, -C₂₋₄alkenyl-, -C₂₋₆alkynyl-, -O-, -S-, -NH-, -N(C₁₋₄alkyl)-, -C₁₋₆alkyl-O-, -C₁₋₆alkyl-S-, -O-C₁₋₆alkyl-, -S-C₁₋₆alkyl-, -O-C₂₋₆alkyl-O-, -S-C₂₋₆alkyl-S-, -SO₂-, -SO₂NH-, -SO₂N(C₁₋₄alkyl)-, -NH-SO₂-, -N(C₁₋₄alkyl)-SO₂-, -C(O)-O- and -O-C(O)-;

- 25 R⁷ is selected from the group consisting of aryl, partially unsaturated carbocyclyl, cycloalkyl, heteroaryl and heterocycloalkyl; wherein the aryl, partially unsaturated carbocyclyl, cycloalkyl, heteroaryl or heterocycloalkyl group is optionally substituted with one or more substituents independently selected from hydroxy, carboxy, halogen, C₁₋₆alkyl, C₁₋₆alkoxy, nitro, cyano, N(R^E)₂, trifluoromethyl, trifluoromethoxy, C₁₋₄alkoxycarbonyl, -SO₂-N(R^E)₂ and -C(O)-N(R^E)₂;

or a pharmaceutically acceptable salt thereof.

21. A compound of the formula (E)



5 wherein

R^3 is selected from the group consisting of aryl, arC₁₋₆alkyl and heteroaryl; wherein the aryl, arC₁₋₆alkyl or heteroaryl group is optionally substituted with one or more substituents independently selected from halogen, hydroxy, carboxy, C₁₋₄alkyl, C₁₋₄alkoxy, trifluoromethyl,

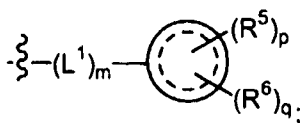
10 trifluoromethoxy, nitro, cyano or N(R^E)₂;

each R^E is independently selected from hydrogen or C₁₋₄alkyl;

n is an integer from 0 to 2;

R^4 is selected from the group consisting of hydroxy, C₁₋₄alkyl and hydroxy substituted C₁₋₄alkyl;

15 Y is selected from the group consisting of hydrogen, C₁₋₄alkyl, t-



butoxycarbonyl and

m is an integer from 0 to 1;

L^1 is selected from the group consisting of C₁₋₆alkyl and C₃₋₆alkenyl;

wherein the double bond of the C₃₋₆alkenyl group is at least one carbon atom

20 removed from the attachment point to the N atom; and wherein the C₁₋₆alkyl or C₃₋₆alkenyl group is optionally substituted with one to two substituents independently selected from hydroxy, fluoro, C₁₋₆alkyl, fluorinated C₁₋₆alkyl or C₁₋₆alkoxy;



is selected from the group consisting of cycloalkyl, partially unsaturated carbocyclyl, aryl, heteroaryl and heterocycloalkyl;

p is an integer from 0 to 5;

R⁵ is selected from the group consisting of hydroxy, carboxy, halogen,

- 5 C₁₋₆alkyl, C₁₋₆alkoxy, nitro, cyano, NR¹R², trifluoromethyl, trifluoromethoxy, C₁₋₄alkoxycarbonyl, -SO-NR¹R², -SO₂-NR¹R² and -C(O)-NR¹R²;

q is an integer from 0 to 1;

R⁶ is selected from the group consisting of -(L²)₀₋₁-R⁷;

- 10 L² is selected from the group consisting of -C₁₋₆alkyl-, -C₂₋₄alkenyl-, -C₂₋₆alkynyl-, -O-, -S-, -NH-, -N(C₁₋₄alkyl)-, -C₁₋₆alkyl-O-, -C₁₋₆alkyl-S-, -O-C₁₋₆alkyl-, -S-C₁₋₆alkyl-, -O-C₂₋₆alkyl-O-, -S-C₂₋₆alkyl-S-, -SO₂-, -SO₂NH-, -SO₂N(C₁₋₄alkyl)-, -NH-SO₂-, -N(C₁₋₄alkyl)-SO₂-, -C(O)-O- and -O-C(O)-;

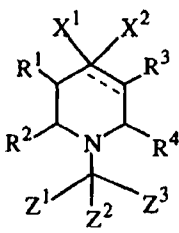
R⁷ is selected from the group consisting of aryl, partially unsaturated carbocyclyl, cycloalkyl, heteroaryl and heterocycloalkyl; wherein the aryl,

- 15 partially unsaturated carbocyclyl, cycloalkyl, heteroaryl or heterocycloalkyl group is optionally substituted with one or more substituents independently selected from hydroxy, carboxy, halogen, C₁₋₆alkyl, C₁₋₆alkoxy, nitro, cyano, N(R^E)₂, trifluoromethyl, trifluoromethoxy, C₁₋₄alkoxycarbonyl, -SO₂-N(R^E)₂ and -C(O)-N(R^E)₂;

- 20 or a pharmaceutically acceptable salt thereof.



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(21) International Application Number: PCT/US99/14165 (22) International Filing Date: 26 July 1999 (26.07.99) (30) Priority Data: 09/122,878 27 July 1998 (27.07.98) US (71) Applicant: SCHERING CORPORATION [US/US]; 2000 Galloping Hill Road, Kenilworth, NJ 07033-0530 (US). (72) Inventors: TULSHIAN, Deen; 4 Saddle Ridge Drive, Lebanon, NJ 08833 (US). HO, Ginny, D.; 42 Chestnut Hill Drive, Murray Hill, NJ 07974 (US). SILVERMAN, Lisa, S.; 214 Hana Road, Edison, NJ 08817 (US). MATASI, Julius, J.; 129 Spruce Mill Lane, Scotch Plains, NJ 07076 (US). McLEOD, Robbie, L.; 13 Creek Trail, Branchburg, NJ 08876 (US). HEY, John, A.; 122 Hopper Avenue, Nutley, NJ 07110 (US). CHAPMAN, Richard, W.; 30 Ditmars Circle, Somerville, NJ 08876 (US). BERCOVICI, Ana; 1 Howell Drive, West Orange, NJ 07052 (US). CUSS, Francis, M.; 14 Byrom Drive, Basking Ridge, NJ 07920 (US).		(74) Agents: MAGATTI, Anita, W. et al.; Schering-Plough Corporation, Patent Department, K-6-1 1990, 2000 Galloping Hill Road, Kenilworth, NJ 07033-0530 (US). (81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LU, LV, MD, MG, MK, MN, MX, NO, NZ, PL, PT, RO, RU, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UZ, VN, YU, ZA, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: HIGH AFFINITY LIGANDS FOR NOCICEPTIN RECEPTOR ORL-1  (I)		
(57) Abstract Compounds of formula (I) or a pharmaceutically acceptable salt or solvate thereof, wherein: the dotted line represents an optional double bond; X¹ is optionally substituted alkyl, cycloalkyl, aryl, heteroaryl or heterocycloalkyl; X² is -CHO, -CN, optionally substituted amino, alkyl, or aryl; or X¹ is optionally substituted benzofused heterocyclyl and X² is hydrogen; or X¹ and X² together form an optionally benzofused spiro heterocyclyl group; R¹, R², R³ and R⁴ are independently H and alkyl, or (R¹ and R⁴) or (R² and R³) or (R¹ and R³) or (R² and R⁴) together can form an alkylene bridge of 1 to 3 carbon atoms; Z¹ is optionally substituted alkyl, aryl, heteroaryl, cycloalkyl or heterocycloalkyl, or -CO₂(alkyl or substituted amino) or CN; Z² is H or Z¹; Z³ is H or alkyl; or Z¹, Z² and Z³, together with the carbon to which they are attached, form bicyclic saturated or unsaturated rings; pharmaceutical compositions therefore, and the use of said compounds as nociceptin receptor inhibitors useful in the treatment of pain, anxiety, cough, asthma, depression and alcohol abuse are disclosed.		

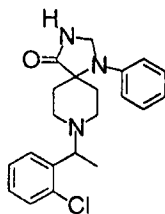
invention relates to a method of treating pain, anxiety, cough, asthma, alcohol abuse or depression, comprising administering to a mammal in need of such treatment an effective amount of a compound of formula I.

In another aspect, the invention relates to a method of treating
5 cough, comprising administering to a mammal in need of such treatment:
(a) an effective amount of a nociceptin receptor ORL-1 agonist; and (b)
an effective amount of a second agent for treating cough, allergy or
asthma symptoms selected from the group consisting of: antihistamines,
5-lipoxygenase inhibitors, leukotriene inhibitors, H₃ inhibitors, β -
10 adrenergic receptor agonists, xanthine derivatives, α -adrenergic
receptor agonists, mast cell stabilizers, anti-tussives, expectorants, NK₁,
NK₂ and NK₃ tachykinin receptor antagonists, and GABA_B agonists.

In still another aspect, the invention relates to a pharmaceutical
composition comprising a nociceptin receptor ORL-1 agonist and a
15 second agent selected from the group consisting of: antihistamines, 5-
lipoxygenase inhibitors, leukotriene inhibitors, H₃ inhibitors, β -
adrenergic receptor agonists, xanthine derivatives, α -adrenergic
receptor agonists, mast cell stabilizers, anti-tussives, expectorants, NK₁,
NK₂ and NK₃ tachykinin receptor antagonists, and GABA_B agonists.

20 In other words, the invention relates to the use of compounds of
claim 1 in the treatment of pain, anxiety, cough, asthma, alcohol abuse
or depression, and to the use of a nociceptin receptor ORL-1 agonist,
alone or in combination with a second agent for treating cough, allergy
or asthma symptoms.

25 In yet another aspect, the present invention relates to a novel
compound not included in the structure of formula I, said compound
being:



30 BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 illustrates the effect in guinea pigs of Compounds A and B (see Example 12) compared to baclofen on capsaicin-induced cough.

47

The quantity of active compound in a unit dose of preparation may be varied or adjusted from about 0.1 mg to 1000 mg, more preferably from about 1 mg. to 300 mg, according to the particular application.

The actual dosage employed may be varied depending upon the requirements of the patient and the severity of the condition being treated. Determination of the proper dosage for a particular situation is within the skill of the art. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day if desired.

The amount and frequency of administration of the compounds of the invention and the pharmaceutically acceptable salts thereof will be regulated according to the judgment of the attending clinician considering such factors as age, condition and size of the patient as well as severity of the symptoms being treated. A typical recommended dosage regimen is oral administration of from 10 mg to 2000 mg/day preferably 10 to 1000 mg/day, in two to four divided doses to provide relief from pain, anxiety, depression, asthma or alcohol abuse. The compounds are non-toxic when administered within this dosage range.

For treating cough, the amount of nociceptin receptor ORL-1 agonist in a unit dose is preferably from about 0.1 mg to 1000 mg, more preferably, from about 1 mg to 300 mg. A typical recommended dosage regimen is oral administration of from 1 mg to 2000 mg/day, preferably 1 to 1000 mg/day, in two to four divided doses. When treating coughing, the nociceptin receptor ORL-1 agonist may be administered with one or more additional agents for treating cough, allergy or asthma symptoms selected from the group consisting of: antihistamines, 5-lipoxygenase inhibitors, leukotriene inhibitors, H₃ inhibitors, β -adrenergic receptor agonists, xanthine derivatives, α -adrenergic receptor agonists, mast cell stabilizers, anti-tussives, expectorants, NK₁, NK₂ and NK₃ tachykinin receptor antagonists, and GABA_B agonists. The nociceptin receptor ORL-1 agonist and the additional agents are preferably administered in a combined dosage form (e.g., a single tablet), although they can be

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Trámite :	11 PATENTEIYII	
Evento :	378 FASENACIONALI	
Actuación :	432 COMUNICACTOADM	
Destinatario :	DILIA MARIA RODRIGUEZ D' ALEMAN Folios 1	

Señor (a) (es)
DILIA MARIA RODRIGUEZ D' ALEMAN
CARRERA 11 NO. 86-53 PISO 6
BOGOTA D.C.

Referencia RESOLUCION : 31441
Fecha : 07/06/2011
Expediente : 9-55461
Trámite : 11 PCT-PATENTE DE INVENCION CAPITULOS I Y II
Evento : 378 FASE NACIONAL INCLUIDO CAPITULO I
Actuación : 432 COMUNICACION ACTO ADMINISTRATIVO

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Evento :	378 FASENACIONALI	
Actuación :	432 COMUNICACTOADM	
Destinatario :	JOSE LUIS REYES VILLAMIZAR Folios 1	

Señor (a) (es)
JOSE LUIS REYES VILLAMIZAR
CARRERA 17 NO 88 - 23 OF 205
BOGOTA D.C.

Referencia RESOLUCION : 31441
Fecha : 07/06/2011
Expediente : 9-55461
Trámite : 11 PCT-PATENTE DE INVENCION CAPITULOS I Y II
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Evento :	378 FASENACIONALI
Actuación :	432 COMUNICACTOADM
Destinatario :	TITO NOE PARRA MURILLO Folios 1

Señor (a) (es)
TITO NOE PARRA MURILLO
CALLE 108 # 51-45
BOGOTA D.C.

Referencia RESOLUCION : 31441
Fecha : 07/06/2011
Expediente : 9-55461
Trámite : 11 PCT-PATENTE DE INVENCION CAPITULOS I Y II
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Trámite :	11 PATENTEIYII	
Evento :	378 FASENACIONALI	
Actuación :	432 COMUNICACTOADM	
Destinatario :	ELIANA ISAURA MORENO BOHORQUEZ Folios 1	

Señor (a) (es)
ELIANA ISAURA MORENO BOHORQUEZ
CARRERA 13 NO. 119-95 OFC. 104
BOGOTA D.C.

Referencia RESOLUCION : 31441
Fecha : 07/06/2011
Expediente : 9-55461
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SUPERINTENDENCIA

**REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO**

RESOLUCION 121441

Por la cual se declara abandonada una solicitud

Rad. PCT/ 09-55461

EL SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

en ejercicio de sus facultades legales, en especial de las conferidas en el numeral 38 del artículo 3° del Decreto 1687 de 2010, y

CONSIDERANDO:

PRIMERO: Que mediante escrito radicado en esta Superintendencia el día 29 de mayo de 2009 con el N° 09-055461-00000-0000, la doctora Dilia María Rodríguez D'Aleman, en su calidad de apoderada de Janssen Pharmaceutica N.V., presentó la solicitud de patente de invención titulada "MÉTODOS PARA EL TRATAMIENTO DEL ABUSO, ADICCIÓN Y DEPENDENCIA DEL ALCOHOL", correspondiente a la solicitud internacional PCT/US 2007/084751 de fecha 15 de noviembre de 2007, para que se iniciara la fase nacional en virtud del Tratado de Cooperación en Materia de Patentes (PCT).

SEGUNDO: Que efectuado el examen de forma en cuanto a los requisitos que debe llenar la solicitud y cumplidas las exigencias legales, se ordenó publicar el extracto en la Gaceta de la Propiedad Industrial N° 619 del 20 de agosto de 2010.

TERCERO: Que mediante escritos radicados en esta Entidad los días 16 y 17 de noviembre de 2010 con los números 09-055461-00004-0000 y 09-055461-00006-0000, encontrándose dentro del término establecido para el efecto, los doctores José Luis Reyes Villamizar, en su calidad de apoderado de Laboratorios Legrand S.A., Tito Noé Parro Murillo, en su calidad de apoderado del Laboratorio Franco Colombiano Lafrancol S.A. y, Eliana Isaura Moreno Bohórquez, en su calidad de apoderada de Procaps S.A., respectivamente, presentaron oposiciones fundamentadas, las cuales cumplieron los requisitos formales previstos por la normativa andina. (Fls. 113 a 125, 131 a 152 y 160 a 251).

CUARTO: Que el artículo 44 de la Decisión 486 de la Comisión de la Comunidad Andina, establece que: *"Dentro del plazo de seis meses contados desde la publicación de la solicitud, independientemente que se hubieren presentado oposiciones, el solicitante deberá pedir que se examine si la invención es patentable. Los Países Miembros podrán cobrar una tasa para la realización de este examen. Si transcurriera dicho plazo sin que el solicitante hubiera pedido que se realice el examen, la solicitud caerá en abandono."*

QUINTO: Que contados seis meses desde la publicación en la Gaceta de la Propiedad Industrial, no se presentó petición de parte de la interesada para efectuar el examen de fondo, por lo que este Despacho considera abandonada la solicitud en los términos del mencionado artículo 44 de la Decisión 486 de la Comisión de la Comunidad Andina y, en consecuencia,



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RESOLUCION

Por la cual se declara abandonada una solicitud

Rad. PCT/ 09-55461

RESUELVE:

ARTÍCULO PRIMERO: Declarar abandonada la solicitud de patente de invención titulada "MÉTODOS PARA EL TRATAMIENTO DEL ABUSO, ADICCIÓN Y DEPENDENCIA DEL ALCOHOL", que entró en fase nacional en virtud del Tratado de Cooperación en Materia de Patentes (PCT).

ARTÍCULO SEGUNDO: Notificar personalmente el contenido de la presente resolución a la doctora Dilia María Rodríguez D'Aleman, en su calidad de apoderada de Janssen Pharmaceutica N.V., y a los doctores José Luis Reyes Villamizar, en su calidad de apoderado de Laboratorios Legrand S.A., Tito Noé Parro Murillo, en su calidad de apoderado del Laboratorio Franco Colombiano Lafrancol S.A. y, Eliana Isaura Moreno Bohórquez, en su calidad de apoderada de Procaps S.A., sociedades opositoras, o a quienes hagan sus veces, entregándoles copia de la misma y advirtiéndoles que contra ella procede el recurso de reposición, ante el Superintendente de Industria y Comercio, el cual podrá ser interpuesto en el momento de la notificación o dentro de los cinco 5 días hábiles siguientes a ella.

NOTIFÍQUESE Y CÚMPLASE

Dada en Bogotá, D.C., a los

27 JUN 2011

EL SUPERINTENDENTE DE INDUSTRIA Y COMERCIO,

JOSÉ MIGUEL DE LA CALLE RESTREPO

Doctora
DILIA MARÍA RODRÍGUEZ D'ALEMAN
Carrera 11 N° 86 – 53, Piso 6.
Bogotá D.C.

Doctor
JOSÉ LUIS REYES VILLAMIZAR
Carrera 17 N° 88 – 23, Of. 205.
Bogotá D.C.

(Continúa en la página siguiente)



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REPÚBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

RESOLUCIÓN

Por la cual se declara abandonada una solicitud

Rad. PCT/ 09-55461

Doctor

TITO NOÉ PARRA MURILLO

Calle 108 N° 51 – 45.

Bogotá D.C.

Doctora

ELIANA ISAURA MORENO BOHÓRQUEZ

Carrera 13 N° 119 – 95, Of. 104.

Bogotá D.C.

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