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Señores

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES

E. _____ S. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 06-042748- -00003-0000

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Ref: Expediente No. 06-042.748

Solicitud de patente de invención titulada: "BETA-LACTAMAS PARA EL
TRATAMIENTO DE TRASTORNOS DEL SISTEMA NERVIOSO CENTRAL".

Solicitante: GLAXO GROUP LIMITED

SOLICITUD DE EXAMEN DE PATENTABILIDAD SEGÚN
EL ARTÍCULO 44 DE LA DECISION 486, GACETA No. 580

CARLOS R. OLARTE, mayor de edad y vecino de Bogotá, D.C., identificado tal como aparece al pie de mi firma, en mi condición de apoderado sustituto tal como consta en la sustitución adjunta, respetuosamente me permito solicitar que se examine si la invención reúne los requisitos de patentabilidad previstos en la misma, dando cumplimiento a lo establecido en el artículo 44 de la Decisión 486 de la comisión de la Comunidad Andina. Adjunto un recibo que de \$404.000 pesos para cubrir la tasa correspondiente, según la Resolución 36155 del año 2006.

Atentamente,

CARLOS R. OLARTE
C.C. 79.782.747 de Bogotá
T.P. 74.295

Anexo: Recibo por \$404.000 pesos
Sustitución

LMB/P2006/000043 0711126

Señores

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES

E. _____ S. _____ D. _____

Ref.: Expediente No. 06-042.748

Solicitud de patente de invención titulada: "BETA-LACTAMAS PARA EL
TRATAMIENTO DE TRASTORNOS DEL SISTEMA NERVIOSO CENTRAL".

Solicitante: GLAXO GROUP LIMITED

SUSTITUCIÓN DE PODER

J. IAN RAISBECK LLINAS, mayor de edad y vecino de Bogotá D.C., identificado como aparece al pie de mi firma, en mi carácter de apoderado de la sociedad de la referencia, respetuosamente me permito manifestar que SUSTITUYO el poder a mi conferido por la mencionada sociedad, en el doctor **CARLOS R. OLARTE** mayor de edad, domiciliado en Bogotá D.C., identificado con la Cédula de Ciudadanía No. 79.782.747 de Bogotá y portador de la Tarjeta Profesional No. 74.295 del Consejo Superior de la Judicatura, para que sea él quien en adelante asuma el trámite de la presente acción.

El apoderado sustituto conserva las mismas facultades del principal.

Atentamente,

J. IAN RAISBECK
C.C. No. 79.376.996 de Bogotá
T.P. 135.799 del C. S. de la J.



US005780466A

United States Patent [19]**Emonds-Alt et al.**[11] **Patent Number:** **5,780,466**[45] **Date of Patent:** **Jul. 14, 1998**

[54] **SUBSTITUTED HETEROCYCLIC COMPOUNDS METHOD OF PREPARING THEM AND PHARMACEUTICAL COMPOSITIONS IN WHICH THEY ARE PRESENT**

[75] **Inventors:** **Xavier Emonds-Alt, Combaillaux; Isabelle Grossriether, Uzès; Patrick Gueule, Teyran; Vincenzo Proietto, Saint Georges D'Orques; Didier Van Broeck, Murviel les Montpellier; Joëlle Taillades, Montpellier, all of France**

[73] **Assignee:** **Sanofi, Paris, France**

[21] **Appl. No.:** **703,729**

[22] **Filed:** **Aug. 27, 1996**

Related U.S. Application Data

[63] **Continuation-in-part of Ser. No. 593,938, Jan. 30, 1996, Pat. No. 5,641,777.**

[30] Foreign Application Priority Data

Jan. 30, 1995	[FR]	France	95 01016
Jul. 4, 1995	[FR]	France	95 08046
Nov. 3, 1995	[FR]	France	95 13005
Jul. 26, 1996	[FR]	France	96 09439

[51] **Int. Cl.⁶** **A61K 31/445; A61K 31/535; C07D 413/06; C07D 471/06**

[52] **U.S. Cl.** **514/228.2; 514/230.8; 514/255; 514/340; 514/341; 514/235.5; 514/228.8; 514/305; 546/268.4; 546/276.4; 546/133; 546/209; 546/210; 544/96; 544/170; 544/360; 544/82; 544/127; 544/129; 544/130; 544/141; 544/362**

[58] **Field of Search** 514/228.2, 230.8, 514/255, 340, 341, 235.5, 228.8, 305; 546/268.4, 276.4, 133, 209, 210; 544/96, 170, 360, 82, 127, 129, 130, 141, 362

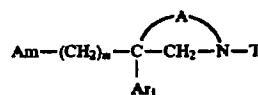
[56] References Cited**U.S. PATENT DOCUMENTS**

5,656,639 8/1997 Emonds-Alt 514/305

Primary Examiner—C. Warren Ivy
Assistant Examiner—D. Margaret M. Mach
Attorney, Agent, or Firm—Bacon & Thomas

[57] ABSTRACT

The invention relates to compounds of the formula



(I)

in which:

A is a divalent radical selected from:

- A₁) —O—CO—
- A₂) —CH₂—O—CO—
- A₃) —O—CH₂—CO—
- A₄) —O—CH₂—CH₂—
- A₅) —N(R₁)—CO—
- A₆) —N(R₁)—CO—CO—
- A₇) —N(R₁)—CH₂—CH₂—
- A₈) —O—CH₂—

in which:

R₁ is a hydrogen or a (C₁–C₄)-alkyl; and

Am is a nitrogen-containing heterocycle.

10 Claims, No Drawings

D₁
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THE UNITED STATES OF AMERICA

IN SENATE

COMMITTEE ON THE JUDICIARY

HEARINGS

ON THE NOMINATION OF

JOHN EDGAR HOOVER

TO BE

ATTORNEY GENERAL

OF THE UNITED STATES

AND

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D) 4-(Benzoyloxy)-2-(3,4-difluorophenyl)-2-(tetrahydropyran-2-yloxy)butylamine

A mixture of 47 g of the compound obtained in the previous step and 10 g of Raney® nickel in 400 ml of EtOH is hydrogenated at RT and at atmospheric pressure. The catalyst is filtered off and the filtrate is concentrated under vacuum. The residue is taken up with water and extracted with ether. The organic phase is washed with water and dried over Na₂SO₄ and the solvent is evaporated off under vacuum to give 45 g of the expected product, which is used as such.

E) 4-(Benzoyloxy)-2-(3,4-difluorophenyl)-2-hydroxybutylamine hydrochloride

A saturated solution of gaseous HCl in ether is added at RT to a solution of 45 g of the compound obtained in the previous step in 250 ml of MeOH until the pH is 1, and the reaction mixture is stirred for 30 minutes at RT. It is concentrated under vacuum, the residue is taken up with ether and the precipitate formed is wrung and washed with ether to give 15 g of the expected product after recrystallization from propan-2-ol. M.p.=202°-204° C.

F) N-(2-Chloroacetyl)-4-(benzoyloxy)-2-(3,4-difluorophenyl)-2-hydroxybutylamine

A solution of 12.2 g of the compound obtained in the previous step and 7.88 g of triethylamine in 100 ml of DCM is cooled to 0° C., a solution of 3.85 g of chloroacetyl chloride in 100 ml of DCM is added dropwise and the reaction mixture is stirred for 30 minutes. It is concentrated under vacuum, the residue is extracted with an ether/AcOEt mixture (50/50; v/v), the organic phase is washed with water, with a buffer solution of pH 4 and with water and dried over Na₂SO₄ and the solvent is evaporated off under vacuum to give 13.5 g of the expected product, which is used as such.

G) 6-[2-(Benzoyloxy)ethyl]-6-(3,4-difluorophenyl)morpholin-3-one

A mixture of 13.5 g of the compound obtained in the previous step and 20.7 g of K₂CO₃ in 100 ml of toluene is refluxed overnight. The reaction mixture is concentrated under vacuum, the residue is taken up with ether and the mixture is filtered. The filtrate is washed with water, with a buffer solution of pH 2 and with water and dried over MgSO₄ and the solvent is evaporated off under vacuum. The residue is chromatographed on silica H using a DCM/MeOH mixture (100/1; v/v) as the eluent to give 4.9 g of the expected product.

Proton NMR spectrum at 200 MHz in DMSO-d₆ δ:

2.35 ppm: m: 2H
3.65 ppm: AB system: 2H
3.8 to 4.35 ppm: u: 4H
7.1 to 7.8 ppm: u: 8H
8.2 ppm: bs: 1H
Preparation 1.11

2-(3,4-Difluorophenyl)-2-(2-hydroxyethyl)morpholine

A suspension of 1.8 g of lithium aluminum hydride in 20 ml of THF is added dropwise at RT to a solution of 2.8 g of the compound obtained in Preparation 1.10 in 20 ml of THF and the mixture is then refluxed for 5 hours. After cooling, 2 ml of water, 2 ml of 4N NaOH and then 6 ml of water are added. The mineral salts are filtered off and the filtrate is concentrated under vacuum. The residue is dissolved in DCM, acidified to pH 1 by the addition of a saturated solution of gaseous HCl in ether, and extracted with water. The aqueous phase is washed with ether, rendered alkaline to pH 8 by the addition of concentrated NaOH solution, and extracted with DCM, the organic phase is washed with water

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and dried over MgSO₄ and the solvent is evaporated off under vacuum to give 0.77 g of the expected product, which is used as such in EXAMPLE 27, step A.
Preparation 1.12

5-[2-(Benzoyloxy)ethyl]-5-(3,4-difluorophenyl)oxazolidin-2-one

1 g of 1,1'-carbonyldiimidazole is added at RT to a solution of 2.1 g of the compound obtained in step E of Preparation 1.10 and 0.63 g of triethylamine in 50 ml of 1,2-dichloroethane and the reaction mixture is then stirred for 1 hour at RT and heated for 2 hours at 50° C. It is concentrated under vacuum, the residue is extracted with DCM, the organic phase is washed with water, with a buffer solution of pH 2 and with water and dried over MgSO₄ and the solvent is evaporated off under vacuum to give 1.5 g of the expected product.

Preparation 1.13

5-(3,4-Dichlorophenyl)-1-methyl-5-[2-

(tetrahydropyran-2-yloxy)ethyl]imidazolidin-2-one

A) 2-(3,4-Dichlorophenyl)-2-(methylamino)-4-(tetrahydropyran-2-yloxy)butylamine

A mixture of 3.4 g of the compound obtained in step E of Preparation 1.8, 0.05 g of p-toluenesulfonic acid monohydrate and 2.1 ml of 3,4-dihydro-2H-pyran in 30 ml of DMF is heated at 60° C. for 45 minutes. The reaction mixture is poured onto ice, rendered alkaline by the addition of concentrated NaOH and extracted with ether, the organic phase is washed with water and dried over MgSO₄ and the solvent is evaporated off under vacuum to give 4.3 g of the expected product, which is used as such.

B) 5-(3,4-Dichlorophenyl)-1-methyl-5-[2-(tetrahydropyran-2-yloxy)ethyl]imidazolidin-2-one

1.6 g of 1,1'-carbonyldiimidazole are added to a solution of 3.2 g of the compound obtained in the previous step in 100 ml of 1,2-dichloroethane and the reaction mixture is stirred for 30 minutes at RT. It is then heated at 60° C. for 2 hours and concentrated under vacuum. The residue is extracted with AcOEt, the organic phase is washed with a buffer solution of pH 2, with saturated NaCl solution and with 10% Na₂CO₃ solution and dried over MgSO₄ and the solvent is evaporated off under vacuum. The residue is chromatographed on silica H using DCM and then a DCM/MeOH mixture (98/2; v/v) as the eluent to give 2.4 g of the expected product in the form of an oil.

Preparation 1.14

6-[3-(Benzoyloxy)propyl]-6-(3,4-dichlorophenyl)morpholin-3-one

A mixture of 7.5 g of the compound obtained in step D of Preparation 1.6, 9.3 g of K₂CO₃ and 3.75 g of sodium iodide in 100 ml of methyl ethyl ketone is refluxed overnight. After cooling, the reaction mixture is concentrated under vacuum, the residue is taken up with ether, the mineral salts are filtered off, the filtrate is washed with a buffer solution of pH 2 and with water, the organic phase is dried over MgSO₄ and the solvent is evaporated off under vacuum. The residue is chromatographed on silica H using DCM and then a gradient of a DCM/MeOH mixture (from 99/1; v/v to 98/2; v/v) as the eluent to give 1.3 g of the expected product.

Proton NMR spectrum at 200 MHz in DMSO-d₆ δ:

1.1 to 2.3 ppm: u: 4H
3.65 ppm: AB system: 2H
3.8 to 4.4 ppm: u: 4H
7.2 to 8.05 ppm: u: 8H

1. The first part of the document is a letter from the President of the United States to the Congress, dated January 1, 1861. It is a very important document, as it sets out the policy of the new administration.

2. The second part of the document is a report from the Secretary of the Treasury, dated January 1, 1861. It contains a detailed account of the financial state of the country.

3. The third part of the document is a report from the Secretary of the Interior, dated January 1, 1861. It contains a detailed account of the state of the public lands and the progress of the various departments under his control.

4. The fourth part of the document is a report from the Secretary of the Navy, dated January 1, 1861. It contains a detailed account of the state of the navy and the progress of the various departments under his control.

5. The fifth part of the document is a report from the Secretary of the War, dated January 1, 1861. It contains a detailed account of the state of the army and the progress of the various departments under his control.

6. The sixth part of the document is a report from the Secretary of the State, dated January 1, 1861. It contains a detailed account of the state of the foreign relations of the United States and the progress of the various departments under his control.

7. The seventh part of the document is a report from the Secretary of the Education, dated January 1, 1861. It contains a detailed account of the state of the public education system and the progress of the various departments under his control.

8. The eighth part of the document is a report from the Secretary of the Agriculture, dated January 1, 1861. It contains a detailed account of the state of the agriculture of the United States and the progress of the various departments under his control.

9. The ninth part of the document is a report from the Secretary of the Commerce, dated January 1, 1861. It contains a detailed account of the state of the commerce of the United States and the progress of the various departments under his control.

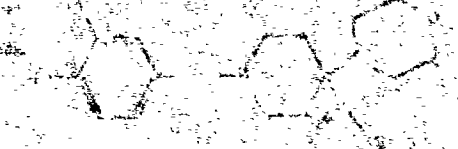
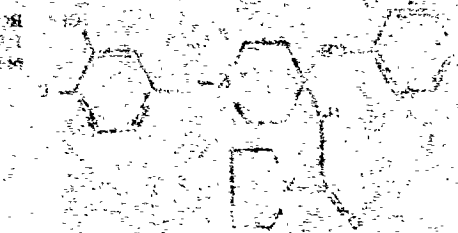
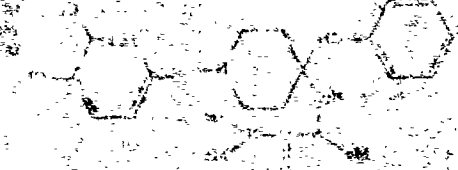
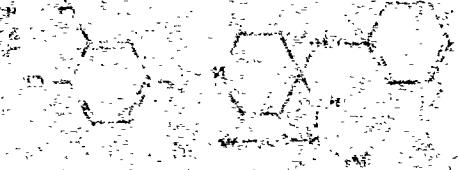
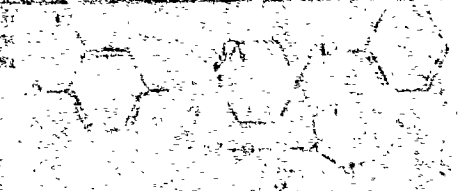
10. The tenth part of the document is a report from the Secretary of the Fish and Game, dated January 1, 1861. It contains a detailed account of the state of the fish and game resources of the United States and the progress of the various departments under his control.

11. The eleventh part of the document is a report from the Secretary of the Land and Survey, dated January 1, 1861. It contains a detailed account of the state of the public lands and the progress of the various departments under his control.

12. The twelfth part of the document is a report from the Secretary of the Indian Affairs, dated January 1, 1861. It contains a detailed account of the state of the Indian population and the progress of the various departments under his control.

13. The thirteenth part of the document is a report from the Secretary of the Marine and Fisheries, dated January 1, 1861. It contains a detailed account of the state of the marine and fisheries resources of the United States and the progress of the various departments under his control.

14. The fourteenth part of the document is a report from the Secretary of the Public Buildings, dated January 1, 1861. It contains a detailed account of the state of the public buildings and the progress of the various departments under his control.



The following table shows the results of the experiments conducted on the various samples of the compound. The data indicates that the compound is highly stable under the conditions tested, and that the reaction rate is significantly lower than that of the control samples. The results are summarized in the table below:

Sample	Reaction Rate (mol/L·h)	Stability (h)
Control 1	0.15	10
Control 2	0.12	8
Sample A	0.08	12
Sample B	0.05	15
Sample C	0.03	18

The experimental results demonstrate that the compound exhibits excellent thermal and chemical stability. The reaction rate is consistently low across all samples, indicating that the compound is not easily degraded under the tested conditions. The stability data further supports this conclusion, showing that the compound can maintain its integrity for extended periods of time. These findings are consistent with the theoretical predictions and provide a strong basis for the application of this compound in various industrial and scientific contexts.

2.0 ppm: t: 2H

2.9 to 3.45 ppm: mt 2H

3.9 ppm: AB system: 2H

4.2 ppm: AB system 2H

4.45 ppm: t: 1H

4.7 ppm: AB system: 2H

7.1 to 8.2 ppm: u: 6H

C) 6-(3,4-dichlorophenyl)-6-[2-(methanesulfonyloxy)ethyl]-4-[3,5-bis(trifluoromethyl)benzyl] morpholin-3-one

0.25 g of methane sulfonyl chloride is added in RT to a solution of 1.1 g of the compound obtained in the previous step. 0.22 g of triethylamine in 30 ml of DCM and the reaction mixture is left under stirring for one hour.

The reaction mixture is concentrated under vacuum. the residue is extracted with AcOEt. the organic phase is washed with water, dried over Na_2SO_4 and the solvent is evaporated under vacuum to give 1.2 g of the expected product which is used as such.

D) 6-(3,4-dichlorophenyl)-6-[2-[4-phenyl-1-azoniabicyclo [2.2.1]hept-1-yl]ethyl]-4-[3,5-bis (trifluoromethyl) benzyl] morpholin-3-one chloride

A mixture of 1.5 g of the compound obtained in the previous step, 0.67 g of 4-phenyl-1-azabicyclo [2.2.1] heptane methanesulfonate and 1 g of K_2CO_3 in 2 ml of DMF is heated at $80^\circ\text{--}100^\circ\text{C}$. for 3 hours. After cooling at RT, the reaction mixture is poured into water, extracted with DCM, the organic phase is washed with a 10% HCl solution, with a saturated solution NaCl, with water, dried over Na_2SO_4 and the solvent is evaporated under vacuum. The residue is chromatographed on silica H eluting with a DCM/MeOH mixture from (100/5; v/v) to (100/7.5; v/v). The product obtained is dissolved in warm DCM, it is poured into pentane and the precipitate formed is wrung to give 0.4 g of the expected product.

Proton NMR spectrum at 200 MHz in DMSO-d_6 δ :

2.0 to 2.7 ppm: u: 6H

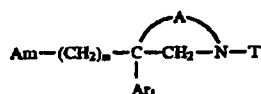
3.0 to 4.0 ppm: u: 10H

4.2 to 5.0 ppm: u: 4H

7.2 to 8.2 ppm: u: 11H

What is claimed is:

1. A compound of the formula



in which:

A is a divalent radical selected from:

A_1) $-\text{O}-\text{CO}-$

A_2) $-\text{CH}_2-\text{O}-\text{CO}-$

A_3) $-\text{O}-\text{CH}_2-\text{CO}-$

A_4) $-\text{O}-\text{CH}_2-\text{CH}_2-$

A_5) $-\text{N}(\text{R}_1)-\text{CO}-$

A_6) $-\text{N}(\text{R}_1)-\text{CO}-\text{CO}-$

A_7) $-\text{N}(\text{R}_1)-\text{CH}_2-\text{CH}_2-$

A_8) $-\text{O}-\text{CH}_2-$

in which R_1 is a hydrogen or a (C_1-C_4) -alkyl;

m is 2 or 3;

Ar_1 is a phenyl which is unsubstituted or monosubstituted or polysubstituted by a substituent selected from a halogen atom, a hydroxyl, a (C_1-C_4) -alkoxy, a (C_1-C_4) -alkyl, a trifluoromethyl and a methylenedioxy, said substituents being identical or different; a thienyl which is unsubstituted or substituted by a halogen atom; a benzothienyl which is unsubstituted or substituted by a halogen atom; a naphthyl which is unsubstituted or

substituted by a halogen atom; an indolyl which is unsubstituted or N-substituted by a (C_1-C_4) -alkyl or a benzyl; an imidazolyl which is unsubstituted or substituted by a halogen atom; a pyridyl which is unsubstituted or substituted by a halogen atom; or a biphenyl;

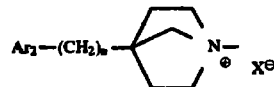
T is a group selected from CH_2-Z , $-\text{CH}(\text{C}_6\text{H}_5)_2$ and $-\text{C}(\text{C}_6\text{H}_5)_3$; T can also be the group $-\text{CO}-\text{B}-\text{Z}$ if A is a divalent radical selected from $-\text{O}-\text{CH}_2-\text{CH}_2-$, $-\text{N}(\text{R}_1)-\text{CH}_2-\text{CH}_2-$ and $-\text{O}-\text{CH}_2-$;

B is a direct bond or a methylene;

Z is an optionally substituted mono-, di- or tricyclic aromatic or heteroaromatic group; and

Ar_2 is a pyridyl; a phenyl which is unsubstituted or monosubstituted or polysubstituted by a substituent selected from a halogen atom, a hydroxyl, a (C_1-C_4) -alkoxy, a (C_1-C_4) -alkyl, a trifluoromethyl, a nitro and a methylenedioxy, said substituents being identical or different; a thienyl; a pyrimidyl; or an imidazolyl which is unsubstituted or substituted by a (C_1-C_4) -alkyl; and

Am is: (i) a group Am_4 of the formula



in which:

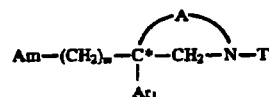
Ar_2 is as defined above;

n is 0 or 1; and

X^- is an anion;

and the salts thereof with mineral or organic acids.

2. An optically pure compound according to claim 1 of the formula



(I*)

in which:

"*" denotes that the carbon atom carrying this label has the determined (+) or (-) absolute configuration; and Am , m, Ar_1 , A and T are as defined for the compounds of formula (I) in claim 1;

and the salts thereof with mineral or organic acids.

3. A compound according to anyone of claim 1 of formula (I) or (I*) in which:

Z is Z' and is:

a phenyl which is unsubstituted or monosubstituted or polysubstituted by a substituent selected from a halogen atom; a trifluoromethyl; a cyano; a hydroxyl; a nitro; a phenyl which is unsubstituted or monosubstituted or polysubstituted by a halogen, a trifluoromethyl, a (C_1-C_4) -alkyl, a hydroxyl or a (C_1-C_4) -alkoxy, said substituents being identical or different; an amino which is unsubstituted or monosubstituted or polysubstituted by a (C_1-C_4) -alkyl; a benzylamino; a carboxyl; a $(\text{C}_1-\text{C}_{10})$ -alkyl; a (C_3-C_6) -cycloalkyl which is unsubstituted or monosubstituted or polysubstituted by a methyl; a $(\text{C}_1-\text{C}_{10})$ -alkoxy; a (C_3-C_6) -cycloalkoxy which is unsubstituted or monosubstituted or polysubstituted by a methyl; a mercapto; a $(\text{C}_1-\text{C}_{10})$ -alkylthio; a formyloxy; a (C_1-C_6) -alkylcarbonyloxy; a formylamino; a (C_1-C_6) -alkylcarbonylamino; a benzoylamino; a (C_1-C_6) -alkoxycarbonyl; a (C_3-C_7) -

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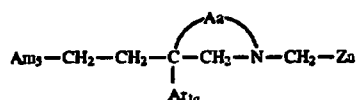
cycloalkoxycarbonyl; a (C₃-C₇)-cycloalkylcarbonyl; a carbamoyl which is unsubstituted or monosubstituted or disubstituted by a (C₁-C₄)-alkyl; a ureido which is unsubstituted or monosubstituted or disubstituted in the 3-position by a (C₁-C₄)-alkyl or a (C₃-C₇)-cycloalkyl; and a (pyrrolidin-1-yl)carbonylamino, said substituents being identical or different;

a naphthyl which is unsubstituted or monosubstituted or polysubstituted by a halogen, a trifluoromethyl, a (C₁-C₄)-alkyl, a hydroxyl or a (C₁-C₄)-alkoxy; or a pyridyl, a thienyl, an indolyl, a quinolyl, a benzothienyl or an imidazolyl; and

Am, m, Ar₁, A and T are as defined for a compound of formula (I) in claim 1;

and the salts thereof with mineral or organic acids.

4. A compound according to anyone of claim 1 of the formula



in which:

Aa is a divalent radical selected from —O—CO—; —CH₂—O—CO—; —O—CH₂—CO—; —N(R₁)—CO— and —N(R₁)—CO—CO—, in which R₁ is a hydrogen or a (C₁-C₄)-alkyl;

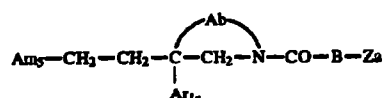
Am₃ is as defined for a compound of formula (I);

Ar_{1a} is a phenyl which is unsubstituted or monosubstituted or polysubstituted by a substituent selected from a halogen atom, a hydroxyl, a (C₁-C₄)-alkoxy, a (C₁-C₄)-alkyl and a trifluoromethyl, said substituents being identical or different; and

Za is a phenyl which is unsubstituted or monosubstituted or polysubstituted by a substituent selected from a halogen atom, a trifluoromethyl, a (C₁-C₁₀)-alkyl, a (C₁-C₁₀)-alkoxy and a hydroxyl, said substituents being identical or different;

and the salts thereof with mineral or organic acids.

5. A compound according to claim 1 of the formula



in which:

Ab is the divalent radical —O—CH₂—CH₂—, —N(R₁)—CH₂—CH₂— or —O—CH₂—;

in which R₁ is a hydrogen or a (C₁-C₄)-alkyl

Am₃ is as defined above for a compound of formula (I)

B is a direct bond or a methylene;

Ar_{1a} is a phenyl which is unsubstituted or monosubstituted or polysubstituted by a substituent selected from a halogen atom, a hydroxyl, a (C₁-C₄)-alkoxy, a (C₁-C₄)-alkyl and a trifluoromethyl, said substituents being identical or different; and

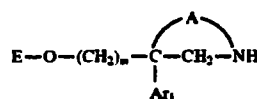
Za is a phenyl which is unsubstituted or monosubstituted or polysubstituted by a substituent selected from a halogen atom, a trifluoromethyl, a (C₁-C₁₀)-alkyl, a (C₁-C₁₀)-alkoxy and a hydroxyl, said substituents being identical or different.

and the salts thereof with mineral or organic acids.

6. A method of preparing the compounds of formula (I) according to claim 1 and the salts thereof, which comprises:

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1) treating a compound of the formula



in which m, Ar₁ and A are as defined for a compound of formula (I) in claim 1 and E is hydrogen or an O-protecting group.

either with a functional derivative of an acid of the formula



in which B and Z are as defined above for (I) in claim 1, if it is intended to prepare a compound of formula (I) in which T is —CO—B—Z,

or with a halogenated derivative of the formula



in which Z is as defined in claim 1 and Hal is a halogen, if it is intended to prepare a compound of formula (I) in which T is —CH₂—Z,

or with a halogenated derivative of the formula

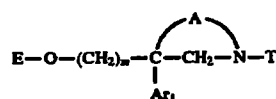


if it is intended to prepare a compound of formula (I) in which T is a group —CH(C₆H₅)₂,

or with a halogenated derivative of the formula

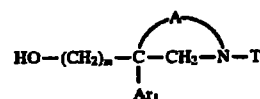


if it is intended to prepare a compound of formula (I) in which T is a group —C(C₆H₅)₃, to give a compound of the formula



in which E, m, Ar₁, A and T are as defined above;

2) optionally removing the O-protecting group by reaction with an acid or a base to give the alcohol of the formula

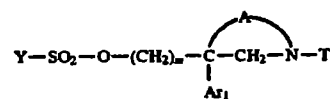


in which m, Ar₁, A and T are as defined above;

3) treating the alcohol (VIII) with a compound of the formula



in which Y is a methyl, phenyl, tolyl or trifluoromethyl group, to give a compound of the formula



in which Y, m, Ar₁, A and T are as defined above;

4-1-2

1. The first step is to identify the problem or question that needs to be answered. This involves understanding the context and the specific information required.

which is to be used for the purpose of the investigation.

1. The first step in the process of the investigation is the identification of the problem. This is done by the investigator who is responsible for the investigation. The investigator must identify the problem and the scope of the investigation. The investigator must also identify the objectives of the investigation and the methods to be used. The investigator must also identify the resources available for the investigation. The investigator must also identify the risks associated with the investigation. The investigator must also identify the stakeholders involved in the investigation. The investigator must also identify the timeline for the investigation. The investigator must also identify the budget for the investigation. The investigator must also identify the personnel involved in the investigation. The investigator must also identify the equipment and materials needed for the investigation. The investigator must also identify the data to be collected. The investigator must also identify the analysis to be performed. The investigator must also identify the conclusions to be drawn. The investigator must also identify the recommendations to be made. The investigator must also identify the follow-up actions to be taken. The investigator must also identify the reporting requirements. The investigator must also identify the communication requirements. The investigator must also identify the documentation requirements. The investigator must also identify the archiving requirements. The investigator must also identify the disposal requirements. The investigator must also identify the security requirements. The investigator must also identify the privacy requirements. The investigator must also identify the ethical requirements. The investigator must also identify the legal requirements. The investigator must also identify the regulatory requirements. The investigator must also identify the industry requirements. The investigator must also identify the customer requirements. The investigator must also identify the employee requirements. The investigator must also identify the shareholder requirements. The investigator must also identify the community requirements. The investigator must also identify the government requirements. The investigator must also identify the international requirements. The investigator must also identify the global requirements. The investigator must also identify the universal requirements. The investigator must also identify the human requirements. The investigator must also identify the natural requirements. The investigator must also identify the artificial requirements. The investigator must also identify the virtual requirements. The investigator must also identify the digital requirements. The investigator must also identify the electronic requirements. The investigator must also identify the magnetic requirements. The investigator must also identify the optical requirements. The investigator must also identify the acoustic requirements. The investigator must also identify the mechanical requirements. The investigator must also identify the electrical requirements. The investigator must also identify the chemical requirements. The investigator must also identify the biological requirements. The investigator must also identify the geological requirements. The investigator must also identify the meteorological requirements. The investigator must also identify the astronomical requirements. The investigator must also identify the cosmological requirements. The investigator must also identify the philosophical requirements. The investigator must also identify the psychological requirements. The investigator must also identify the sociological requirements. The investigator must also identify the anthropological requirements. The investigator must also identify the historical requirements. The investigator must also identify the archaeological requirements. The investigator must also identify the paleontological requirements. The investigator must also identify the geological requirements. The investigator must also identify the meteorological requirements. The investigator must also identify the astronomical requirements. The investigator must also identify the cosmological requirements. The investigator must also identify the philosophical requirements. The investigator must also identify the psychological requirements. The investigator must also identify the sociological requirements. The investigator must also identify the anthropological requirements. The investigator must also identify the historical requirements. The investigator must also identify the archaeological requirements. The investigator must also identify the paleontological requirements.

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1. The first step is to identify the problem or question that needs to be answered. This involves understanding the context and the specific requirements of the task.

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一、政治思想：政治思想是人的政治立场、政治观点、政治态度的总称。政治思想是人的政治立场、政治观点、政治态度的总称。政治思想是人的政治立场、政治观点、政治态度的总称。

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1. The first step in the process is to identify the problem or issue that needs to be addressed. This involves gathering information and understanding the context of the problem.

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1. The first step is to identify the problem or question that needs to be answered. This involves understanding the context and the specific requirements of the task.



US005677317A

United States Patent [19]

Miller

[11] Patent Number: 5,677,317
[45] Date of Patent: Oct. 14, 1997

[54] LACTAM COMPOUNDS WHICH ARE
USEFUL IN THE TREATMENT OF ASTHMA

[75] Inventor: Scott Carson Miller, Newark, Del.

[73] Assignee: Zeneca Limited, London, United Kingdom

[21] Appl. No.: 629,299

[22] Filed: Apr. 8, 1996

Related U.S. Application Data

[62] Division of Ser. No. 332,290, Oct. 31, 1994, Pat. No. 5,534,525.

[30] Foreign Application Priority Data

Nov. 3, 1993 [GB] United Kingdom 9322643

[51] Int. Cl.⁶ C07D 413/12; A61K 31/445

[52] U.S. Cl. 514/316; 514/318; 514/826;
546/188; 546/193; 546/194; 546/203

[58] Field of Search 546/188, 193,
546/194, 208; 514/316, 318, 826

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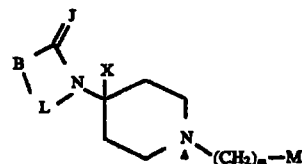
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Primary Examiner—Zinna Northington Davis
Attorney, Agent, or Firm—Robert J. Harris

[57] ABSTRACT

Compounds of formula I



wherein J, B, L, X, m and M have any of the meanings given in the specification, their N-oxides, and their pharmaceutically acceptable salts are nonpeptide antagonists of neurokinin A and useful for the treatment of asthma, etc. Also disclosed are pharmaceutical compositions, processes for preparing the compounds of formula I and intermediates.

11 Claims, No Drawings

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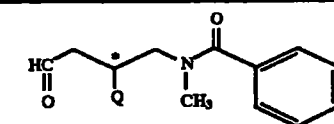
sodium hydroxide, and extracted with dichloromethane. The organic extracts were dried, evaporated, and dissolved in ether. A precipitate formed that was filtered off to give the 1-benzyl-4-methyl-4-(2-oxoperhydropyrimidin-1-yl)piperidine as a white solid (3.2 g); MS: $m/z=288(M+1)$; NMR (CD_3OD): 7.30 (m,5), 3.51 (s,2), 3.23 (m,2), 3.15 (m,2), 2.50 (m,4), 2.34 (m,2), 1.82 (m,4), 1.29 (s,3).

- c. 4-Methyl-4-(2-oxoperhydropyrimidin-1-yl)piperidine. 10
Using the procedure of Example 1.o., replacing 1-benzyl-4-methyl-4-(2-oxoperhydropyrimidin-1-yl)piperidine with 1-benzyl-4-methyl-4-(2-oxoperhydropyrimidin-1-yl)piperidine, the piperidine was obtained as a white solid; MS: $m/z=198(M+1)$; NMR (CD_3OD): 3.26 (m,2), 3.17 (m,2), 2.77 (m,4), 2.44 (m,2), 1.89 (m,2), 1.67 (m,2), 1.31 (s,3).

FORMULAE



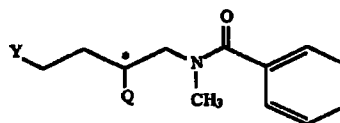
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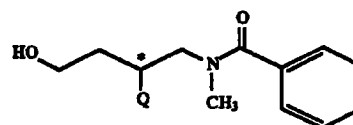
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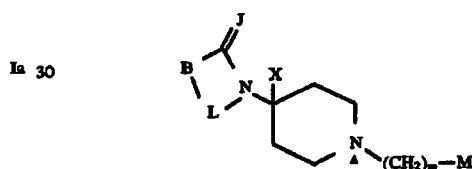
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VIc

What is claimed is:

1. A compound of formula I:



Ia

Ib wherein:

X is (1-6C)alkyl, $-CH_2OR^a$, $-CH_2SR^a$, $-CH_2S(=O)$
 R^a , $-CH_2S(=O)_2R^a$, $-C(=O)R^a$, $-C(=O)OR^a$,
 $-C(=O)NR^bR^c$, $-C(R^a)(OR^a)(OR^a)$, $-CH_2N(R^a)C$
 $(=O)R^b$, $-CH_2N(R^a)C(=O)OR^b$ or $-CH_2N(R^a)C$
 $(=O)NR^bR^c$;

B is a direct bond and L is a hydrocarbon chain in which the 1-position is bound to B and L is selected from trimethylene, tetramethylene, cis-1-butenylene and cis, cis-butadienylene; or B is $N(R^b)$ and L is a hydrocarbon chain selected from ethylene, trimethylene and cis-vinylene; or B is N and L is a hydrocarbon chain in which the 1-position is bound to B and L is cis,cis-prop-2-en-1-ylidene-3-yl;

J and J' are independently oxygen or sulfur;

R^a , R^b and R^c are independently hydrogen or (1-6C)alkyl; R^b and R^c are independently hydrogen or (1-6C)alkyl in which said (1-6C)alkyl may be substituted by a group selected from hydroxy and (1-3C)alkoxy, or said (1-6C)alkyl may be terminally substituted by a group selected from hydroxy, (1-3C)alkoxy, phenyl, $-C(=O)OR^d$ and $-C(=O)NR^dR^e$; or

R^b and R^c together with the nitrogen to which they are attached form a pyrrolidino, piperidino, morpholino, thiomorpholino (or its S-oxide) or piperazinyl group (which piperazinyl group may bear a methyl or ethyl group at the 4-position);

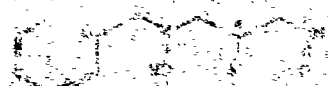
R^d and R^e are independently (1-3C)alkyl or together form a divalent hydrocarbon chain selected from ethylene and trimethylene;

R^a is (1-6C)alkyl; R^d , R^e and R^f are independently hydrogen or (1-3C)alkyl;

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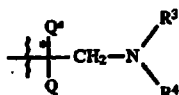
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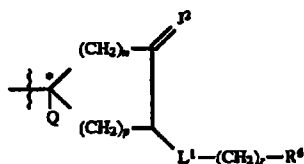
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m is 2 or 3;

M is a residue of formula Ia:



or formula Ib:



wherein

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

Q^o is hydrogen, (1-4C)alkyl, or a radical of formula $-(CH_2)_q-NR^7R^8$ in which q is 2 or 3 and R⁷ and R⁸ are independently (1-4C)alkyl or NR⁷R⁸ is piperidino or 4-benzylpiperidino;

R³ is hydrogen, methyl or (2-6C)n-alkyl which may bear a terminal amino radical;

R⁴ is $-C(=O)R^5$, $-C(=O)OR^5$ or $-C(=J^1)NHR^5$ in which J¹ is oxygen or sulfur and R⁵ is hydrogen, (1-6C)alkyl, phenyl(1-3C)alkyl (in which the phenyl may bear one or more halo, hydroxy, (1-4C)alkoxy or (1-4C)alkyl substituents), pyridyl(1-3C)alkyl, naphthyl(1-3C)alkyl, pyridylthio(1-3C)alkyl, styryl, 1-methylimidazol-2-ylthio(1-3C)alkyl, aryl (which may bear one or more halo, hydroxy, (1-4C)alkoxy or (1-4C)alkyl substituents), heteroaryl (which may bear one or more halo, hydroxy, (1-4C)alkoxy or (1-4C)alkyl substituents), or (when R⁴ is $-COR^5$) α -hydroxybenzyl;

n is 0, 1, 2 or 3;

p is 1 or 2, and when p is 2, n is 1 and J² is two hydrogens;

J² is oxygen or two hydrogens;

L¹ is carbonyl or methylene;

r is 0, 1, 2, or 3; and

R⁶ is phenyl which may bear one or more halo, trifluoromethyl, (1-4C)alkyl, hydroxy or (1-4C)alkoxy substituents (and particularly one or more chloro or fluoro substituents); naphthyl which may bear one or more halo, trifluoromethyl, (1-4C)alkyl or hydroxy substituents; pyridyl; thienyl; indolyl; quinolinyl; benzothienyl or imidazolyl; or when L¹ is carbonyl, the group $-(CH_2)_r-R^5$ may represent aryl, heteroaryl or a benzyl group bearing an α -substituent selected from hydroxy, (1-4C)alkoxy and (1-4)alkyl, and further wherein the aryl, heteroaryl or phenyl portion of the benzyl group may bear one or more substituents selected independently from halo, trifluoromethyl, (1-4C)alkyl, hydroxy and (1-4C)alkyl, hydroxy and (1-4C)alkoxy (and particularly one or more chloro or fluoro substituents);

or the N-oxide of the piperidino nitrogen indicated by Δ ; or a pharmaceutically acceptable salt thereof;

or a quaternary ammonium salt thereof in which the piperidino nitrogen indicated by Δ is a quadricovalent ammonium nitrogen wherein the fourth radical on the nitrogen R⁹ is (1-4C)alkyl or benzyl and the associated counterion A is a pharmaceutically acceptable anion; provided the compound of formula I is not a compound wherein:

X is (1-6C)alkyl, $-CH_2OR^a$, $-CH_2SR^a$, $-CH_2S(=O)R^a$, $-CH_2S(=O)_2R^a$, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=J^a)NR^bR^c$, $-C(R^a)(OR^d)(OR^e)$, $-CH_2N(R^a)C(=J^a)R^f$, $-CH_2N(R^a)C(=O)OR^f$ or $-CH_2N(R^a)C(=J^a)NR^bR^c$;

B is a direct bond and L is a hydrocarbon chain in which the 1-position is bound to B and L is selected from tetramethylene, cis-1-butenylene and cis-cis-butadienylene;

J and J^a are independently oxygen or sulfur;

R^a, R^b and R^c are independently hydrogen or (1-6C)alkyl;

R^b and R^c are independently hydrogen or (1-6C)alkyl in which said (1-6C)alkyl may be substituted by a group selected from hydroxy and (1-3C)alkoxy, or said (1-6C)alkyl may be terminally substituted by a group selected from hydroxy, (1-3C)alkoxy, phenyl, $-C(=O)OR^d$ and $-C(=O)NR^bR^c$; or

R^b and R^c together with the nitrogen to which they are attached form a piperidino group;

R^d and R^e are independently (1-3C)alkyl or together form a divalent hydrocarbon chain selected from ethylene and trimethylene;

R^f is (1-6C)alkyl;

R^d, R^e and R^f are independently hydrogen or (1-3C)alkyl;

m is 2 or 3;

M is a residue of formula Ia or formula Ib wherein

Q is phenyl which may bear one or two substituents independently selected from halo, trifluoromethyl, hydroxy, (1-3C)alkoxy, (1-3C)alkyl and methylenedioxy; or Q naphthyl which may bear a halo substituent; or Q is biphenyl;

Q^o is hydrogen, (1-4C)alkyl, or a radical of formula $-(CH_2)_q-NR^7R^8$ in which q is 2 or 3 and R⁷ and R⁸ are independently (1-4C)alkyl or NR⁷R⁸ is piperidino;

R³ is hydrogen, methyl or (2-6C)n-alkyl which may bear a terminal amino radical;

R⁴ is $-C(=O)R^5$, $-C(=O)OR^5$ or $-C(=J^1)NHR^5$ in which J¹ is oxygen or sulfur and R⁵ is hydrogen, (1-6C)alkyl, phenyl(1-3C)alkyl (in which the phenyl may bear one or more halo, hydroxy, (1-4C)alkoxy or (1-4C)alkyl substituents), naphthyl(1-3C)alkyl, styryl, aryl (which may bear one or more halo, hydroxy, (1-4C)alkoxy or (1-4C)alkyl substituents), or (when R⁴ is $-COR^5$) α -hydroxybenzyl;

n is 0, 1, 2 or 3;

p is 1 or 2, and when p is 2, n is 1 and J² is two hydrogens;

J² is oxygen or two hydrogens;

L¹ is carbonyl or methylene;

r is 0, 1, 2, or 3; and

R⁶ is phenyl which may bear one or more halo, trifluoromethyl, (1-4C)alkyl, hydroxy or (1-4C)alkoxy; or naphthyl which may bear one or more halo, trifluoromethyl, (1-4C)alkyl or hydroxy substituents; or when L¹ is carbonyl, the group $-(CH_2)_r-R^5$ may represent an aryl, or a benzyl group bearing an α -substituent selected from hydroxy, (1-4C)alkoxy and

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2. The second part of the document is a report from the Secretary of the Treasury, dated January 1, 1861. It contains a detailed account of the financial state of the country at the beginning of the year.

3. The third part of the document is a report from the Secretary of the Interior, dated January 1, 1861. It contains a detailed account of the state of the public lands and the progress of the various departments under his control.

4. The fourth part of the document is a report from the Secretary of the Navy, dated January 1, 1861. It contains a detailed account of the state of the navy and the progress of the various departments under his control.

5. The fifth part of the document is a report from the Secretary of the War, dated January 1, 1861. It contains a detailed account of the state of the army and the progress of the various departments under his control.

6. The sixth part of the document is a report from the Secretary of the State, dated January 1, 1861. It contains a detailed account of the state of the foreign relations of the United States and the progress of the various departments under his control.

7. The seventh part of the document is a report from the Secretary of the Education, dated January 1, 1861. It contains a detailed account of the state of the public schools and the progress of the various departments under his control.

8. The eighth part of the document is a report from the Secretary of the Agriculture, dated January 1, 1861. It contains a detailed account of the state of the agriculture of the United States and the progress of the various departments under his control.

9. The ninth part of the document is a report from the Secretary of the Commerce, dated January 1, 1861. It contains a detailed account of the state of the commerce of the United States and the progress of the various departments under his control.

10. The tenth part of the document is a report from the Secretary of the Fish and Game, dated January 1, 1861. It contains a detailed account of the state of the fish and game of the United States and the progress of the various departments under his control.

11. The eleventh part of the document is a report from the Secretary of the Land and Survey, dated January 1, 1861. It contains a detailed account of the state of the public lands and the progress of the various departments under his control.

12. The twelfth part of the document is a report from the Secretary of the Indian Affairs, dated January 1, 1861. It contains a detailed account of the state of the Indian population of the United States and the progress of the various departments under his control.

(1-4)alkyl, and further wherein the aryl, or phenyl portion of the benzyl group may bear one or more substituents selected independently from halo, trifluoromethyl, (1-4C)alkyl, hydroxy and (1-4C)alkoxy;

or the N-oxide of the piperidino nitrogen indicated by Δ ; or a pharmaceutically acceptable salt thereof;

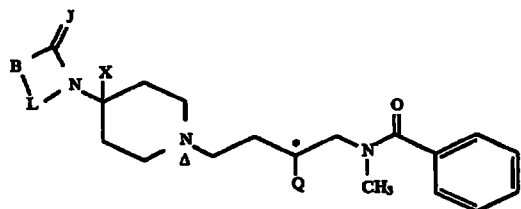
or a quaternary ammonium salt thereof in which the piperidino nitrogen indicated by Δ is a quadricovalent ammonium nitrogen wherein the fourth radical on the nitrogen R^p is (1-4C)alkyl or benzyl and the associated counterion A is a pharmaceutically acceptable anion.

2. A compound as claimed in claim 1 wherein, R^b and R^c are independently hydrogen or (1-6C)alkyl; or R^b and R^c together with the nitrogen to which they are attached form a pyrrolidino, piperidino, morpholino, thiomorpholino (or its S-oxide) or piperaziny group (which piperaziny group may bear a methyl or ethyl group at the 4-position); or the N-oxide of the piperidino nitrogen indicated by Δ ; or a pharmaceutically acceptable salt thereof; or a quaternary ammonium salt thereof.

3. A compound as claimed in claim 1, wherein m is 2; (1-6C)alkyl is methyl, ethyl, propyl, isopropyl or butyl; (1-3C)alkyl is methyl or ethyl; Q is phenyl which may bear one or two substituents selected from halo, trifluoromethyl and methylenedioxy; R^p is methyl or benzyl; and A is chloride, bromide or methanesulfonate.

4. A compound as claimed in claim 1, wherein M is formula Ib; n is 1 or 2; p is 1; J^2 is two hydrogens; L^1 is carbonyl; r is 0 or 1; and R^e is phenyl which may bear one or two halo or (1-4C)alkoxy substituents.

5. A compound of formula I as claimed in claim 1, which is a compound of formula Ic:



or the N-oxide of the piperidino nitrogen indicated by Δ ; or a pharmaceutically acceptable salt thereof; or a quaternary ammonium salt thereof; wherein J, B, L, X, Q, R^p and A have the values defined for a compound of formula I.

6. A compound as claimed in claim 5 wherein, B is a direct bond and L is a hydrocarbon chain in which the 1-position is bound to B and L is trimethylene, or the N-oxide of the piperidino nitrogen indicated by Δ ; or a pharmaceutically acceptable salt thereof; or a quaternary ammonium salt thereof.

7. A compound of formula I as claimed in claim 5, wherein B is $N(R^b)$ and L is a hydrocarbon chain selected from ethylene, trimethylene and cis-vinylene; or B is N and L is a hydrocarbon chain in which the 1-position is bound to

B and L is cis,cis-prop-2-en-1-ylidene-3-yl; or the N-oxide of the piperidino nitrogen indicated by Δ ; or a pharmaceutically acceptable salt thereof; or a quaternary ammonium salt thereof.

8. A pharmaceutical composition comprising a compound of formula I as defined in claim 1;

or the N-oxide of the piperidino nitrogen indicated by Δ ; or a pharmaceutically acceptable salt thereof;

or a quaternary ammonium salt thereof in which the piperidino nitrogen indicated by Δ is a quadricovalent ammonium nitrogen wherein the fourth radical on the nitrogen R^p is (1-4C)alkyl or benzyl and the associated counterion A is a pharmaceutically acceptable anion; and a pharmaceutically acceptable diluent or carrier.

9. A method of treating a disease in a human or other mammal in need thereof in which NKA is implicated and antagonism of its action is desired, comprising: administering an effective dose of a compound of formula I as defined in claim 1;

or the N-oxide of the piperidino nitrogen indicated by Δ ; or a pharmaceutically acceptable salt thereof;

or a quaternary ammonium salt thereof in which the piperidino nitrogen indicated by Δ is a quadricovalent ammonium nitrogen wherein the fourth radical on the nitrogen R^p is (1-4C)alkyl or benzyl and the associated counterion A is a pharmaceutically acceptable anion.

10. A method of treating asthma in a human or other mammal, comprising: administering an effective dose of a compound of formula I as defined in claim 1;

or the N-oxide of the piperidino nitrogen indicated by Δ ; or a pharmaceutically acceptable salt thereof;

or a quaternary ammonium salt thereof in which the piperidino nitrogen indicated by Δ is a quadricovalent ammonium nitrogen wherein the fourth radical on the nitrogen R^p is (1-4C)alkyl or benzyl and the associated counterion A is a pharmaceutically acceptable anion.

11. A compound of formula I as claimed in claim 1, which is selected from:

(S)-N-[2-(3,4-dichlorophenyl)-4-[4-(methoxycarbonyl)-4-(2-oxoperhydropyrimidin-1-yl)piperidino]butyl]-N-methylbenzamide;

(S)-N-[2-(3,4-dichlorophenyl)-4-[4-(2-oxoperhydropyrimidin-1-yl)-4-(pyrrolidin-1-ylcarbonyl)piperidino]butyl]-N-methylbenzamide;

(S)-N-[2-(3,4-dichlorophenyl)-4-[4-(methylaminocarbonyl)-4-(2-oxoperhydropyrimidin-1-yl)piperidino]butyl]-N-methylbenzamide; and

(S)-N-[2-(3,4-dichlorophenyl)-4-[4-methyl-4-(2-oxoperhydropyrimidin-1-yl)piperidino]butyl]-N-methylbenzamide, or a pharmaceutically acceptable salt thereof.

* * * * *

1. The first step in the process is to identify the problem or issue that needs to be addressed. This involves gathering information and understanding the context of the problem.

1. The first step in the process is to identify the problem or issue that needs to be addressed. This involves gathering information and understanding the context of the problem.

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 2. 定期存款账户的开立，须由客户填写《定期存款开户申请书》，并提供有效身份证件。
 3. 本行定期存款账户分为整存整付、零存整付、整存零付、零存零付四种类型。
 4. 定期存款的期限分为三个月、六个月、九个月、十二个月、十八个月、二十四个月、三十六个月、四十八个月、六十个月、七十二个月、八十四个月、九十六个月、一百零八个月、一百二十个月。
 5. 定期存款的利率按照中国人民银行规定的利率执行。
 6. 定期存款账户的开立，须由客户本人或授权代理人办理。
 7. 本行定期存款账户的开立，须符合中国人民银行的相关规定。

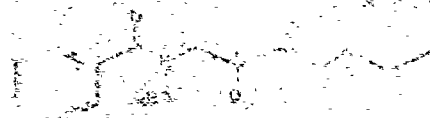
1. The first of these is the fact that the
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1. The first step in the process of the investigation is the identification of the problem. This involves a thorough review of the available information and a clear definition of the issue at hand. Once the problem is identified, the next step is to gather relevant data and information. This can be done through various methods, including interviews, surveys, and document analysis. The third step is to analyze the data and information gathered. This involves identifying patterns, trends, and relationships that may be relevant to the problem. Finally, the fourth step is to develop and implement a solution. This involves creating a plan of action and putting it into practice. The process of investigation is a continuous one, and it may be necessary to revisit previous steps as more information is gathered and the problem evolves.

1. The first step in the process is to identify the problem or issue that needs to be addressed. This involves gathering information and understanding the context of the problem.

1. 凡在本行开立存款账户的客户，均可向本行申请开立支票。
 2. 支票的有效期为自签发之日起 10 个工作日内。
 3. 支票的金额不得超过账户余额。
 4. 支票的签发人必须是账户持有人或其授权代理人。
 5. 支票的收款人必须是合法的收款单位或个人。
 6. 支票的签发必须使用本行提供的支票簿。
 7. 支票的签发必须加盖本行规定的印章。
 8. 支票的签发必须填写完整，不得涂改。
 9. 支票的签发必须遵守国家的法律法规。
 10. 支票的签发必须遵守本行的规章制度。

1. The first step in the process is to identify the problem or issue that needs to be addressed. This involves gathering information and understanding the context of the problem.

[illegible]

1. The first step in the process is to identify the problem or issue that needs to be addressed. This involves gathering information and understanding the context of the situation.

2. Once the problem is identified, the next step is to define the objectives and goals of the project. This helps to clarify what is to be achieved and provides a clear direction for the work.

3. The third step is to develop a plan or strategy to address the problem. This involves identifying the resources needed, the tasks to be completed, and the timeline for the project.

4. The fourth step is to implement the plan. This involves putting the strategy into action and monitoring progress to ensure that the project is on track.

5. The final step is to evaluate the results of the project. This involves assessing the outcomes against the objectives and goals, and identifying any lessons learned for future projects.

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LACTAM COMPOUNDS WHICH ARE USEFUL IN THE TREATMENT OF ASTHMA

This is a divisional of application Ser. No. 08/332,290 filed on 31 Oct. 1994, now U.S. Pat. No. 5,534,525.

This invention concerns novel lactam derivatives, and, more particularly, novel 4,4-disubstituted piperidines, in which one of the substituents is a lactam derivative bonded at its nitrogen, which antagonize the pharmacological actions of one of the endogenous neuropeptide tachykinins known as neurokinins, particularly at the neurokinin 2 (NK2) receptor. The novel lactam derivatives are useful whenever such antagonism is desired. Thus, such compounds may be of value in the treatment of those diseases in which an NK2 receptor is implicated, for example, in the treatment of asthma and related conditions. The invention also provides pharmaceutical compositions containing the novel lactam derivatives for use in such treatment, methods for their use, and processes and intermediates for the manufacture of the novel lactam derivatives.

The mammalian neurokinins comprise a class of peptide neurotransmitters which are found in the peripheral and central nervous systems. The three principal neurokinins are Substance P (SP), Neurokinin A (NKA) and Neurokinin B (NKB). There are also N-terminally extended forms of at least NKA. At least three receptor types are known for the three principal neurokinins. Based upon their relative selectivities favoring the neurokinin agonists SP, NKA and NKB, respectively, the receptors are classified as neurokinin 1 (NK1), neurokinin 2 (NK2) and neurokinin 3 (NK3) receptors, respectively. In the periphery, SP and NKA are localized in C-afferent sensory neurons, which neurons are characterized by non-myelinated nerve endings known as C-fibers, and are released by selective depolarization of these neurons, or selective stimulation of the C-fibers. C-Fibers are located in the airway epithelium, and the tachykinins are known to cause profound effects which clearly parallel many of the symptoms observed in asthmatics. The effects of release or introduction of tachykinins in mammalian airways include bronchoconstriction, increased microvascular permeability, vasodilation and activation of mast cells. Thus, the tachykinins are implicated in the pathophysiology and the airway hyperresponsiveness observed in asthmatics; and blockade of the action of released tachykinins may be useful in the treatment of asthma and related conditions. Peptidic NK2 antagonists have been reported. For example, a cyclic hexapeptide known as L-659,877 has been reported as a selective NK2 antagonist. Nonpeptidic NK2 antagonists also have been reported, for example in European Patent Application, Publication Number (EPA) 428434, EPA 474561, EPA 512901, EPA 512902, EPA 515240, EPA 559538, as well as in WO 94/10146. I have discovered a series of nonpeptidic NK2 antagonists, and this is the basis for my invention.

According to the invention, there is provided a Compound of the invention which is a compound of formula I (formula set out hereinbelow following the Examples, together with other formulae denoted by Roman numerals) wherein

X is (1-6C)alkyl—CH₂OR^a, —CH₂SR^a, —CH₂S(=O)R^a, —CH₂S(=O)₂R^a, —C(=O)R^a, —C(=O)OR^a, —C(=J¹)NR^bR^c, —C(R^d)(OR^e)(OR^f), —CH₂N(R^g)C(=J²)R^h, —CH₂N(R^g)C(=O)ORⁱ or —CH₂N(R^g)C(=J²)NR^bR^c;

B is a direct bond and L is a hydrocarbon chain in which the 1-position is bound to B and L is selected from trimethylene, tetramethylene, cis-1-butenylene and cis-cis-

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butadienylene; or B is N(R^h) and L is a hydrocarbon chain selected from ethylene, trimethylene and cis-vinylene; or B is N and L is a hydrocarbon chain in which the 1-position is bound to B and L is cis,cis-prop-2-en-1-ylidin-3-yl;

J and J² are independently oxygen or sulfur;

R^a, R^b and R^c are independently hydrogen or (1-6C)alkyl;

R^b and R^c are independently hydrogen or (1-6C)alkyl in which said (1-6C)alkyl may be substituted by a group selected from hydroxy and (1-3C)alkoxy, or said (1-6C)alkyl may be terminally substituted by a group selected from hydroxy, (1-3C)alkoxy, phenyl, —C(=O)ORⁱ and —C(=O)NR^bR^c; or

R^b and R^c together with the nitrogen to which they are attached form a pyrrolidino, piperidino, morpholino, thiomorpholino (or its S-oxide) or piperazinyl group (which piperazinyl group may bear a methyl or ethyl group at the 4-position);

R^d and R^e are independently (1-3C)alkyl or together form a divalent hydrocarbon chain selected from ethylene and trimethylene;

R^f is (1-6C)alkyl;

R^g, R^h and Rⁱ are independently hydrogen or (1-3C)alkyl;

m is 2 or 3;

M is a residue of formula Ia or formula Ib wherein

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

Q^a is hydrogen, (1-4C)alkyl, or a radical of formula —(CH₂)_q—NR⁷R⁸ in which q is 2 or 3 and R⁷ and R⁸ are independently (1-4C)alkyl or NR⁷R⁸ is piperidino or 4-benzylpiperidino;

R³ is hydrogen, methyl or (2-6C)n-alkyl which may bear a terminal amino radical;

R⁴ is —C(=O)R⁵, —C(=O)OR⁵ or —C(=J¹)NHR⁵ in which J¹ is oxygen or sulfur and R⁵ is hydrogen, (1-6C)alkyl, phenyl(1-3C)alkyl (in which the phenyl may bear one or more halo, hydroxy, (1-4C)alkoxy or (1-4C)alkyl substituents), pyridyl(1-3C)alkyl, naphthyl(1-3C)alkyl, pyridylthio(1-3C)alkyl, styryl, 1-methylimidazol-2-ylthio(1-3C)alkyl, aryl (which may bear one or more halo, hydroxy, (1-4C)alkoxy or (1-4C)alkyl substituents), heteroaryl (which may bear one or more halo, hydroxy, (1-4C)alkoxy or (1-4C)alkyl substituents), or (when R⁴ is —COR⁵) α-hydroxybenzyl;

n is 0, 1, 2 or 3;

p is 1 or 2, and when p is 2, n is 1 and J² is two hydrogens;

J² is oxygen or two hydrogens;

L¹ is carbonyl or methylene;

r is 0, 1, 2, or 3; and

R⁶ is phenyl which may bear one or more halo, trifluoromethyl, (1-4C)alkyl, hydroxy or (1-4C)alkoxy substituents (and particularly one or more chloro or fluoro substituents); naphthyl which may bear one or more halo, trifluoromethyl, (1-4C)alkyl or hydroxy substituents; pyridyl; thienyl; indolyl; quinolinyl; benzothienyl or imidazolyl; or when L¹ is carbonyl, the group —(CH₂)_r—R⁶ may represent aryl, heteroaryl or a benzyl group bearing an α-substituent selected from hydroxy, (1-4C)alkoxy and (1-4)alkyl, and further wherein the aryl, heteroaryl or phenyl portion of the benzyl group may bear one or more substituents selected independently from halo,

1. The first part of the report is a general statement of the purpose and scope of the study. It is followed by a brief review of the literature on the subject.

2. The second part of the report is a description of the methods used in the study. This includes a description of the subjects, the instruments used, and the procedures followed.

3. The third part of the report is a presentation of the results of the study. This is followed by a discussion of the results and their implications.

4. The fourth part of the report is a conclusion. This is followed by a list of references and an appendix.

5. The fifth part of the report is a list of references. This is followed by an appendix.

6. The sixth part of the report is an appendix. This is followed by a list of references and an appendix.

7. The seventh part of the report is a list of references. This is followed by an appendix.

8. The eighth part of the report is an appendix. This is followed by a list of references and an appendix.

9. The ninth part of the report is a list of references. This is followed by an appendix.

10. The tenth part of the report is an appendix. This is followed by a list of references and an appendix.

11. The eleventh part of the report is a list of references. This is followed by an appendix.

12. The twelfth part of the report is an appendix. This is followed by a list of references and an appendix.

13. The thirteenth part of the report is a list of references. This is followed by an appendix.

14. The fourteenth part of the report is an appendix. This is followed by a list of references and an appendix.

15. The fifteenth part of the report is a list of references. This is followed by an appendix.

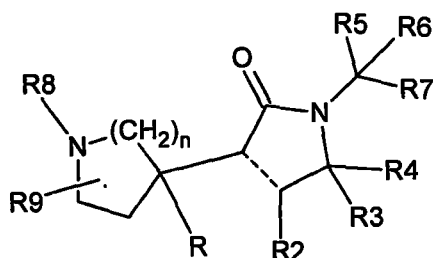
16. The sixteenth part of the report is an appendix. This is followed by a list of references and an appendix.

17. The seventeenth part of the report is a list of references. This is followed by an appendix.

18. The eighteenth part of the report is an appendix. This is followed by a list of references and an appendix.

Reivindicaciones

Reivindicaciones 1 a 9: Se reivindica un compuesto de fórmula (I):



Reivindicación 10: Se reivindica un procedimiento para preparar un compuesto de acuerdo con las cláusulas precedentes que comprende las etapas de:

- a) Ciclización de un compuesto de fórmula (IV) o
- b) Ciclización de un compuesto de fórmula (V), o
- c) Ciclización de un compuesto de fórmula (VII), o
- d) La reacción de un compuesto de fórmula (VIIA) con un aldehído $\text{CH}(\text{O})(\text{CH}_2)_m\text{R}_{10}$ de fórmula (VIIIa) para proporcionar un compuesto de fórmula (I), o
- e) Ciclización de un compuesto de fórmula (VIa) en presencia de un ácido para obtener un compuesto de fórmula (I), o
- f) N-alquilación de un compuesto de fórmula (VIII) con un compuesto de fórmula (IX) $\text{L-C}(\text{R}_5)(\text{R}_6)(\text{R}_7)$ para proporcionar un compuesto de fórmula (I),

opcionalmente para cualquiera de los pasos (a) a (f) eliminar cualquier grupo protector y/o convertir un compuesto de fórmula (I) en otro compuesto de fórmula (I) y/o separación de un compuesto de fórmula (I) en o un derivado del mismo en los enantiómeros del mismo.

Reivindicaciones 11 a 13: Se reivindica el compuesto para ser usado en terapia y el uso de los compuestos para la preparación de un medicamento para utilizarse en el tratamiento de condiciones mediadas por las taquicininas y/o la inhibición selectiva de la proteína del transportador de la recaptación de la serotonina.

Reivindicación 14: Se reivindica una composición farmacéutica que comprende un compuesto de conformidad con las reivindicaciones precedentes.

Reivindicación 15: Se reivindica un método para el tratamiento de condiciones mediadas por las taquicininas.

Sustento Descriptivo

La solicitud hace referencia a derivados de lactama, procedimientos para su preparación y a las composiciones farmacéuticas que los contienen. Los compuestos son antagonistas de los receptores de taquicicina, incluyendo la sustancia P y otras neurocininas tanto *in vitro* como *in vivo*.

Se han identificado tres tipos de receptores de taquicininas: NK1, NK2 y NK3 que están ampliamente distribuidas a través del sistema nervioso central y periférico. Los compuestos de la invención son antagonistas del receptor NK1 y son inhibidores selectivos de la recaptación de serotonina.

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- Una vez catalogada la invención ésta se clasificó en la sección: **A 61 K³¹₄₄₃₉**
// **A 61 P²⁵₀₀** de la **Clasificación Internacional de Patentes**.

3. De la solicitud de Patente

3.1. Reivindicaciones (artículo 30 D. 486)

Teniendo en cuenta el contenido y alcance de la materia reivindicada esta Superintendencia se permite señalar lo siguiente:

- Las cláusulas 1 a 7 definen las características de la estructura Markush de la fórmula (I) e incluyen términos que evocan géneros funcionales y no permiten una interpretación inequívoca del grado de complejidad que presenta la fórmula, una vez se producen las sustituciones sobre la misma. Es el caso de las expresiones que forman parte de las opciones contempladas para el caso de los radicales R₅, R₉ y R₁₀, a continuación relacionadas:

Grupo bicíclico heterocíclico fusionado de 9 a 10 miembros

Grupo heteroarilo de 5 ó 6 miembros

Cicloalquilo de C₃₋₇

Al respecto es preciso requerir al señor solicitante en los términos del presente examen técnico para que identifique claramente cuáles son las especies químicas y funcionales que sustituyen la estructura Markush contempladas dentro de los géneros antes indicados, lo anterior, atendiendo las normas por la IUPAC para la denominación de compuestos orgánicos¹ y las modalidades particulares de la invención que presentan las cláusulas 8 y 9.

¹ ARYL GROUPS:

Groups derived from arenes by removal of a hydrogen atom from a ring carbon atom. NOC Rule A-13.5. Groups similarly derived from heteroarenes are sometimes subsumed in this definition (see heteroaryl groups). E.g. o-tolyl.

ARENES:

Monocyclic and polycyclic aromatic hydrocarbons. NOC Rule A-12.4. (See aromatic compounds).

AROMATIC COMPOUNDS:

Historically, the term "aromatic" originally referred to the smell of selected compounds that later were found to contain benzene or fused benzene rings in the structure. In a structural sense, it designates compounds that, in accordance with the theory of Hückel, have a cyclic, delocalized (4n+2) pi-electron system. This includes arenes and their substitution products. E.g. benzene, naphthalene, toluene. The term has been generalized to include aromatic heterocyclic structures, such as thiophene and pyridine, but it is more precise to call compounds of the latter type heteroaromatic. See also arenes, heteroarenes. GTPOC (aromatic).

HETEROARENES:

Heterocyclic compounds formally derived from arenes by replacement of one or more methine (-C=) and/or vinylenes (-CH=CH-) groups by trivalent or divalent heteroatoms, respectively, in such a way as to maintain the continuous π -electron system characteristic of aromatic systems and a number of out-of-plane π -electrons corresponding to the Hückel rule (4n + 2); an alternative term is hetarenes. Comprehensive Heterocyclic Chemistry, Vol. 1, Ed. O. Meth-Cohn, Pergamon, 1984, p. 3.

HETEROARYL GROUPS:

The class of heterocyclyl groups derived from heteroarenes by removal of a hydrogen atom from any ring atom; an alternative term is hetaryl. E.g. 2-pyridyl (pyridin-2-yl), indol-1-yl.

HETEROCYCLYL GROUPS:

Univalent groups formed by removing a hydrogen atom from any ring atom of a heterocyclic compound. E.g. 4-pyridyl, pyrrolidin-1-yl, pyrrolidin-2-yl.

CYCLOALKYL GROUPS:

Univalent groups derived from cycloalkanes by removal of a hydrogen atom from a ring carbon atom.

URL: <http://www.chem.qmul.ac.uk/iupac/class/rings.html#12>.

Glossary of class names of organic compounds and reactive intermediates based on structure (IUPAC Recommendations 1994). Miscellaneous.

En lo que respecta al documento D2 las diferencias estriban en que el anillo de lactama no se encuentra sustituido por un grupo metilen-arilo como en el caso de la materia reivindicada.

Del problema técnico objetivo y del efecto inesperado:

De acuerdo con la divulgación que acompaña la solicitud de patente los derivados de lactama se presentan como una alternativa terapéutica para el manejo de condiciones mediadas por las taquicinas, en particular por la taquicina NK1, debido a que las moléculas presentan actividad como antagonistas del receptor de la taquicina NK1, incluyendo la sustancia P. Además, las sustancias presentan actividad como inhibidores selectivos de la recaptación de serotonina.

Se indica además que la afinidad de unión por el receptor de la NK1 se ha determinado en un ensayo *in vitro* midiendo la capacidad de los compuestos de desplazar la Tyr8-Sustancia P de los receptores de la NK1 en células de ovario de hámster chino.

Al respecto es preciso señalar que el documento D2 señala la capacidad de las estructuras de causar la inhibición en la actividad de las taquicinas, en particular, de la NK2, por lo que la actividad farmacológica de los derivados de lactama constituye parte fundamental del estado de la técnica divulgado en la publicación señalada.

En consecuencia, una persona versada en ciencias farmacéuticas se encontraría motivada a diseñar derivados de lactama con afinidad específica por el receptor NK1, debido a la información divulgada en los antecedentes D1 y D2, por lo que esta Superintendencia considera que la materia reivindicada no constituye un verdadero salto en la regla técnica y se deriva de manera evidente a partir del estado del arte.

Por las razones expuestas anteriormente esta dependencia encuentra que la materia reivindicada carece de altura inventiva y por lo tanto no cumple con las disposiciones normativas que señala el artículo 18 del ordenamiento jurídico andino.

8. Conclusión:

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

N°	Documento N°	Reivindicaciones Afectadas	Requisito que Afecta
D1	US5780466	1 a 15	Nivel Inventivo
D2	US5677317	1 a 15	Nivel Inventivo

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.