

1202

Señores

SUPERINTENDENCIA DE INDUSTRIA Y COMF
DIVISION DE NUEVAS CREACIONES

E. _____ S. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 06-029042- -00004-0000

Fecha: 2009-10-20 16:48:20 Dep. 2020 NUECREACION
Tra. 11 PATENTEIYII Eve: 379 FASENACIONALII
Act. 538 PETICION Folios: 2

Ref.: Expediente No. 06-029.042

Solicitud de Patente de Invención titulada: "DERIVADOS DE TROPANO".

Solicitante: PFIZER INC.

Nuestra Ref: P2006/000050

SOLICITUD DE EXAMEN DE PATENTABILIDAD SEGÚN
EL ARTÍCULO 44 DE LA DECISION 486, GACETA No. 607

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, 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 recibo por el monto de \$452.000 pesos para cubrir la tasa correspondiente, según la Resolución 55819 del año 2008.

Atentamente,

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

Anexo: Recibo por \$452.000 pesos

2.203

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 09 - 77,869
FECHA : OCTUBRE 15 DE 2009

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 06-029042- -00004-0000

Fecha: 2009-10-20 16:48:20 Dep. 2020 NUECREACION
Tra. 11 PATENTEIYII Eve: 379 FASENACIONALII
Act. 538 PETICION Folios: 2

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	Vr. PAGO
DEARTE RAISBEK	CONSIGNACION	BANCO DE BOGOTA	062754387	130888623	15/10/2009	5,283,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
50005-01-01	SOLICITUDES	85 EXAMEN DE PATENTABILIDAD DE INVEN	452,000.00
TOTAL :			\$ 452,000.00

CON: CUATROCIENTOS CINCUENTA Y DOS MIL PESOS

RESPONSABLE :

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

204



Industria y Comercio
SUPERINTENDENCIA

DIVISIÓN DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 06-29042

EL EXTRACTO DE LA PRESENTE SOLICITUD DE **PATENTE DE INVENCION**

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **607** DE

FECHA **31 DE AGOSTO DE 2009** EL TÉRMINO HÁBIL SEÑALADO POR LA

LEY EXPIRA EL **26 DE NOVIEMBRE DE 2009**

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI

NO

_____ **X** _____

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
29 November 2001 (29.11.2001)

PCT

(10) International Publication Number
WO 01/90106 A2

(51) International Patent Classification⁷: **C07D 451/00**

Sandwich, Kent CT13 9NJ (GB). **WOOD, Anthony** [GB/GB]; Pfizer Global Research and Development, Ramsgate Road, Sandwich, Kent CT13 9NJ (GB).

(21) International Application Number: **PCT/IB01/00806**

(22) International Filing Date: **9 May 2001 (09.05.2001)**

(74) **Agents: WOOD, David, J. et al.**; Pfizer Limited, Ramsgate Road, Sandwich, Kent CT13 9NJ (GB).

(25) Filing Language: **English**

(26) Publication Language: **English**

(30) Priority Data:

0014046.7 26 May 2000 (26.05.2000) GB
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(81) **Designated States (national):** AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(71) **Applicant (for GB only): PFIZER LIMITED** [GB/GB]; Ramsgate Road, Sandwich, Kent CT13 9NJ (GB).

(84) **Designated States (regional):** ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, 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, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

(71) **Applicant (for all designated States except GB, US): PFIZER INC.** [US/US]; 235 East 42nd Street, New York, NY 10017 (US).

(72) **Inventors; and**

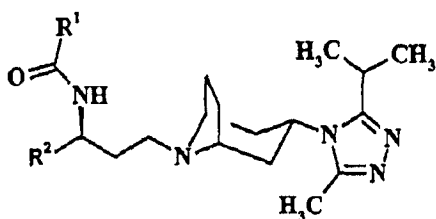
(75) **Inventors/Applicants (for US only): PERROS, Manousos** [GR/GB]; Pfizer Global Research and Development, Ramsgate Road, Sandwich, Kent CT13 9NJ (GB). **PRICE, David, Anthony** [GB/GB]; Pfizer Global Research and Development, Ramsgate Road, Sandwich, Kent CT13 9NJ (GB). **STAMMEN, Blanda, Luzia, Christa** [DE/GB]; Pfizer Global Research and Development, Ramsgate Road,

Published:

— without international search report and to be republished upon receipt of that report

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

(54) Title: TROPANE DERIVATIVES USEFUL IN THERAPY



(I)

(57) **Abstract:** The present invention provides compounds of the formula (I): wherein R¹ is C₃₋₆ cycloalkyl optionally substituted by one or more fluorine atoms, or C₁₋₆ alkyl optionally substituted by one or more fluorine atoms, or C₃₋₆ cycloalkylmethyl optionally ring-substituted by one or more fluorine atoms; and R² is phenyl optionally substituted by one or more fluorine atoms, to pharmaceutically acceptable salts and solvates thereof, and to processes for the preparation of, intermediates used in the preparation

of, compositions containing and the uses of, such compounds.

WO 01/90106 A2

Tropane derivatives useful in therapy

This invention relates to tropane derivatives useful in the treatment of a variety of disorders, including those in which the modulation of CCR5
5 receptors is implicated. More particularly, the present invention relates to 3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-exo-8-azabicyclo[3.2.1]octane derivatives and to processes for the preparation of, intermediates used in the preparation of, compositions containing and the uses of, such derivatives. Disorders that may be treated or prevented by the present derivatives include
10 HIV and genetically related retroviral infections (and the resulting acquired immune deficiency syndrome, AIDS), and inflammatory diseases.

The compounds of the present invention are modulators, especially antagonists, of the activity of chemokine CCR5 receptors. Modulators of the CCR5 receptor may be useful in the treatment of various inflammatory
15 diseases and conditions, and in the treatment of infection by HIV-1 and genetically related retroviruses. The name "chemokine", is a contraction of "chemotactic cytokines". The chemokines comprise a large family of proteins which have in common important structural features and which have the ability to attract leukocytes. As leukocyte chemotactic factors, chemokines
20 play an indispensable role in the attraction of leukocytes to various tissues of the body, a process which is essential for both inflammation and the body's response to infection. Because chemokines and their receptors are central to the pathophysiology of inflammatory and infectious diseases, agents which are active in modulating, preferably antagonizing, the activity of chemokines
25 and their receptors, are useful in the therapeutic treatment of such inflammatory and infectious diseases.

The chemokine receptor CCR5 is of particular importance in the context of treating inflammatory and infectious diseases. CCR5 is a receptor for chemokines, especially for the macrophage inflammatory proteins (MIP)
30 designated MIP-1 α and MIP-1 β , and for a protein which is regulated upon activation and is normal T-cell expressed and secreted (RANTES).

General Example

A formulation of the tablet could typically contain from 0.01mg to 500mg of active compound whilst tablet fill weights may range from 50mg to 1000mg.

5 An example of a formulation for a 10mg tablet is illustrated below:

<u>Ingredient</u>	<u>%w/w</u>
Compound of the formula (I) or salt	10.000*
Lactose	64.125
10 Starch	21.375
Croscarmellose sodium	3.000
Magnesium stearate	1.500

* Quantity adjusted in accordance with drug activity.

15

The tablets are manufactured by a standard process, for example, direct compression or a wet or dry granulation process. The tablet cores may be coated with appropriate overcoats.

20

Solid compositions of a similar type may also be employed as fillers in gelatin or HPMC capsules. Preferred excipients in this regard include lactose, starch, a cellulose, milk sugar or high molecular weight polyethylene glycols. For aqueous suspensions and/or elixirs, the compounds of the
25 formula (I) may be combined with various sweetening or flavouring agents, colouring matter or dyes, with emulsifying and/or suspending agents and with diluents such as water, ethanol, propylene glycol and glycerin, and combinations thereof.

The compounds of the formula (I) can also be administered
30 parenterally, for example, intravenously, intra-arterially, intraperitoneally, intrathecally, intraventricularly, intraurethrally, intrasternally, intracranially,

Biological activity

- 5 The compounds of Examples 1-5 were tested in the assay for CCR5 binding following the procedures disclosed in Combadiere *et al.*, *J. Leukoc. Biol.* **60**, 147-52 (1996) (mentioned above). All of the tested compounds were found to have an IC_{50} value of less than 10 nM.

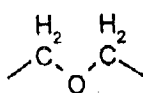


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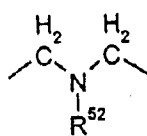
WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

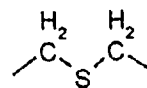
(51) International Patent Classification ⁷ : A61K 31/445, C07D 451/04, A61K 31/46		A1	(11) International Publication Number: WO 00/38680
			(43) International Publication Date: 6 July 2000 (06.07.00)
(21) International Application Number: PCT/IB99/02048		Sandwich, Kent CT13 9NJ (GB). EDWARDS, Martin, Paul [GB/GB]; Pfizer Central Research, Ramsgate Road, Sandwich, Kent CT13 9NJ (GB).	
(22) International Filing Date: 23 December 1999 (23.12.99)			
(30) Priority Data: 9828420.1 23 December 1998 (23.12.98) GB 9921375.3 10 September 1999 (10.09.99) GB		(74) Agent: SPIEGEL, Allen, J.; c/o Simpson, Alison, Urquhart-Dykes & Lord, 30 Welbeck Street, London W1M 7PG (GB).	
(71) Applicant (for GB only): PFIZER LIMITED [GB/GB]; Ramsgate Road, Sandwich, Kent CT13 9NJ (GB).		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, 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).	
(71) Applicant (for all designated States except GB US): PFIZER, INC. [US/US]; 235 East 42nd Street, New York, NY 10017 (US).		Published With international search report.	
(72) Inventors; and (75) Inventors/Applicants (for US only): ARMOUR, Duncan, Robert [GB/GB]; Pfizer Central Research, Ramsgate Road, Sandwich, Kent CT13 9NJ (GB). PRICE, David, Anthony [GB/GB]; Pfizer Central Research, Ramsgate Road, Sandwich, Kent CT13 9NJ (GB). STAMMEN, Blanda, Luzia, Christa [DE/GB]; Pfizer Central Research, Ramsgate Road, Sandwich, Kent CT13 9NJ (GB). WOOD, Anthony [GB/GB]; Pfizer Central Research, Ramsgate Road, Sandwich, Kent CT13 9NJ (GB). PERROS, Manousos [GR/GB]; Pfizer Central Research, Ramsgate Road,			
(54) Title: AZABICYCLOALKANES AS CCR5 MODULATORS			
(57) Abstract			
Compounds of the Formula (I) [Region α] - [Region β] - [Region γ] - [Region δ] which are useful as modulators of chemokine activity. The invention also provides pharmaceutical formulations and methods of treatment using these compounds.			



(4.2.4)



(4.2.5)



(4.2.6)

—where:

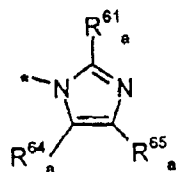
— R^{52} is a member selected from the group consisting of hydrogen; phenyl; (C_1-C_4) alkyl substituted by 0 or 1 substituent independently selected from (C_1-C_2) alkoxy and $-CO_2R^4$; (C_3-C_6) cycloalkyl; $-CO_2R^4$; $\rightarrow O$; $C(=O)(C_1-C_3)$ alkyl; $-C(=O)NR^4_aR^4_b$; $-S(=O)(C_1-C_4)$ alkyl; and (C_1-C_2) alkylcarbonyl; where R^4 , R^4_a , and R^4_b are as defined above, but selected on an independent basis;

— R^{51} is absent or is a member selected from the group consisting of (C_1-C_4) alkyl substituted by 0 or 1 substituent independently selected from (C_1-C_2) alkoxy and $-CO_2R^4$ where R^4 is as defined above; and $\rightarrow O$; it being understood that in the case where substituent R^{51} is present, the nitrogen atom is in quaternary form; and

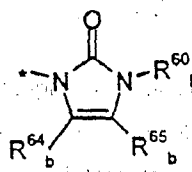
— k , l and m are each an integer selected from 0, 1, 2, and 3;

$[R_{\text{egion } \delta}]$ is a member selected from the group consisting of:

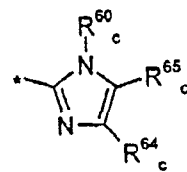
15 -A. a two-nitrogen-atom-containing five-membered heterocyclic moiety of partial Formulas (5.0.0) through (5.0.10):



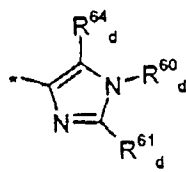
(5.0.0)



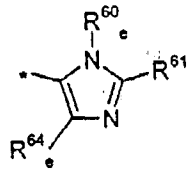
(5.0.1)



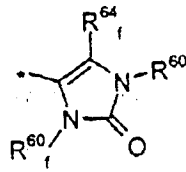
(5.0.2)



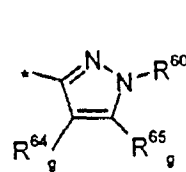
(5.0.3)



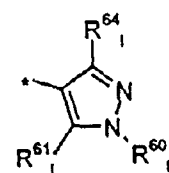
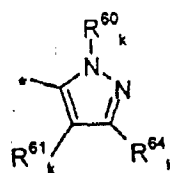
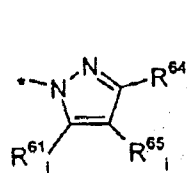
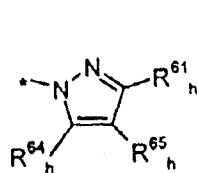
(5.0.4)



(5.0.5)



(5.0.6)



(5.0.7)

(5.0.8)

(5.0.9)

(5.0.10)

—wherein: the symbol: "*" indicates the point of attachment of each of the moieties of partial Formulas (5.0.0) through (5.0.10), inclusive, to Region Y;

— R^{60}_b through R^{60}_g , inclusive, R^{60}_k , and R^{60}_l are each a member selected from the group consisting of hydrogen; $-\text{CO}_2\text{R}^4$; $-\text{C}(=\text{O})\text{NR}^4_a\text{R}^4_b$; $-\text{S}(=\text{O})_p\text{NR}^4_a\text{R}^4_b$; where: R^4 , R^4_a , and R^4_b are as defined above but selected on an independent basis; $-\text{O}$; $(\text{C}_1\text{--}\text{C}_2)\text{alkylcarbonyl}$; $-(\text{C}_1\text{--}\text{C}_4)\text{alkyl}$; $-(\text{CH}_2)_n(\text{C}_3\text{--}\text{C}_7)\text{cycloalkyl}$; $-(\text{C}_2\text{--}\text{C}_3)\text{alkenyl}$; $-(\text{CH}_2)_n(\text{phenyl})$; and $-(\text{CH}_2)_n(\text{HET}_1)$, where n is an integer independently selected from 0, 1, and 2; wherein said $(\text{C}_1\text{--}\text{C}_4)\text{alkyl}$, alkenyl, cycloalkyl, phenyl, and heterocyclyl groups are independently substituted with 0 to 3 substituents R^{66} , where:

— HET_1 is a heterocyclyl group selected from the group consisting of thienyl; oxazolyl; isoxazolyl; thiazolyl; isothiazolyl; pyrazolyl; oxadiazolyl; thiadiazolyl; triazolyl; pyridyl; pyrazinyl; pyridazinyl; pyrimidinyl; parathiazinyl; and morpholinyl; where:

— R^{66} is a member selected from the group consisting of $-\text{F}$; $-\text{Cl}$; $-\text{OH}$; cyano; $-\text{C}(=\text{O})\text{OR}^{68}$; $-\text{C}(=\text{O})\text{NR}^{68}\text{R}^{69}$; $-\text{NR}^{68}\text{R}^{69}$; $-\text{NR}^{68}\text{C}(=\text{O})\text{R}^{69}$; $-\text{NR}^{68}\text{C}(=\text{O})\text{OR}^{69}$; $-\text{NR}^{68}\text{S}(=\text{O})_2\text{R}^{69}$; $-\text{S}(=\text{O})_2\text{NR}^{68}\text{R}^{69}$; $(\text{C}_1\text{--}\text{C}_4)\text{alkyl}$ including dimethyl, and $(\text{C}_1\text{--}\text{C}_4)\text{alkoxy}$ wherein said alkyl and alkoxy are each independently substituted with 0 to 3 substituents independently selected from F and Cl; $(\text{C}_1\text{--}\text{C}_2)\text{alkoxycarbonyl}$; $(\text{C}_1\text{--}\text{C}_2)\text{alkylcarbonyl}$; and $(\text{C}_1\text{--}\text{C}_2)\text{alkylcarbonyloxy}$, where:

— R^{68} and R^{69} are each a member selected from the group consisting of hydrogen; and $(\text{C}_1\text{--}\text{C}_2)\text{alkyl}$; and where said:

— R^{61}_a ; R^{61}_d ; R^{61}_e ; and R^{61}_h through R^{61}_i , inclusive; R^{64}_a through R^{64}_i , inclusive; R^{65}_a through R^{65}_c , inclusive; and R^{65}_g through R^{65}_i , inclusive are each a member selected from the group consisting of hydrogen; $-\text{OH}$; $-\text{CF}_3$; cyano; $-(\text{C}_1\text{--}\text{C}_3)\text{alkoxy}$; $-\text{C}(=\text{O})\text{OR}^4$; $-\text{C}(=\text{O})\text{NR}^4_a\text{R}^4_b$; $-\text{NR}^4_a\text{R}^4_b$; $-\text{NR}^4_a\text{C}(=\text{O})\text{R}^4_b$; $-\text{NR}^4_a\text{C}(=\text{O})\text{OR}^4_b$; $-\text{NR}^4_a\text{S}(=\text{O})_p\text{R}^4_b$; $-\text{S}(=\text{O})_p\text{NR}^4_a\text{R}^4_b$; where: R^4 , R^4_a , and R^4_b are as defined further above but selected on an independent basis; $-(\text{C}_1\text{--}\text{C}_4)\text{alkyl}$; $-(\text{CH}_2)_n(\text{C}_3\text{--}\text{C}_7)\text{cycloalkyl}$; $-(\text{C}_2\text{--}\text{C}_3)\text{alkenyl}$; $-(\text{CH}_2)_n(\text{phenyl})$; and $-(\text{CH}_2)_n(\text{HET}_1)$, where n is an integer selected from 0, 1, and 2; wherein said $(\text{C}_1\text{--}\text{C}_4)\text{alkyl}$, alkenyl, cycloalkyl, phenyl, and heterocyclyl groups where heterocyclyl groups is as defined above, are independently substituted with 0 to 3 substituents R^{66} where:

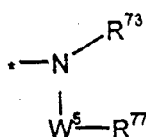
— R^{66} is as defined above, or:

— R^{64}_a through R^{64}_c , inclusive; R^{64}_g through R^{64}_i , inclusive; R^{65}_a through R^{65}_c , inclusive; and R^{65}_g through R^{65}_i , inclusive may be taken together in their same subscript denominated pairs along with the remaining portions of the moieties of partial Formulas (5.0.0) through (5.0.2), and (5.0.6) through (5.0.8), to form a fused bicyclic ring system comprising a member independently selected from the group consisting of benzimidazolyl; purinyl, i.e.,

imidazopyrimidinyl; and imidazopyridinyl; wherein said fused bicyclic ring system is independently substituted with 0 to 3 substituents R^{66} , where R^{66} has the same meaning as set out further above, except that it is independently selected therefrom;

5 -B. a (substituted)-amide, carbamate, or urea moiety selected from the group consisting of:

-1. alkyl-, cycloalkyl-, and alkenyl-(substituted)-amide, carbamate, or urea moieties of partial Formula (5.1.0):

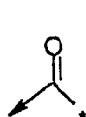


(5.1.0)

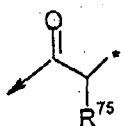
10 ---wherein: the symbol " * " is as defined above;

--- R^{73} is a member selected from the group consisting of hydrogen and (C_1, C_2) alkyl;

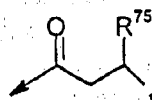
--- W^5 is selected from the group consisting the moieties of partial Formulas (5.1.1) through (5.1.12):



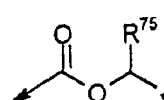
(5.1.1)



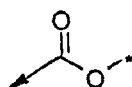
(5.1.2)



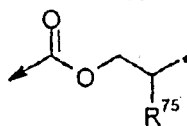
(5.1.3)



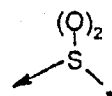
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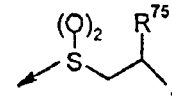
(5.1.5)



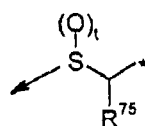
(5.1.6)



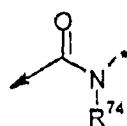
(5.1.7)



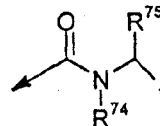
(5.1.8)



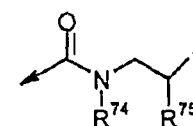
(5.1.9)



(5.1.10)



(5.1.11)



(5.1.12)

20 ---wherein: the symbol: "→" indicates the point of attachment of the moiety W^5 represented by partial Formulas (5.1.1) through (5.1.12), inclusive, to the nitrogen atom in partial Formula (5.1.0), and the symbol: " * " indicates the point of attachment of the moiety W^5 to R^{77} as defined further below;

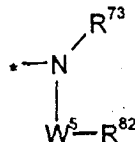
—R⁷⁴ and R⁷⁵ are each selected from the group consisting of hydrogen; (C₁.C₂)alkyl substituted by 0 or 1 substituent independently selected from OH; and (C₁.C₂)alkoxy; and

—R⁷⁷ is a member selected from the group consisting of (C₁.C₆)alkyl; (C₂.C₆)alkenyl; and -(CH₂)_n(C₃.C₇)cycloalkyl, where n is an integer selected from 0, 1, and 2; and wherein said alkyl, alkenyl, and cycloalkyl groups comprising R⁷⁷ are substituted with 0 to 3 substituents R⁷⁸, where:

—R⁷⁸ is a member selected from the group consisting of oxo; -OH; -(C₁.C₂)alkyl; -(C₁.C₃)alkoxy; -CF₃; -C(=O)OR⁷⁹; -C(=O)NR⁷⁹R⁸⁰; -NR⁷⁹R⁸⁰; -NR⁷⁹C(=O)R⁸⁰; -NR⁷⁹C(=O)OR⁸⁰; -NR⁷⁹S(=O)₂R⁸⁰; and -S(=O)₂NR⁷⁹R⁸⁰, where:

—R⁷⁹ and R⁸⁰ are each a member independently selected from the group consisting of hydrogen; and (C₁.C₄)alkyl; and

-2. aryl and heterocyclyl-(substituted)-amide, carbamate, or urea moieties of partial Formula (5.2.0):



(5.2.0)

—wherein: the symbol: "*"; R⁷³; and W⁵ have the same meanings as under the definitions of partial Formula (5.1.0) above, except that they are independently selected therefrom; and under W⁵ the symbols: "→" and "*" are as defined under partial Formula (5.1.0); and

—R⁸² is a member selected from the group consisting of phenyl; cinnolyl; furyl; thienyl; pyrrolyl; oxazolyl; isoxazolyl; thiazolyl; isothiazolyl; imidazolyl; imidazolyl; pyrazolyl; pyrazolyl; oxadiazolyl; thiadiazolyl; triazolyl; pyridyl; pyrazinyl; pyridazinyl; pyrimidinyl; parathiazinyl; indolyl; isoindolyl; indolyl; benzo[b]furanyl; 2;3-dihydrobenzofuranyl; benzo[b]thiophenyl; 1H-indazolyl; benzimidazolyl; benzthiazolyl; quinolyl; isoquinolyl; phthalazinyl; quinazolyl; quinoxalyl; wherein:

—the aryl or heterocyclyl moiety is substituted by 0 to 3 substituents R⁷⁸ where R⁷⁸ is as defined above, but selected on an independent basis; or

-C. a (substituted)-heterocyclyl moiety independently selected from the group consisting of:

-1. a heterocyclyl moiety of partial Formula (5.3.0):

- 108 -

The title compound of preparation 67 (86mg, 0.23mmol) in dichloromethane (2.5ml) was added to tetrahydropyran-4-carboxylic acid (30mg, 0.23mmol), 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (53mg, 0.28mmol), N-diisopropylethylamine (44 μ l, 0.25 mmol) and 1-hydroxybenzotriazole hydrate (34mg, 0.25mmol) in dichloromethane (2.5ml). The reaction mixture was stirred for 16 hours at room temperature. The solvent was evaporated under reduced pressure and the residue taken up in ethyl acetate, washed with water, brine, dried (MgSO₄) filtered and evaporated under reduced pressure. The residual pale brown solid was purified by column chromatography on silica gel, using an elution gradient of dichloromethane:methanol:0.88 ammonia (98:2:0.25 to 95:5:0.5) to afford the title compound as a white solid, 48mg.

Found C, 70.59; H, 7.83; N, 10.94%

C₃₀H₃₆N₄O₂ · 1.3H₂O requires C, 70.64; H, 8.02; N, 10.98%

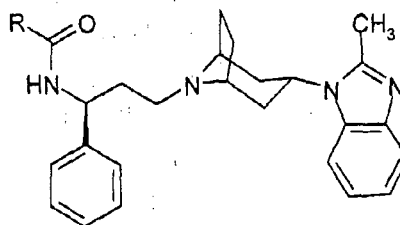
¹H NMR (400 MHz, CDCl₃): δ [ppm] 1.65 (2H, bm), 1.71-1.92 (6H, m), 1.96-2.22 (4H, m), 2.37 (1H, m), 2.46-2.68 (7H, m), 3.39-3.50 (4H, m), 3.98 (2H, m), 4.54 (1H, m), 5.20 (1H, m), 6.79 (1H, m), 7.13-7.21 (2H, m), 7.23-7.30 (1H, m), 7.30-7.40 (4H, m), 7.42-7.54 (1H, m), 7.62-7.72 (1H, m)

LRMS: m/z 487.3 (MH⁺)

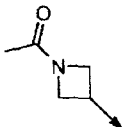
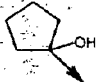
Melting point [°C]: 95-96

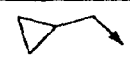
EXAMPLES 5 - 16

The compounds of the following tabulated examples with the general structure:



were prepared using a similar method to Example 4 from the title compound of preparation 67 and the corresponding acids.

Example Number	R	Yield (%)	Characterization Data
5 1-Acetyl- <i>N</i> - {(1 <i>S</i>)-3-[3- <i>exo</i> -(2- methyl-1 <i>H</i> - benzimidazol-1-yl)- 8-azabicyclo[3.2.1] oct-8-yl]-1-phenyl propyl]-3-azetidine carboxamide		41	Found C, 68.66; H, 7.40; N, 13.00% C ₃₀ H ₃₇ N ₅ O ₂ ·1.5H ₂ O requires C, 68.42; H, 7.66; N, 13.30% ¹ H NMR (400 MHz, CDCl ₃): δ [ppm] 1.61-1.84 (4H, m), 1.84 (3H, s), 1.93-2.20 (4H, bm), 2.44-2.71 (7H, m), 3.24 (1H, m), 3.42 (2H, bs), 4.04-4.15 (3H, m), 4.42 (1H, q), 4.56 (1H, m), 5.24 (1H, bm), 7.11-7.21 (6H, m), 7.44-7.56 (1H, m), 7.63-7.73 (1H, m) LRMS: m/z 500.7 (MH ⁺)
6 1-Hydroxy- <i>N</i> -{(1 <i>S</i>)-3-[3- <i>exo</i> -(2- methyl-1 <i>H</i> - benzimidazol-1-yl)- 8-azabicyclo[3.2.1] oct-8-yl]-1-phenyl propyl]cyclo pentanecarboxamid e		29	Found C, 71.31; H, 7.58; N, 10.87% C ₃₀ H ₃₈ N ₄ O ₂ ·0.7H ₂ O·0.1CH ₂ Cl ₂ requires C, 71.20; H, 7.86; N, 11.03% ¹ H NMR (400 MHz, CDCl ₃): δ [ppm] 1.47-1.92 (10H, m), 1.96-2.14 (5H, m), 2.14-2.28 (2H, m), 2.50 (2H, m), 2.53-2.67 (5H, m), 3.41 (2H, bs), 4.52 (1H, m), 5.20 (1H, m), 7.12-7.23 (2H, m), 7.23-7.30 (1H, m), 7.30- 7.41 (4H, m), 7.51-7.60 (1H, m), 7.62-7.70 (1H, m), 7.82 (1H, d). LRMS: m/z 487.2 (MH ⁺) Melting point [°C]: 90-91

7 2-Methyl-N- {(1S)-3-[3-exo-(2- methyl-1H- benzimidazol-1-yl)- 8-azabicyclo[3.2.1] oct-8-yl]-1-phenyl propyl}cyclo propanecarboxamid e		84 Found C, 74.17; H, 8.04; N, 11.63% $C_{29}H_{36}N_4O \cdot 0.75H_2O$ requires C, 74.09; H, 8.04; N, 11.92% ^1H NMR (400 MHz, $CDCl_3$): δ [ppm] 0.98-1.26 (6H, m), 1.32-1.41 (1H, m), 1.62-1.80 (4H, m), 1.93-2.18 (4H, m), 2.43-2.72 (7H, m), 3.38-3.52 (2H, m), 4.54 (1H, m), 5.20 (1H, q), 7.05 (1H, bd), 7.11-7.22 (2H, m), 7.24- 7.30 (1H, m), 7.32-7.40 (4H, m), 7.47-7.54 (1H, m), &.62-7.71 (1H, m) LRMS: m/z 457.6 (MH^+) Melting point [$^{\circ}C$]: 105-106
8 2- Cyclopropyl-N- {(1S)-3-[3-exo-(2- methyl-1H- benzimidazol-1-yl)- 8-azabicyclo [3.2.1]oct-8-yl]-1- phenylpropyl} acetamide		83 Found C, 73.28; H, 7.99; N, 11.77% $C_{29}H_{36}N_4O \cdot 1H_2O$ requires C, 73.39; H, 8.07; N, 11.88% ^1H NMR (400 MHz, $CDCl_3$): δ [ppm] 0.21 (2H, m), 0.61 (2H, m), 0.97-1.08 (1H, m), 1.61-1.80 (4H, m), 1.96-2.14 (4H, bm), 2.21 (2H, m), 2.44-2.68 (7H, m), 3.42 (2H, bs), 4.54 (1H, m), 5.24 (1H, m), 6.88 (1H, d), 7.16-7.22 (2H, m), 7.24-7.30 (1H, m), 7.32-7.41 (4H, m), 7.47-7.56 (1H, m), 7.62-7.70 (1H, m) LRMS: m/z 456.9 (MH^+) Melting point [$^{\circ}C$]: 85-86

216

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

2020
Bogotá, D.C.,

Abogado:
Carlos R. OLARTE

ASUNTO: Radicación No. 06 02 9042
 Trámite 011
 Evento 379
 Actuación 430
 Oficio
 Folios 08189

Como resultado del Examen de Fondo, realizado con fundamento en el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se comunica:

Documentos estudiados:

Descripción: Folios 67 a 144 como se radicó inicialmente.

Reivindicaciones: Folios 191 a 199 como se radicó inicialmente.

Prioridad: GB 0323236.0 (03-10-2003);
 GB 0325020.6 (27-10-2003);
 GB 0418566.6 (19-08-2004)

Objeto de la Invención

Título de la invención: "Derivados de tropano"

Problema Técnico Planteado: "Necesidad de derivados de tropano , procedimientos para su preparación, de composiciones que los contienen y a su uso"

Solución: "Derivados de 8-azabicyclo"

IPC: C07D 471/04, A61K 31/4188; A61P 31/18

El objeto de la presente solicitud es:

Reivindicación 1 – 7: Un compuesto de acuerdo a la formula I;
Reivindicación 8 y 9: Una composición farmacéutica que incluye un compuesto de formula I;
Reivindicación 10-15: Un compuesto de formula I para uso como medicamento;
Reivindicación 16: Uso de un compuesto de fórmula I;

Reivindicación 17: Un procedimiento para preparar un compuesto de formula I;
 Reivindicación 18: Un procedimiento para preparar un compuesto de formula II, IV, VI, VII, XVI, XVIII, XX o XXIII;
 Reivindicación 19: Un compuesto de formula;
 Reivindicación 20 – 22: Una combinación.

Reivindicaciones relativas a un uso o a un segundo uso (Art 14 y 21 D 486)

La reivindicación 16 se refiere al uso de los compuestos en mención. Se requiere la eliminación de dicha reivindicación ya que constituye una excepción de patentabilidad.

Análisis de la Solicitud de Patente

Reivindicaciones (Art 30 D 486, Art 22 PCT)

Claridad y Concisión: Las reivindicaciones 10 a la 15 no añaden ninguna característica técnica esencial a los compuestos que se están reclamando, haciendo que el capítulo carezca de claridad. Se requiere al solicitante para que elimine estas reivindicaciones del capítulo reivindicatorio.

Determinación del Estado de la Técnica

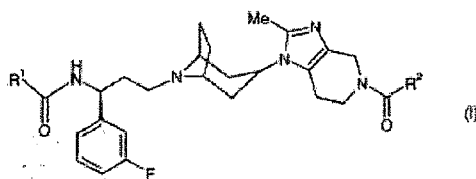
El Estado de la Técnica se determinó con base en la fecha de prioridad 03-10-2003 y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

Item	Documento	Título	Fecha de Publicación
D1	WO 01/90106	<i>Tropane derivatives useful in therapy</i>	29.11.2001
D2	WO 00/38680	<i>Azabicycloalkanes as CCR5 modulators</i>	06.07.2000

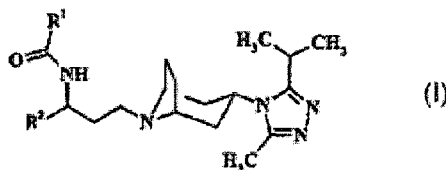
Análisis de Patentabilidad (Art 14 D486)

Nivel Inventivo (Art18 D486)

La reivindicación 1 dice: "Un compuesto de fórmula I o una sal, solvato o derivado farmacéuticamente aceptable del mismo en la que R1 es alquilo folio 191



D1 enseña compuestos de acuerdo a la formula I, en donde R₁ es C₃₋₆ cicloalquilo opcionalmente sustituidos por uno o más átomos de carbono, o C₁₋₆ alquilo opcionalmente sustituidos por uno o más átomos de flúor, o C₃₋₆ cicloalquilmetil opcionalmente sustituidos por anillo y R₂ es fenil opcionalmente sustituido por uno o mas átomos de flúor, sales farmacéuticamente aceptables y solvatos de los mismos, procesos



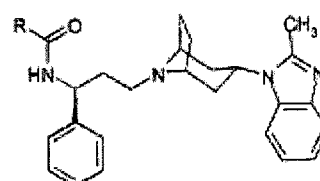
para su preparación e intermediarios (portada). Esta invención se relaciona con los derivados de tropano usados en el tratamiento de una variedad de desordenes incluyendo esos en los cuales la modulación de receptores CCR5 es implicada (p.1, lin. 1-5). Presenta ejemplos de composiciones que contienen el compuesto de formula I o su sal (p.22, lin. 1-15). D1 presenta que todos los compuestos fueron testeados para obtener un de IC50 de 10 nM.

La solicitud se diferencia de D1 en el sistema heterociclo aromático fusionado con un heterociclo que sustituye el grupo central.

El Efecto Técnico que logra la diferencia es una disminución en el valor IC50, que para los ejemplos 1 y 5 se reportan valores de 130 y 120 pm.

El Problema Técnico Objetivo de esta solicitud es proveer antagonistas del receptor CCR5 más potentes y selectivos.

D2 revela compuestos moduladores de la actividad de CCR5, con cuatro regiones variables independientes a saber alfa-beta-gama- delta (portada; p. 2, ln. 1-10), específicamente D2 revela compuestos (p.108-115) como los ejemplos 5 a 16 de acuerdo a la estructura. Dentro de las regiones presentadas, se llama la atención sobre la región delta, (p.11, ln. 15-25; p. 12-15) que es definida como un heterociclo aromático de cinco miembros dos de los cuales son nitrógeno, y que puede formar un sistema fusionado biciclo con los sustituyentes mostrados para R₆₀-R₆₅ (p.12).



El experto en la materia habría sido sugerido por D2 a modificar las regiones definidas en D2 (alfa-beta-gama-delta) que son presentadas por los compuestos presentados por D1, como es el caso de la región delta, la cual es la principal diferencia entre los compuestos presentados por D1 y por la presente solicitud. De manera que, D2 le habría sugerido otros sustituyentes para la región en cuestión.

Se concluye que las reivindicaciones 1 y sus dependientes pueden carecen de nivel inventivo.

Conclusión

Los requisitos de Patentabilidad de la presente Solicitud se encuentran afectados así:

	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	WO 01/90106	1-22	Nivel inventivo
D2	WO 00/38680	1-22	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 60 días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.


ALIX CARMENZA CÉSPEDES DE VERGEL
Directora de Nuevas Creaciones (C)

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

25 JUN. 2010

CONCEPTO TECNICO NUMERO: 1537	EXAMINADOR TÉCNICO Código:202092
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