

Castillo Grau & Asociados
ABOGADOS

SUPERINDUSTRIA Y COMERCIO
Radicacion : 00030779 00000003 Folios: 2
Fecha (ARD): 2002-11-07 16:35:27
Tramite : 002 PATENTES D 1 REGISTRO/ 538 PETICION
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

Señores
DIVISIÓN DE NUEVAS CREACIONES
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Bogotá, D.C.

Re.: Código 02-01-538
Expediente No. 00-30.779
Solicitud de Patente
SMITHKLINE BEECHAM p.l.c.

En relación con el Expediente de la referencia por medio del presente escrito muy respetuosamente me permito solicitarles se sirvan proceder a efectuar el EXAMEN DE PATENTABILIDAD de la solicitud aquí contenida.

Para tal efecto acompaño el comprobante de pago por concepto de \$ 318.000.00, recibo No. 74. 314/02

De Ustedes Atentamente,

GERMAN CASTILLO GRAU
T.P. # 2.978 del C.S.J.

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tax

Industria y Comercio
SUPERINTENDENCIA

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 02 - 74,314
FECHA : NOVIEMBRE 7 DE 2002

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***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	Vr. PAGO
CASTILLO GRAU Y ASOCIADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	6635317	06/11/2002	3,350,200.00

***** CONCEPTO *****

CANT. CIENTISTICO.	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	85 EXAMEN DE PATENTABILIDAD DE INVEN
	TOTAL :	\$ 318,000.00

SON: TRESCIENTOS DIEZ Y OCHO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

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19149

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES

2020/
Bogotá, D.C.,

Doctor
Germán Castillo Grau
Apoderado

Oficio N° 00-12729

REFERENCIA	Radicación	00 30779
	Trámite	002
	Evento	001
	Actuación	430
	Folios	007

Como resultado del examen de patentabilidad de la solicitud de patente de invención N° 00 30779, realizado según el artículo 45 de la decisión 486 de la comisión de la Comunidad Andina, se notifica:

Documentos estudiados:

- . Descripción: folios 4-19
- . Ejemplos: folios 19-79
- . Capítulo reivindicatorio estudiado: folios 80-85
- . Se reivindica prioridad, presentada en Gran Bretaña el 01.05.99, bajo el número 9910048.9 y la 0002096.6 de 28.01.00

Objeto de la invención

Según las reivindicaciones 1 a 20 de la presente solicitud, se refiere a compuestos de pirimidinona de fórmula (I), su método de síntesis y composiciones farmacéuticas que los contienen. Tales compuestos son inhibidores de la enzima Lp-PLA2 para el tratamiento de la aterosclerosis.

Clasificación internacional de patentes A 61 K 31/505

Claridad de la solicitud

El art. 30 de la decisión 486 contempla que *“Las reivindicaciones definirán la materia que se desea proteger mediante la patente. Deben ser claras y concisas y estar enteramente sustentadas por la descripción”*

Teniendo en cuenta lo anterior, los términos “grupo arilo o heteroarilo” y “cadena lateral de aminoácido” utilizados en el capítulo reivindicatorio son tan generales que abarcan compuestos que pueden diferir de los compuestos revelados en la descripción y los ejemplos de la presente solicitud. No es razonable asumir que todos los compuestos que caen dentro de éstas definiciones tan generales puedan tener una actividad biológica equivalente.

Favor hacer las aclaraciones y correcciones del caso

Excepciones a la patentabilidad

El art. 20 d de la decisión 486 contempla que *“No serán patentables los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnóstico aplicados a los seres humanos o a animales”*

El contenido de las reivindicaciones 18 y 19 que trata de “Un método para tratar una enfermedad...”, no es patentable.

Determinación del estado de la técnica:

Consultadas las fuentes de información con que cuenta este despacho, se encontraron los siguientes documentos, anteriores a la fecha de prioridad de la presente solicitud - 01.05.99-, relacionados con la materia de la presente solicitud:

Nº	Documento	Título	Fecha de publicación
1	GB 1582527	“Derivados de pirimidona y tiopirimidona”	07.01.81

Evaluación de los requisitos de patentabilidad:

El artículo 14 de la decisión 486 de la comisión de la comunidad andina establece que: *“Los países miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial”*

En cumplimiento del artículo 14 de la decisión 486 de la comisión de la comunidad andina, se procedió a evaluar los requisitos de novedad, nivel inventivo y aplicación industrial con el fin de establecer la patentabilidad de la invención reivindicada en la solicitud en estudio.

Evaluación del NIVEL INVENTIVO

El artículo 18 de la decisión 486 establece que *“Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica”*

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La publicación GB 1582527 se relaciona con derivados de pirimidona y tiopirimidona que tienen actividad bloqueadora de los receptores de la histamina H2.

Teniendo en cuenta el objeto de la solicitud, el cual es proveer compuestos derivados de pirimidona que tienen actividad biológica (esto debido a la utilización de términos generales en el capítulo reivindicatorio, tal como se explicó en el punto de claridad de la solicitud), es una derivación evidente del estado de la técnica ya que los documentos citados enseñan compuestos similares que tienen una actividad biológica.

Un técnico con sus conocimientos y las enseñanzas de los documentos citados llegaría a sintetizar los compuestos que se pretenden proteger.

En conclusión los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

Nº	Documento	Reivindicaciones afectadas	Requisito que afecta
1	GB 1582527	1-17, 20	Nivel Inventivo

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

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo 5 del título primero de la Circular Única N° 10 de 2001

Álix Carmenza Céspedes de Vergel
Jefe de la División de Nuevas Creaciones

05 MAYO 2005

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

CONCEPTO TÉCNICO Número 0557	EXAMINADOR TÉCNICO Código 202024
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PATENT SPECIFICATION

(11) 1 582 527

1 582 527

- (21) Application No. 53001/75 (22) Filed 29 Dec. 1975
(21) Application No. 48605/76 (22) Filed 22 Nov. 1976
(23) Complete Specification filed 25 March 1977
(44) Complete Specification published 7 Jan. 1981
(51) INT CL³ C07D 401/00; A61K 31/505; C07D 403/00, 405/00, 409/00, 413/00, 417/00; (C07D 401/00, 213/04, 215/02, 217/00, 233/54, 239/46); (C07D 403/00, 233/54, 237/06, 239/24); (C07D 403/00, 239/46, 241/10); (C07D 405/00, 233/54, 239/46, 307/34); (C07D 409/00, 233/54, 239/46, 333/04); (C07D 413/00, 233/54, 239/46, 263/30); (C07D 417/00, 213/04, 233/54, 275/00, 277/20, 285/04)

(19)



(52) Index at acceptance

C2C 1371 1380 1382 1410 1440 1470 1510 1530 1534 1535
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247 250 251 252 253 254 255 256 25Y 28X 29X 29Y
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453 45Y 461 462 463 464 491 553 612 614 620 624
625 628 62Y 630 638 650 652 655 656 658 65X 662 670
672 680 682 694 758 761 762 770 802 80Y AA BB BK
LF LK MB MC MD NB NG NL QS RM UL

- (72) Inventors GRAHAM JOHN DURANT, CHARON ROBIN
GANELLIN and THOMAS HENRY BROWN

(54) PYRIMIDONE DERIVATIVES AND THIOPYRIMIDONE

(71) We, SMITH KLINE & FRENCH LABORATORIES LIMITED, of Mundells, Welwyn Garden City, Hertfordshire, England, a British company, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to pyrimidone derivatives, to processes for preparing these compounds and to pharmaceutical compositions containing them.

Many physiologically active substances elicit their biological actions by interaction with specific sites known as receptors. Histamine is such a substance and has a number of biological actions. Those biological actions of histamine which are inhibited by drugs commonly called "anti-histamines" of which mepyramine, diphenhydramine and chlorpheniramine are examples, are mediated through histamine H₁-receptors (Ash and Schild, *Brit. J. Pharmac. Chemother.*, 27, 427, (1966)), and drugs with this activity are hereinafter referred to as histamine H₁-antagonists. However, other of the biological actions of histamine are not inhibited by histamine H₁-antagonists and actions of this type which are inhibited by a compound described by Black et al. (*Nature*, 236, 385, (1972)) and called burimamide are mediated through receptors which are defined by Black et al. as histamine H₂-receptors. Thus histamine H₂-receptors may be defined as those histamine receptors which are not blocked by mepyramine but are blocked by burimamide. Compounds which block histamine H₂-receptors are referred to as histamine H₂-antagonists.

Blockade of histamine H₂-receptors is of utility in inhibiting the biological actions of histamine which are not inhibited by histamine H₁-antagonists. Histamine H₂-antagonists are therefore useful, for example, as inhibitors of gastric acid secretion, as anti-inflammatory agents and as agents which act on the cardiovascular system, for example, as inhibitors of the effects of histamine on blood pressure. In the treatment of certain conditions, for example, inflammation and in inhibiting the actions of histamine on blood pressure, a combination of histamine H₁- and H₂-antagonists is useful.

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The ingredients are screened, mixed and filled into a hard gelatin capsule. Similarly, the other compounds of Formula I may be formulated into pharmaceutical compositions by the procedures of Examples 20 and 21.

The pharmaceutical compositions prepared as in the foregoing examples are administered to a subject within the dose ranges given hereabove to block histamine H_2 -receptors.

EXAMPLE 22.

2 - [2 - (5 - methyl - 4 - imidazolymethylthio) - ethylamino] - 5 - (3 - quinolylmethyl) - 4 - pyrimidone trihydrochloride

- (i) A solution of 3-quinolineacrylic acid (63.71 g) and concentrated sulphuric acid (25 ml) in ethanol (350 ml) was refluxed for 18 hours. The product was obtained according to the procedure of Example 8 (i), giving ethyl 3-quinolineacrylate, m.p. 86.5—88° (Ex ethanol-water).
(Found: C, 73.8; H, 5.8; N, 6.0; $C_{12}H_{11}NO_2$ requires: C, 74.0; H, 5.8; N, 6.2%)
- (ii) 3-quinolineacrylate (51.68 g) was dissolved in ethanol (170 ml) and hydrogenated at 37° and a pressure of 50 psi using 10% Palladium on charcoal to give ethyl 3-quinolinepropionate.
- (iii) Ethyl 3-quinolinepropionate (47.99 g) and ethyl formate (16.3 g) were added over a period of 3 hours to a stirred mixture of sodium wire (4.8 g) and dry ether (150 ml) cooled by an ice-bath. The mixture was stirred for 20 hours at room temperature, evaporated to dryness and the residue was treated with thiourea (15.9 g) and ethanol (130 ml) and refluxed for 7 hours. The mixture evaporated to dryness and the residue was dissolved in water and acetic acid added to pH 4. The mixture was filtered to give 5 - (3 - quinolinemethyl) - 2 - thiouracil, m.p. 281—6° (decomp.) (ex. acetic acid-water).
- (iv) A solution of 5 - (3 - quinolinemethyl) - 2 - thiouracil (17.51 g), methyl iodide (9.2 g) and sodium hydroxide (5.4 g) in water (200 ml) and ethanol (200 ml) was stirred at 75° for 1 hour, allowed to cool and acetic acid added to pH 4 to give 5 - (3 - quinolinemethyl) - 2 - methylthio - 4 - pyrimidone, m.p. 215.5—218° (ex. ethanol).
- (v) An intimate mixture of 5 - (3 - quinolinemethyl) - 2 - methylthio - 4 - pyrimidone (2.1 g) and 2 - (5 - methyl - 4 - imidazolymethylthio) - ethylamine (1.3 g) was heated at 150—5° for 6 hours. The cooled mixture was triturated with hot water and treated with dilute ethanolic HCl to give the title compound, m.p. 184—9° (ex. ethanol-water).

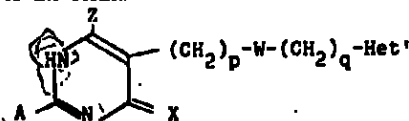
EXAMPLE 23.

2 - [2 - (2 - thiazolymethylthio)ethylamino] - 5 - (3 - quinolylmethyl) - 4 - pyrimidone trihydrochloride

- An intimate mixture of 5 - (3 - quinolinemethyl) - 2 - methylthio - 4 - pyrimidone (2.0 g) and 2 - (2 - thiazolymethylthio) - ethylamine (1.2 g) was heated at 145° for 4 hours. After cooling the residue was triturated with hot water and treated with dilute ethanolic HCl to give the title compound, m.p. 217.5—221.5° (ex. ethanol-water).
(Found: C, 45.9; H, 4.3; N, 13.3; S, 12.2; Cl, 19.7. $C_{22}H_{19}N_5OS_2 \cdot 3HCl$ requires: C, 46.3; H, 4.3; N, 13.5; S, 12.4; Cl, 20.5%)

WHAT WE CLAIM IS:—

1. A compound of the formula:—

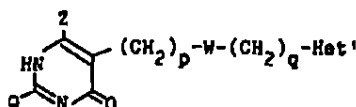


- where X is oxygen or sulphur, A is $Het-CH_2Y(CH_2)_z-NH-$ where Het is a 2- or 4-imidazolyl group optionally substituted with lower alkyl, halogen, trifluoromethyl or hydroxymethyl; a 2-pyridyl group optionally substituted with lower alkyl, lower alkoxy, halogen, amino or hydroxy; a 2-thiazolyl group; a 3-isothiazolyl group optionally substituted with chlorine or bromine; a 3 - (1,2,5) - thiadiazolyl group optionally substituted with chlorine or bromine, or a 2 - (5 - amino - 1,3,4 - thiadiazolyl) group; Y is sulphur or methylene and A is also lower alkylthio, benzylthio or halogen when X is oxygen; Z is hydrogen or lower alkyl; X is oxygen or sulphur;

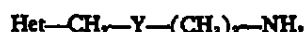
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- W is methylene, oxygen or sulphur; p and q are such that their sum is from 1 to 4 when W is oxygen or sulphur, or from 0 to 4 when W is methylene; Het' is a 5 or 6 membered heteroaryl group optionally substituted by lower alkyl, lower alkoxy, or may have a phenyl group or substituted phenyl group fused to it.
- 5 2. A compound according to claim 1 where Het' is a pyridyl, furyl, thienyl, thiazolyl, oxazolyl, isothiazolyl, imidazolyl, pyrazinyl, pyridazinyl or pyrimidyl group, optionally substituted by lower alkyl, lower alkoxy, or may have a phenyl group or substituted phenyl group fused to it. 5
- 10 3. A compound according to claim 2 where Het' is a 2-furyl, 2-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-thiazolyl, 2-imidazolyl, 2-pyrimidyl, 2-pyrazinyl or 4-pyridazyl group, optionally substituted with lower alkyl or lower alkoxy. 10
4. A compound according to claim 3 where Het' is a 2-furyl, 2-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-thiazolyl, 2-imidazolyl, 2-pyrimidyl, 2-pyrazinyl, or 4-pyridazyl group optionally substituted with lower alkyl.
- 15 5. A compound according to claim 4 where Het' is a 2-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl or 2-thiazolyl group. 15
6. A compound according to claim 5 where Het' is a 3-pyridyl group.
7. A compound according to any one of claims 1 to 6 where Z is hydrogen.
8. A compound according to any one of claims 1 to 7 where W is methylene and p and q are both 0.
- 20 9. A compound according to any one of claims 1 to 8 where X is oxygen. 20
10. A compound according to claim 9 where A is lower alkylthio, benzylthio or halogen.
11. A compound according to claim 10 where A is methylthio.
- 25 12. 5 - (4 - pyridylmethyl) - 2 - methylthio - 4 - pyrimidone. 25
13. 5 - (3 - pyridylmethyl) - 2 - methylthio - 4 - pyrimidone.
14. A compound as claimed in any one of claims 1 to 9 where A is:—
- Het—CH₂—Y—(CH₂)_p—NH—
- and acid addition salts thereof.
- 30 15. A compound according to claim 14 where Het is a 2-thiazolyl, 5-methyl-4-imidazolyl, 5-bromo-4-imidazolyl, 3-bromo-2-pyridyl, 3-chloro-2-pyridyl, 3-methoxy-2-pyridyl or 3-hydroxy-2-pyridyl group. 30
16. A compound according to any one of claims 14 or 15 where Y is sulphur.
- 35 17. 2 - [2 - (5 - Methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - (4 - pyridylmethyl) - 4 - pyrimidone. 35
18. 2 - [2 - (2 - Thiazolylmethylthio)ethylamino] - 5 - (4 - pyridylmethyl) - 4 - pyrimidone.
19. 2 - [2 - (3 - Bromo - 2 - pyridylmethylthio)ethylamino] - 5 - (4 - pyridylmethyl) - 4 - pyrimidone.
- 40 20. 2 - [2 - (5 - Methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - (2 - thienylmethyl) - 4 - pyrimidone. 40
21. 2 - [2 - (5 - Methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - (2 - pyridylmethyl) - 4 - pyrimidone.
22. 2 - [2 - (5 - Methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - (3 - pyridylmethyl) - 4 - pyrimidone.
- 45 23. 2 - [2 - (3 - Bromo - 2 - pyridylmethylthio)ethylamino] - 5 - (2 - pyridylmethyl) - 4 - pyrimidone. 45
24. 2 - [2 - (5 - Methyl - 4 - imidazolylmethylthio)ethylamino] - 5 - (2 - thiazolylmethyl) - 4 - pyrimidone.
- 50 25. 2 - [2 - (2 - Thiazolylmethylthio)ethylamino] - 5 - (3 - pyridylmethyl) - 4 - pyrimidone. 50
26. 2 - [2 - (3 - Bromo - 2 - pyridylmethylthio)ethylamino] - 5 - (3 - pyridylmethyl) - 4 - pyrimidone.
27. 2 - [4 - (3 - Methoxy - 2 - pyridyl)butylamino] - 5 - (3 - pyridylmethyl) - 4 - pyrimidone.
- 55 28. 2 - [4 - (3 - Amino - 2 - pyridyl)butylamino] - 5 - (3 - pyridylmethyl) - 4 - pyrimidone. 55
29. A pharmaceutically acceptable acid addition salt of a compound according to any one of claims 14 to 28.
- 60 30. A process for preparing a compound according to claim 1 where A is Het—CH₂Y(CH₂)_p—NH— and X is oxygen, which comprises reacting an isocytosine of formula:— 60

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where Z, W, p, q, and Het' are as defined in claim 1 and Q is a group which is displaceable by an amine, with an amine of formula:—



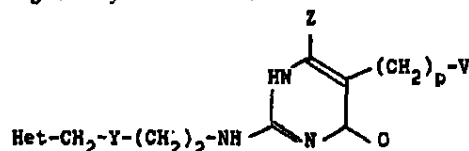
5 where Het and Y are as defined in claim 1, and thereafter optionally converting the compound so obtained into a salt. 5

31. A process according to claim 30 where Q is lower alkylthio, benzylthio or halogen.

32. A process according to claim 31 where Q is methylthio.

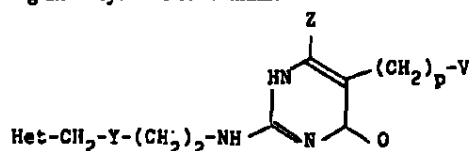
10 33. A process for preparing a compound as claimed in claim 14 where X is oxygen and W is sulphur which comprises either 10

a) reacting an isocytosine of formula:—



15 where Het, Y, Z and p are as defined in claim 1 and V is mercapto, with a compound of formula $\text{U}(\text{CH}_2)_q \text{Het}'$ where q and Het' are as defined in claim 1, and U is chloro or bromo, provided that q may be 0 only if U is an 'active' halogen; or 15

b) reacting an isocytosine of formula:—



20 where Het, Y, Z and p are as defined in claim 1 and V is chloro or bromo with a compound of formula $\text{U}(\text{CH}_2)_q \text{Het}'$ where q and Het' are as defined in claim 1 and U is mercapto, and thereafter optionally converting the compound so obtained into a salt. 20

34. A process for preparing a compound according to claim 14 where X is sulphur which comprises reacting a corresponding compound where X is oxygen with phosphorus pentasulphide and thereafter optionally converting the compound so obtained into a salt. 25

35. A compound according to claim 14 where X is oxygen whenever prepared by a process according to any one of claims 30 to 33. 25

36. A compound according to claim 14 where X is sulphur whenever prepared by a process according to claim 34.

30 37. A process for preparing a compound according to claim 14 substantially as hereinbefore illustrated in any one of Examples 1 to 5. 30

38. A process for preparing a compound according to claim 14 substantially as hereinbefore illustrated in any one of Examples 1 to 19, 22 and 23.

35 39. A compound according to claim 14 whenever prepared by a process according to any one of claims 30 to 33, 34, and 35. 35

40. A pharmaceutical composition comprising a compound according to any one of claims 14 to 29, 35, 36 or 39, or a pharmaceutically acceptable acid addition salt thereof and a pharmaceutically acceptable carrier.

40 41. A pharmaceutical composition substantially as hereinbefore illustrated in Example 20 or 21. 40

G. H. HARGREAVES,
Agent for the Applicants.