

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIRECCIÓN DE NUEVAS CREACIONES

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Abogada
LUZ CLEMENCIA DE PÁEZ
(Apoderado)

ASUNTO	Radicación	07109913
	Trámite	011
	Evento	378
	Actuación	519
	Oficio	
	Folios	015

10058

Patente de Invención	☒	Patente de Modelo de Utilidad	☐
Vía Nacional	☐		
Vía PCT (fase nacional)	☒	Cap. I	☒
		Cap. II	☐
No. Sol. Internacional	PCT/EP2006/061680		
Fecha de Presentación Internacional	19/04/2006		

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

1. Documentos estudiados:

- | | | |
|----------------------------------|------------------------------|------------|
| 1.1. <u>Descripción:</u> | Folios: 218 a 377 | 18/10/2007 |
| 1.2. <u>Reivindicaciones:</u> | Folios: 378 a 396 | 18/10/2007 |
| | Folios: 435 a 457 | 28/06/2011 |
| 1.3. <u>Rta del solicitante:</u> | Folios: 427 a 431. | |
| 1.4. <u>Prioridad:</u> | DE 102005019201.7 21/04/2005 | |

2. Análisis de la prioridad:

La prioridad de la presente solicitud corresponde al objeto reivindicado.

3. Objeto de la invención:

Título de la solicitud: Dihidrotienopirimidinas para el tratamiento de enfermedades inflamatorias.

El problema planteado en esta solicitud consiste en la necesidad de compuestos

para el tratamiento de enfermedades inflamatorias, trastornos gastrointestinales y de las vías respiratorias y enfermedad cancerígena.

Para resolver este problema técnico la solicitud en estudio proporciona compuestos derivados de dihidrotienopirimidinas como inhibidores de la enzima PDE-4.

El objeto de la presente Solicitud se relaciona con la Clasificación Internacional de Patentes (CIP): C07D 495/004.

4. De la solicitud de patente

4.1. Reivindicaciones (artículo 30 D 486)

De acuerdo con lo revelado en el capítulo reivindicatorio, y a pesar de las modificaciones realizadas, hay un número elevado de compuestos por lo que no se puede afirmar, con toda certeza, que tendrían la misma actividad de los compuestos mostrados en la tabla presentada en la respuesta del solicitante (Fls. 459 y 460).

5. **Análisis de la(s) oposición(es):** (artículo 43 D. 486)

No se presentaron oposiciones al objeto reivindicado.

6. **Determinación del estado de la técnica:**

La fecha que se ha tenido en cuenta para determinar el estado de la técnica es:

Fecha de presentación de la solicitud prioritaria 21/04/2005.

Teniendo en cuenta la fecha indicada, se buscaron documentos del estado de la técnica relacionados, con fecha de publicación anterior a esta.

Se encontraron como anterioridades que pueden afectar la patentabilidad del objeto de la presente solicitud:

Nº	Documento	Título	Fecha de Publicación
D1	WO 03/055890	Thienopyrimidine derivative compounds as inhibitors of prolypeptidase, inducers of apoptosis and cáncer treatment agents	10 de julio de 2003
D2	WO 03/059913	ROH-kinase inhibitors	24 de julio de 2003

D2 (Fls. 502 a 507): divulga derivados de tienopirimidina para el tratamiento del cáncer.

D3 (Fls. 508 a 512): divulga derivados de tienopirimidina como inhibidores de ROH-quinasa para enfermedades del corazón.

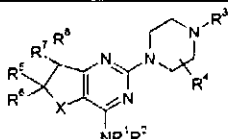
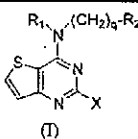
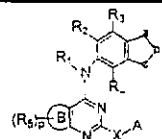
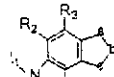
7. **Examen de patentabilidad (artículo 14 D486)**

7.1. Novedad (artículo 16 D486)

La reivindicación 1 de la presente solicitud se refiere a:

Compuestos de la fórmula 1 así como sus sales de adición de ácidos farmacológicamente tolerables con un ácido orgánico o inorgánico seleccionado del grupo que consiste de ácido succínico, ácido bromhídrico, ácido acético, ácido fumárico, ácido maleico, ácido metanosulfónico, ácido láctico, ácido fosfórico, ácido clorhídrico, ácido sulfúrico, ácido tartárico y ácido cítrico.

Comparación de las características técnicas esenciales, con las del estado de la técnica:

Características técnicas esenciales	D2	D3
	 (I)	
X= O, S, SO, SO2	S	O, N, S
Piperazina sustituida por R3 y R4	X= NR3R4 en donde R3 y R4 forman un anillo heterocíclico, saturado con nitrógenos como heteroátomos	A= heteroaril sustituido, que puede ser piperazina sustituida por fenilo
R5, R6, R7, R8= H, alquilo C1-4, alquenilo C1-4	H	H; R5= alquilo, alquenilo opcionalmente sustituido; p=0-3
R1= H, alquilo C1-6, alquenilo C2-6, alquinilo C2-6, arilo C6-10, heteroarilo C5-10- alquilenilo C1-6	H	H
R2= H o anillo C3-10 heterocíclico aromático o no aromático	Heterociclo aromático o no aromático C4-8, con heteroátomos O y S	

Las características esenciales del compuesto de la reivindicación 1 habían sido divulgadas previamente en D2, el cual enseña derivados de tienopirimidina que contiene el anillo de tienopirimidina (pág. 1, línea 22, Fl. 503), el grupo amino unido a la pirimidina (pág. 1, líneas 22, 25 Fl. 503, pág. 2, líneas 1 a 9, Fl. 504) y el anillo de piperazina (pág. 1, líneas 22, 24 Fl. 503, pág. 3, líneas 22 a 29, Fl. 505).

En consecuencia, la reivindicación 1 carece de novedad, según lo divulgado en el documento D2.

De igual manera, las características esenciales del compuesto de la reivindicación 1 habían sido divulgadas previamente en D3, el cual enseña compuestos derivados de tienopirimidina (pág. 96, Fl. 510) que tiene unido un anillo de piperazina (pág. 96, Fl. 510) y tiene un grupo amino unido al anillo de pirimidina (pág. 96, Fl. 510).

La(s) reivindicación(ones) dependiente(s) 2 a 23 no menciona(n) alguna característica que haga nuevo al compuesto de la reivindicación 1, por lo cual se considera que no es(son) nueva(s).

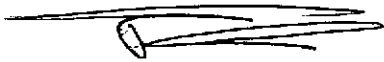
8. Conclusión:

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

Nº	Documento Nº	Reivindicaciones afectadas	Requisito que afecta
D1	WO 03/055890	1 a 23	Novedad
D2	WO 03/059913	1 a 23	Novedad

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 quinto del título primero de la Circular Única Nº 10 de 2001.



JOSÉ LUIS SALAZAR LÓPEZ
Director de Nuevas Creaciones (c)

El anterior requerimiento fue notificado por fijación en lista, de fecha 08 JUN. 2012

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Revisado por: Gloria Jacqueline Alfonso R. 

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PCT

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WO 03/055890 A1(51) International Patent Classification⁷: C07D 495/04,
A61K 31/505 // (C07D 495/04, 333:00, 239:00)

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20 December 2002 (20.12.2002)

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(30) Priority Data:
60/343,048 21 December 2001 (21.12.2001) US(71) Applicant (for all designated States except US): BAYER
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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, OM, PH, PL, PT, RO, RU, SC, SD, SE,
SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US,
UZ, VC, VN, YU, ZA, ZM, ZW.(84) Designated States (regional): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,
ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK,
TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ,
GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

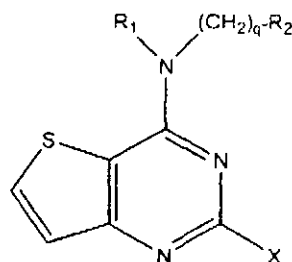
- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations
- of inventorship (Rule 4.17(iv)) for US only

Published:

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

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: THIENOPYRIMIDINE DERIVATIVE COMPOUNDS AS INHIBITORS OF PROLYLPEPTIDASE, INDUCERS OF APOPTOSIS AND CANCER TREATMENT AGENTS



(I)

(57) Abstract: The compounds of the invention are thienopyrimidine derivatives of the formula (I); wherein X is OR3 or NR3R4; q, R1, R2, R3, and R4 are described in the specification. These compounds are useful for the inhibiting the prolylpeptidase, inducing apoptosis and treating cancer.

**Thienopyrimidine Derivative Compounds as Inhibitors of
Prolylpeptidase, Inducers of Apoptosis and Cancer
Treatment Agents**

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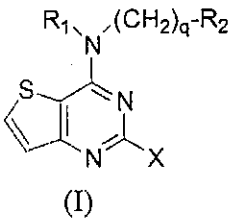
DESCRIPTION OF THE INVENTION

The present invention relates to:

- (1) thienopyrimidine derivative compounds or purified stereoisomers or stereoisomer mixtures of said compounds and salts or prodrug forms thereof;
- (2) pharmaceutical compositions comprising one or more of the compounds or purified stereoisomers or stereoisomer mixtures of the invention, or their salts or prodrugs forms thereof, with a pharmaceutically acceptable ingredient;
- (3) methods of preparing the thienopyrimidine derivative compounds of (1); and
- (4) methods for inhibiting prolylpeptidase, inducing apoptosis and treating cancer in mammals by administering an effective amount of (1) or (2) to a patient in need thereof.

Description of the Compounds

The compounds described as being part of the invention are thienopyrimidine derivative compounds which have the structural formula (I) defined below:



wherein,

X is OR₃ or NR₃R₄;

R₁ is selected from the group consisting of hydrogen and -(C₁-C₅) alkyl;

R₂ is selected from the group consisting of

- (a) -(C₆-C₈) cycloalkyl;
- (b) phenyl; and

(c) a saturated or fully unsaturated four to eight membered heterocyclic ring containing one to three heteroatoms independently selected from the group consisting of oxygen and sulfur;

wherein (a) - (c) are optionally substituted with one to three substituents selected from the group consisting of amino, cyano, halogen, hydroxy, nitro, -
(C₁-C₅) alkoxy, -(C₁-C₅) alkylamino, -(CH₂)_nC(=O)R₅, -(CH₂)_nC(=O)OR₅, -
(CH₂)_nC(=O)NR₆R₇ and -(C₁-C₅) linear or branched alkyl optionally substituted by halogen;

R₃ is selected from the group consisting of hydrogen and -(C₁-C₅) alkyl;

R₄ is selected from the group consisting of:

(a) -(CH₂)_m-A, where A is:

(a1) -(C₃-C₈) cycloalkyl, optionally substituted with cyano, -(C₁-C₅) alkoxy, amino, -(C₁-C₅) alkylamino, or hydroxy,

(a2) a saturated or fully unsaturated four to eight membered heterocyclic ring, containing one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said heterocyclic ring system contains at least one carbon atom and wherein said ring is optionally substituted with up to three substituents selected from the group consisting of amino, cyano, halogen, hydroxy, nitro, oxo, -(C₁-C₅) alkoxy, -(C₁-C₅) alkylamino, and -(C₁-C₅) linear or branched alkyl optionally substituted by halogen,

(a3) a fused bicyclo ring wherein one ring is a saturated or fully unsaturated five to six membered heterocyclic ring which contains one to three heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said heterocyclic ring contains at least one carbon atom, and the other ring is a saturated or fully unsaturated five to eight membered carbocycle,

(a4) (C₆-C₁₀)-aryl substituted with a saturated or fully unsaturated five to six membered heterocyclic ring, containing one to two

heteroatoms selected from the group consisting of nitrogen and oxygen,

(b) $-(CH_2)_p-O-A$, where A is:

(b1) hydrogen,

(b2) $-(C_1-C_5)$ linear or branched alkyl,

(b3) $-(C_3-C_8)$ cycloalkyl, optionally substituted with cyano, $-(C_1-C_5)$ alkoxy-, amino, $-(C_1-C_5)$ alkylamino, or hydroxy,

(b4) a saturated or fully unsaturated four to eight membered heterocyclic ring, containing one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said ring contains at least one carbon atom,

(b5) $-(C_6-C_{10})$ -aryl,

wherein (b4) and (b5) are optionally substituted with up to three substituents selected from the group consisting of amino, cyano, halogen, hydroxy, nitro, oxo, $-(C_1-C_5)$ alkoxy-, $-(C_1-C_5)$ alkylamino and $-(C_1-C_5)$ linear or branched alkyl optionally substituted by halogen;

or,

R_3 and R_4 form, together with the nitrogen to which they are attached, a saturated or fully unsaturated four to eight-membered heterocyclic ring, containing zero to four additional heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, and wherein said ring structure contains at least one carbon atom and wherein said ring is optionally substituted by one to two substituents selected from the group consisting of amino, cyano, hydroxy, $-(C_1-C_5)$ alkoxy-, $-(C_1-C_5)$ alkylamino and $-(C_1-C_5)$ linear or branched alkyl optionally substituted by halogen;

R_5 is:

(a) hydrogen,

- (b) $-(C_1-C_5)$ linear or branched alkyl optionally substituted with halogen,
or
- (c) $-(C_6-C_{10})$ -aryl optionally substituted with halogen;

5 R_6 and R_7 are independently selected from the group consisting of

- (a) hydrogen,
- (b) $-(C_1-C_5)$ linear or branched alkyl, and
- (c) phenyl,

10 wherein (b) to (c) are optionally substituted with one to two substituents selected from the group consisting of

- 1) amino,
- 2) cyano,
- 3) halogen,
- 4) hydroxy,
- 15 5) nitro,
- 6) oxo,
- 7) $-(C_1-C_5)$ alkoxy,
- 8) $-(C_1-C_5)$ alkylamino and
- 9) $-(C_1-C_5)$ linear or branched alkyl optionally substituted by
20 halogen,
- 10) a four to eight membered saturated or fully unsaturated heterocyclic ring containing one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said ring contains at least one carbon atom, and
- 25 11) a fused bicyclo ring wherein one ring is a saturated or fully unsaturated four to eight membered heterocyclic ring which contains one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said heterocyclic ring contains at least one carbon atom, wherein
30 said heterocyclic ring contains at least one carbon atom and the other ring is a saturated or fully unsaturated three to eight membered carbocycle;

m and p are independently an integer from 0 - 5;

n is an integer from 0 - 3;

q is an integer from 0 - 1; and

q + (m or p) equals an integer from 1 - 6;

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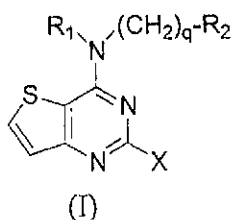
or a purified stereoisomer or stereoisomer mixture of said compound or a salt of said compound or purified stereoisomer or stereoisomer mixture thereof.

Pharmaceutically acceptable salts of these compounds as well as commonly used prodrugs
10 of these compounds are also within the scope of the invention.

Detailed Description

The preferred compounds of the invention have general formula (I) and are further defined
below. In the following description of these preferred compounds, the definitions for the
15 various groups and variables represent the preferred definitions when they differ from those
as broadly defined above, and are to be understood as independent of each other.

The preferred compounds of the invention have the formula (I)



20

wherein,

X is NR_3R_4 ;

R_1 is selected from the group consisting of hydrogen and $-(\text{C}_1-\text{C}_5)$ alkyl;

R_2 is selected from the group consisting of

25

(a) $-(\text{C}_6-\text{C}_8)$ cycloalkyl;

(b) phenyl; and

(c) a fully unsaturated five membered heterocyclic ring containing one heteroatom independently selected from the group consisting of oxygen and sulfur;

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D3

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(21) International Application Number: PCT/US03/00606

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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, OM, PH, PL, PT, RO, RU, SC, SD, SE,
SG, SK, SI, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ,
VC, VN, YU, ZA, ZM, ZW.

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(84) Designated States (*regional*): ARIPO patent (GH, GM,
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Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,
ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI,
SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN,
GQ, GW, ML, MR, NE, SN, TD, TG).

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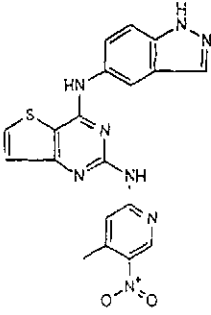
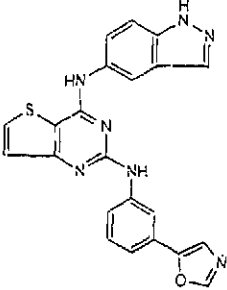
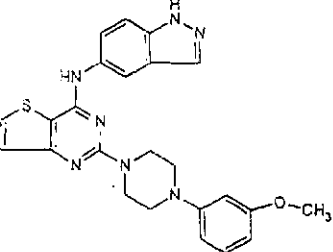
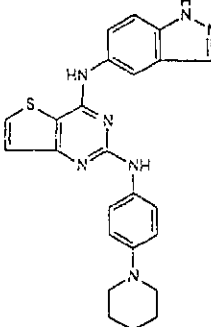
For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: ROH-KINASE INHIBITORS

(57) Abstract: Disclosed are compounds and derivatives thereof, their synthesis, and their use as Rho-kinase inhibitors. These compounds of the present invention are useful for inhibiting tumor growth, treating erectile dysfunction, and treating other indications mediated by Rho-kinase, e.g., coronary heart disease.

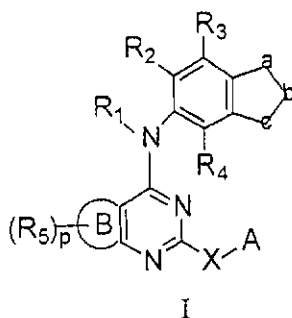


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113		418.10	418.44
114		425.11	425.47
115		457.17	457.56
116		441.17	441.56

WE CLAIM:

1. A compound of formula I



wherein X is $-(CH_2)_x-$, $-O-(CH_2)_n-$, $-S-(CH_2)_n-$, $-NR_7-CO-(CH_2)_n-$,

$-NR_7-SO_2-(CH_2)_n-$, $-NR_7-(CH_2)_n-$, or $-(O)C-NR_7-$,

each n is an integer which is independently 0, 1, 2 or 3,

x is 0-3

p is 0-3

a and c are each independently $-CR_5=$, $-N=$, or $-NR_6-$, wherein one of a or c is $-NR_6-$,

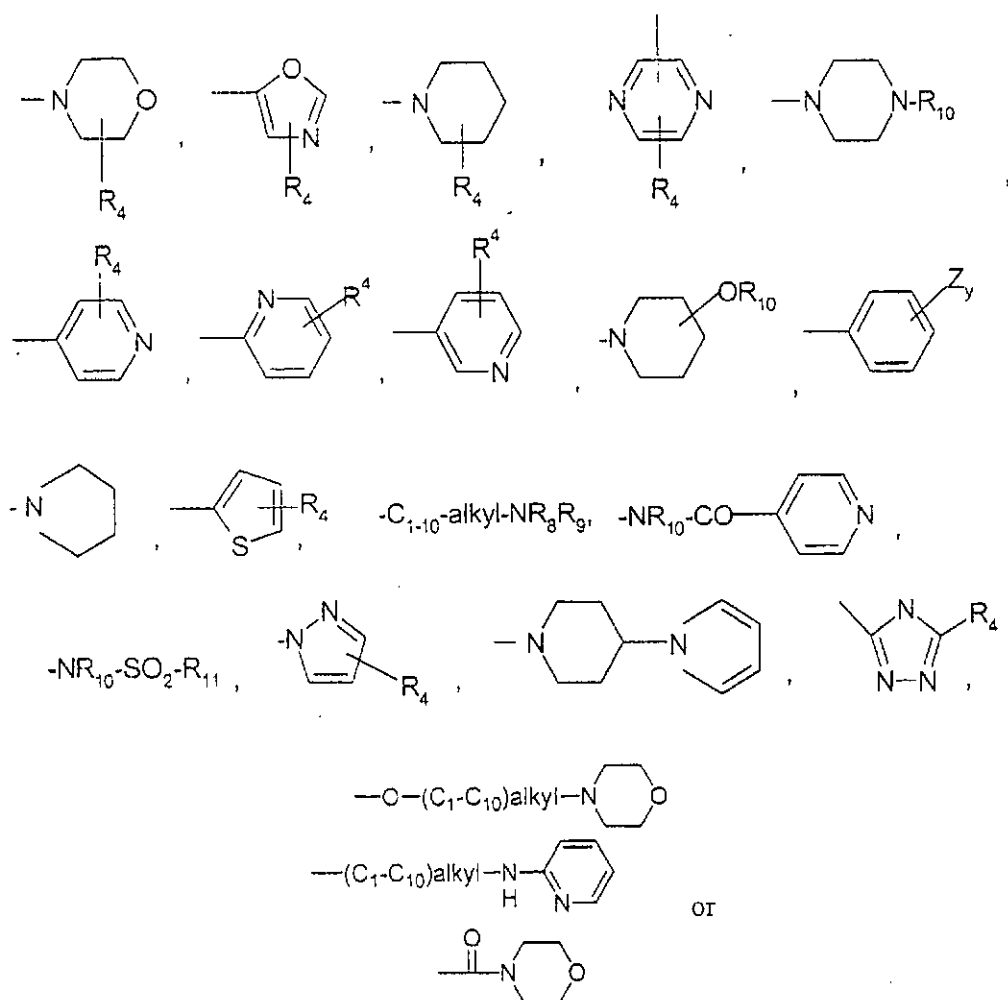
and b is $-CR_5=$ or $-N=$;

A is H, halogen, $-CO-OR_8$, $-CO-R_8$, cyano, $-OR_8$, $-NR_8R_9$, $-CO-NR_8R_9$, $-NR_8-CO-R_9$,

$-NR_8-CO-OR_9$, $-NR_8-SO_2-R_9$, $-SR_8$, $-SO_2-R_8$, $-SO_2-NR_8R_9$, $NR_8-CO-NHR_9$,

or

A is cyclohexyl; or C_{5-12} -aryl or C_{5-12} -heteroaryl each optionally independently substituted up to 3 times by (i) C_1-C_{10} alkyl or C_2-C_{10} -alkenyl, each optionally substituted with halogen up to perhalo; (ii) C_3-C_{10} cycloalkyl; (iii) aryl; (iv) heteroaryl; (v) halogen; (vi) $-CO-OR_8$; (vii) $-CO-R_8$; (viii) cyano; (ix) $-OR_8$; (x) $-NR_8R_{13}$; (xi) nitro; (xii) $-CO-NR_8R_9$; (xiii) $-C_{1-10}$ -alkyl- $-NR_8R_9$; (xiv) $-NR_8-CO-R_{12}$; (xv) $-NR_8-CO-OR_9$; (xvi) $-NR_8-SO_2-R_9$; (xvii) $-SR_8$; (xviii) $-SO_2-R_8$; (xix) $-SO_2-NR_8R_9$; (xx) $NR_8-CO-NHR_9$; or (xxi) aryl or heteroaryl substituted by halogen, C_{1-10} -alkyl, C_{1-10} -alkoxyphenyl, naphthyl, $-OR_{10}$,



wherein each Z independently is halogen, hydroxy, hydroxy-C₁₋₁₀-alkyl, -CN, -NO₂, C₁₋₁₀-alkoxycarbonyl, -NR₁₀-CO-R₁₁ or -NR₁₀-CO-OR₁₁;

Y is 0-3;

Ring B represents a fused 5- or 6-membered heterocyclic ring containing 1-2 O,N, and/or S atoms and 1-5 C atoms;

R₁, and R₆-R₁₁ are each independently H and C₁₋₆ alkyl;

R₂-R₅ are each independently (i) C₁₋₁₀ alkyl or C₂₋₁₀-alkenyl each optionally substituted by amino, N-lower alkylamino, N,N-dilower alkylamino, N-lower alkanoylamino, hydroxy, cyano, -COOR₁₀, -COR₁₄, -OCOR₁₄, -OR₁₀, C₅₋₁₀-

heteroaryl, C₅₋₁₀-heteroaryloxy, C₅₋₁₀-heteroaryl-C₁₋₁₀-alkoxy or halogen up to perhalo; (ii) C₃₋₁₀ cycloalkyl, in which 1-3 carbon atoms are optionally independently replaced by O, N or S; (iii) C₃₋₁₀-cycloalkenyl; (iv) partially unsaturated C₅₋₁₀-heterocyclyl; (v) aryl; (vi) heteroaryl; (vii) halogen; (viii) -CO-OR₁₀; (ix) -OCOR₁₀; (x) -OCO₂R₁₀; (xi) -CHO; (xii) cyano; (xiii) -OR₁₆; (xiv) -NR₁₀R₁₅; (xv) nitro; (xvi) -CO-NR₁₀R₁₁; (xvii) -NR₁₀-CO-R₁₂; (xviii) -NR₁₀-CO-OR₁₁; (xix) -NR₁₀-SO₂-R₁₂; (xx) -SR₁₆; (xxi) -SOR₁₆; (xxii) -SO₂-R₁₆; (xxiii) -SO₂-NR₁₀R₁₁; (xxiv) NR₁₀-CO-NHR₁₁; (xxv) amidino; (xxvi) guanidino; (xxvii) sulfo; (xxviii) -B(OH)₂; (xxix) -OCON(R₁₀)₂; or (xxx) -NR₁₀CON(R₁₀)₂;

R₁₂ is H, C₁₋₆-alkyl or C₅₋₁₀-aryl,

R₁₃ is H, C₁₋₆-alkyl or C₁₋₆-alkoxy,

R₁₄ is lower alkyl or phenyl;

R₁₅ is lower alkyl, halogen, amino, N-lower alkyl amino, N,N-dilower alkylamino, N-lower alkanoylamino, OH, CN, COOR₁₀, -COR₁₄ or -OCOR₁₄;

R₁₆ is hydrogen, C₁₋₆-alkyl optionally substituted by halogen, up to perhalo, or C₅₋₁₀-heteroaryl;

or a pharmaceutically acceptable salt thereof,

with the provisos that A is not hydrogen when x is 0;

-X-A is not CH₃ when B represents a thieno[3,2b]fused ring, and b and c are -CR₅=, and a is NH;

and A is not phenyl when X is NH, B forms an imidazo fused ring, and -a-b-c- is -CR₅=N-NR₆- or -NR₆=N-CR₅-.

2. The compound according to claim 1, wherein A is 2- or 3-furyl, 2- or 3-thienyl, 2- or 4-triazinyl, 1-, 2- or 3-pyrrolyl, 1-, 2-, 4- or 5-imidazolyl, 1-, 3-, 4- or 5-pyrazolyl, 2-, 4- or 5-oxazolyl, 3-, 4- or 5-isoxazolyl, 2-, 4- or 5-thiazolyl, 3-, 4- or 5-isothiazolyl, 2-, 3- or 4-pyridyl, 2-, 4-, 5- or 6-pyrimidinyl, 1,2,3-triazol-1-, -4- or 5-