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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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Señora Jefe de la
DIVISION DE NUEVAS CREACIONES
Superintendencia de Industria y Comercio
E. S. D.

311

Trámite : 002 Evento : 001 Actuación : 444

Referencia : Expediente No. 04.020.069
Asunto : Solicitud de patente para: "NUEVAS
DIHIDRO-PTERIDINONAS".
Solicitante : BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG
Fecha de
solicitud : 4 de Marzo de 2004

1. Yo, Emilio FERRERO, obrando como apoderado del solicitante en el asunto antes identificado, me refiero al Oficio No. 10420 notificado por fijación en lista del 31 de Agosto de 2007.

2. Mediante el Oficio No. 10420 se puso en conocimiento del solicitante el informe del examen de fondo que contiene las observaciones hechas por su Despacho sobre la presente solicitud de patente. Con el memorial radicado el 23 de Noviembre de 2007 solicité prórroga para dar respuesta al Oficio No. 10420. Atiendo a las observaciones de la manera siguiente:

3. Claridad de la solicitud:

En forma resumida su Despacho afirma lo siguiente:

3.1 El título de la solicitud no debería incluir el término "y su utilización como medicamentos". Se solicita realizar la corrección respectiva.

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3.2 CAPÍTULO REIVINDICATORIO:

Con relación al capítulo reivindicatorio su Despacho en forma resumida cita lo siguiente:

"Se le requiere al interesado definir o especificar las sustituciones y los números de carbono a los que hace referencia".

"Para las reivindicaciones 1 a 3 se encuentra el término "eventualmente sustituidos, pero no especifican los sustituyentes que los conforman. Se solicita hacer la aclaración o corrección al respecto".

"Para las reivindicaciones 1 a 4 se encuentra el término "eventualmente en forma de tautómeros, sus racematos, sus enantiómeros, sus diastereoisómeros y sus mezclas, así como eventualmente de sus sales por adición de ácidos farmacológicamente inocuas" los cuales deben ser eliminados o sustentados ya que los grupos estructurales que lo conforman no pueden ser claramente identificados"

"En la reivindicación 2 la cual es dependiente de la reivindicación 1, para los sustituyentes R₃ y R₄ aparecen un nuevo radical definido como (H) por lo cual se está ampliando la característica reivindicada en 1. Se solicita realizar la corrección o aclaración respectiva".

"Para la reivindicación 9 se encuentra el término "o sus sales fisiológicamente compatibles". El cual debe ser eliminado o sustentado"

"Para las reivindicaciones 5 y 6 la caracterización realizada para el compuesto no es la correcta ya que se está caracterizando por su uso"

"La reivindicación 7 no es patentable ya que se refiere a un método terapéutico".

"La reivindicación 8 referida al uso no es patentable".

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4. Evaluación de la novedad y del nivel inventivo:

4.1 **Novedad:**

El examinador afirma que D1 (EP 0429149) afecta la novedad de las reivindicaciones 1-6,9 ya que D1 enseña pteridinonas tricíclicas con actividad caracterizada por ser útiles en el tratamiento de enfermedades cardiovasculares y desórdenes cerebrovasculares. De acuerdo al análisis del examinador, los compuestos de la anterioridad D1 son iguales a los compuestos de la presente solicitud, tras hacer los reemplazos respectivos de los sustituyentes.

4.2 **Nivel inventivo:**

Con relación al requisito de nivel inventivo su Despacho enuncia que el documento D2 (WO 0119825) afecta el nivel inventivo de las reivindicaciones 10 a 11 de la presente invención.

Su Despacho afirma que el método de preparación de la reivindicación 10 obtiene un compuesto que se divulgaba previamente en D2, además dicho método no está conformado por pasos sorprendentes para el experto en la materia, ni tampoco ofrece ventajas adicionales con respecto al procedimiento descrito en la anterioridad.

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Con respecto a los intermediarios de síntesis de la reivindicación 11 su Despacho enuncia que no son sorprendentes para el Experto en la Materia debido a lo divulgado por D2.

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Así mismo cita su Despacho que D3 (Química Orgánica, Grupo editorial Iberoamérica, Sección 13.3) afecta el nivel inventivo del procedimiento de la reivindicación 12 de la presente solicitud ya que de acuerdo al análisis de su Despacho, dicho procedimiento no está conformado por pasos sorprendentes para el experto en la materia.

5. Modificación a una solicitud en trámite:

5.1 Con el objeto de atender las anteriores observaciones y de conformidad con lo establecido en el artículo 34 de la Decisión 486, que permite al solicitante en cualquier momento del trámite efectuar modificaciones, sin ampliar el objeto de la invención inicialmente solicitado, me permito presentar un nuevo capítulo reivindicatorio, que comprende 5 reivindicaciones.

5.2 Se cancelaron las reivindicaciones originales 5 a 8 del pliego reivindicatorio.

5.3 Con respecto a las reivindicaciones de proceso 10 a 12, mi representada aunque no está de acuerdo con su Despacho con respecto a que dichas reivindicaciones no poseen nivel inventivo, pero con el fin de agilizar el

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trámite de esta solicitud, elimina las mismas del nuevo pliego reivindicatorio.

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5.4 Ahora bien, con respecto a la terminología empleada en las reivindicaciones 1 a 3, mi representada aclara lo siguiente:

En el nuevo pliego reivindicatorio, específicamente en la reivindicación 1 se introdujo la definición de "arilo", "heteroarilo", "cicloalquilo", "heterocicloalquilo" y "opcionalmente sustituido".

Respetuosamente se informa a su Despacho que dichas definiciones son también válidas para las posteriores reivindicaciones ya que éstas se refieren a la reivindicación 1, en lo que concierne a la definición de los compuestos de formula general (I).

Dichas definiciones se encuentran debidamente sustentadas en la memoria descriptiva originalmente presentada.

El término un "heterocicloalquilo opcionalmente sustituido" se retiró de la reivindicación 1.

5.5 Clarificación a otras expresiones empleadas en las reivindicaciones 1 a 4:

Mi representada confirma que "los tautómeros, racematos, enantiómeros, diastereoisómeros y sus mezclas" corresponden a compuestos a ser protegidos. Un tautómero es por

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definición uno de dos o más isómeros estructurales que existen en equilibrio y son fácilmente convertidos de una forma isomérica a otra.

Diastereoisómeros son por definición estereoisómeros que no son enantiómeros. Un enantiómero es por definición uno de un par de isómeros ópticos.

Un racemato es una mezcla de enantiómeros. Los compuestos de acuerdo con la presente invención tienen al menos un centro óptico, y por lo tanto, pueden estar presentes en la forma de sus isómeros, como mezcla o en forma aislada. Por ejemplo, los compuestos reivindicados específicamente en las reivindicaciones 5 o 6 se reclaman en la forma de uno de los enantiómeros (la forma Z). Además, como puede observarse de la tabla de los compuestos ilustrados, la configuración de R^3 o R^4 se da para todos los compuestos ilustrados.

Por lo anteriormente expuesto, mi representada enuncia que estas expresiones son claras.

No obstante lo anterior, mi representada esta de acuerdo en cancelar la expresión " y sus mezclas".

Con relación a la expresión "sales de adición ácida farmacológicamente aceptable", mi representada aclara que la misma es clara per se y porque efectivamente hace parte de la materia reivindicada en la presente solicitud de patente. Es más, algunos ejemplos de los compuestos son

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sales tales como por ejemplo, el ejemplo 63 (Por favor ver la descripción de su síntesis, página 25). Lo mismo, también aplica para los ejemplos 218, 65 y 171. Por lo tanto, estas expresiones se han dejado en el nuevo pliego reivindicatorio.

5.6 Clarificación de la reivindicación 2 con respecto al ámbito de las definiciones dadas para los sustituyentes R^3 y R^4 :

Respetuosamente, mi representada enuncia que no existe ninguna extensión en el ámbito de la definición de R^3 y R^4 en la reivindicación 2 cuando se compara con la reivindicación 1.

5.7 Clarificación de la expresión "sales fisiológicamente aceptables" empleada en la anterior reivindicación 9 (que ahora corresponde a la reivindicación 5):

Mi representada menciona que de conformidad con las anteriores explicaciones para las reivindicaciones 1 a 4, dicha expresión es clara y por lo tanto, se mantiene en la reivindicación 5.

5.8 Corrección voluntaria en la definición de R^5 en la reivindicación 2.

Mi representada advierte de un error con respecto a la definición de R^5 en la reivindicación 2. Para subsanar

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dicho error, se eliminó la expresión "y cicloalqueno C_3-C_6 " de la definición de R^5 en la reivindicación 2.

Así mismo, teniendo en cuenta la observación de su Despacho, se modificó el título de la siguiente forma:
"NUEVAS DIHIDRO-PTERIDINONAS".

Con las anteriores explicaciones y modificaciones se concluye que el nuevo pliego reivindicatorio cumple con el requisito de claridad establecido en artículo 30 de la Decisión 486.

6. Argumentos en favor de la patentabilidad de la presente invención.

Su Despacho establece que el documento D1 (EP 042 9149) afecta la novedad de las reivindicaciones relacionadas con el compuesto y la composición farmacéutica de la presente invención.

En primer lugar, respetuosamente se informa a su Despacho que en el Informe de la Búsqueda Internacional, el documento EP 0429 149 se calificó como categoría A.

Esto significa que dicho documento define el estado del arte general, el cual se considera que no tiene ninguna relevancia particular con relación a la invención estudiada. En otras palabras, el documento D1 fue calificado como un documento que no afecta la novedad ni el nivel inventivo de la presente solicitud.

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D1 no revela ningún compuesto que esté cubierto por las reivindicaciones de la presente solicitud. Sin embargo, solamente con la finalidad de que se agilice el trámite de la solicitud Colombiana, mi representada eliminó la definición cíclica para R^3R^5 o R^4R^5 en las actuales reivindicaciones para remover la superposición con la definición de ABD en D1.

7. Concesión de una solicitud foránea:

Por último, aunque compartimos la opinión de su Despacho, en cuanto a que la concesión de una solicitud de patente en otros países, equivalente a la solicitud Colombiana, no obliga a su Despacho a otorgar el privilegio de patente para la misma invención, sí constituye un antecedente favorable para el estudio de patentabilidad que respetuosamente solicitamos tener en cuenta. Por lo tanto informamos a su Despacho que la presente invención fue otorgada por la Oficina de Patentes Europea con número de patente: EP 1 427730, sin ninguna limitación en las reivindicaciones aparte de la clarificación en la terminología de la reivindicación 1. (Anexo copia de la carátula y reivindicaciones de dicha patente para su información).

Así mismo, se informa a su Despacho que la invención en estudio también fue otorgada en la Oficina de Patentes Estadounidense con número de patente US 6,806,272 sin ninguna limitación a los compuestos reclamados.

8. Conclusión:

Teniendo en cuenta los argumentos arriba citados así como el nuevo capítulo reivindicatorio que se presenta con este escrito, se concluye que la presente invención además de ser novedosa también cumple con el requisito de altura inventiva.

Puesto que se han atendido a cabalidad las observaciones hechas por su Despacho sobre la presente solicitud de patente, respetuosamente solicito se continúe con su tramitación.

9. ACLARACION.

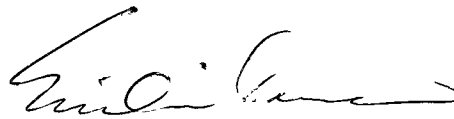
Respetuosamente ponemos de presente al Despacho que por un error mecanográfico involuntario se indicó como solicitante en el petitorio a la sociedad Boehringer Ingelheim Pharma & CO. KG, debiendo ser **Boehringer Ingelheim Pharma GMBH & CO. KG**, razón por la cual solicito que el título de patente se otorgue a esta última, de acuerdo con la legitimación que le da el documento de cesión y de poder que obra en el expediente.

10. Anexos:

- Nuevo pliego reivindicatorio conformado por 5 reivindicaciones.
- Formulario para modificaciones.

- Recibo por concepto de modificaciones en solicitud pendiente.
- Carátula y reivindicaciones de la patente EP 1427730 y US 6,806,272.

Bogotá,
Señora Jefe,



EMILIO FERRERO

T.P.A. No. 31.929

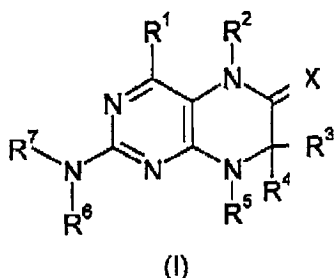
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No. M-2008-115927\MGT

FORMULARIO UNICO DE CORRECCIONES Y MODIFICACIONES

1	SOLICITUD DE: ☐ Corrección de Error Material ☒ Modificación a una solicitud	
2 SOLICITANTE	Nombre: BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG Sociedad constituida y existente bajo las leyes de Alemania. Dirección: Binger Straße 173, 55216 Ingelheim am Rhein, Alemania Domicilio: Ingelheim am Rhein, Alemania Teléfono: 546 09 70 Fax: 249 40 70 E-mail: clientes@cavelier.com	IDENTIFICACION C.C. ☐ NIT ☐ C.E. ☐ Otro ☐ Número: _____
3 REPRESENTANTE O APODERADO	Nombre: Emilio FERRERO Dirección: Carrera 4ª No. 72-35 Teléfono: 347 36 11 Fax: 217 92 11 E-mail: cavelier@cavelier.com	IDENTIFICACION C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Número: <u>438.019 TP 31.929</u>
4	Número de expediente: <u>04.020.069</u>	
5	Descripción de la corrección o modificación solicitada: Presento nuevo capítulo reivindicatorio compuesto por 5 reivindicaciones, nuevo título como sigue: "Nuevas dihidro-pteridinonas" para dar respuesta a las observaciones del examen de fondo. Así mismo se advierte a su Despacho que el nombre correcto de la solicitante es: BOEHRINGER INGELHEIM PHARMA GMBH & CO.KG.	
6	Comprobante de pago No. <u>07-105,453</u> Fecha: <u>28 de diciembre de 2007</u> <u>08-204</u> <u>2 de enero de 2008</u>	
7	Anexos ☒ Comprobante de pago de la tasa por valor de \$103.000.00 ☐ Poderes, si fuere el caso ☐ Documento que acredita la existencia y representación legal de las partes, cuando sean personas jurídicas.	
8	NOMBRE: EMILIO FERRERO FIRMA:  C.C. 438.019 de Usaquén T.P.A. 31.929	

REIVINDICACIONES

- 1) Compuestos de la fórmula general (I),



En donde

R^1 denota un grupo seleccionado entre hidrógeno, NH_2 , XH , halógeno y un grupo alquilo- C_1-C_3 opcionalmente sustituido por uno más átomos de halógeno,

R^2 denota un grupo seleccionado entre hidrógeno, CHO , XH , $-X$ -alquilo- C_1-C_2 y opcionalmente un grupo alquilo- C_1-C_3 sustituido,

R^3 , R^4 que pueden ser idénticos o diferentes denotan un grupo seleccionado de entre alquilo- C_1-C_{10} opcionalmente sustituido, alqueno- C_2-C_{10} , alquino- C_2-C_{10} , arilo, heteroarilo, cicloalquilo- C_3-C_8 , X -arilo, $-X$ -heteroarilo, $-X$ -cicloalquilo, NR^8 -arilo, $-NR^8$ -heteroarilo, $-NR^8$ -cicloalquilo, $-NR^8$ -heterocicloalquilo, heterocicloalquilo- C_3-C_8 , $-X$ -heterocicloalquilo, o un grupo seleccionado de entre hidrógeno, halógeno, $COXR^8$, $CON(R^8)_2$, COR^8 y XR^8 , o

R^3 y R^4 juntos denotan un puente alquilo de 2 a 5 miembros que puede contener 1 a 2 heteroátomos.

R^5 denota hidrógeno o un grupo seleccionado entre alquilo- C_1-C_{10} opcionalmente sustituido, alqueno- C_2-C_{10} , alquino- C_2-C_{10} , arilo, heteroarilo, y cicloalquilo- C_3-C_6 ,

R^6 denota arilo o heteroarilo opcionalmente sustituido,

R^7 denota hidrógeno o $-CO-X$ -alquilo- C_1-C_4 , y

X en cada caso independientemente de otro denota O o S,

R^8 en cada caso independientemente de otro denota hidrógeno o un grupo seleccionado de entre alquilo- C_1-C_4 , opcionalmente sustituido, alqueno- C_2-C_4 , alquino- C_2-C_4 , y fenilo,

y en donde, a menos que se establezca otra cosa,

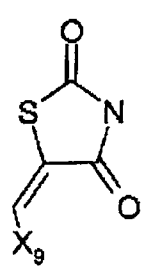
los sustituyentes opcionales de los grupos alquilo mencionados anteriormente se seleccionan del grupo que consiste de flúor, cloro, bromo, yodo, $-CN$, $-OCOCH_3$, arilo, heteroarilo, heterocicloalquilo saturados o insaturados, grupos amina, y sistemas de anillo bicíclicos saturados o insaturados,

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los sustituyentes opcionales de los grupos alquenoilo mencionados anteriormente se seleccionan del grupo que consiste de flúor, cloro, bromo, y yodo,

los sustituyentes opcionales de los grupos alquinoilo mencionados anteriormente se seleccionan del grupo que consiste de flúor, cloro, bromo y yodo,

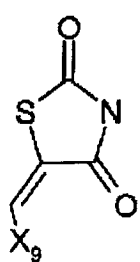
los sustituyentes opcionales de los grupos arilo mencionados anteriormente se seleccionan del grupo que consiste de -OH, -NO₂, -CN, -OCHF₂, -OCF₃, -NH₂, halógeno, alquilo-C₁-C₁₀, alquilo-O-C₁-C₃, -N-metil-tetrahidro-oxazinilo, -COOH, -COO-alquilo-C₁-C₄, -CONH₂, -CONH-alquilo-C₁-C₁₀, CONH-cicloalquilo-C₃-C₆, -CONH-heterocicloalquilo, -CONH-heteroarilo, -CONH-arilo, -CONMealquilo-C₁-C₃, benzimidazol y un grupo de la fórmula



los sustituyentes opcionales de los grupos heteroarilo mencionados anteriormente se seleccionan del grupo que consiste de -OH, -NO₂, -CN, -OCHF₂, -OCF₃, -NH₂, halógeno, alquilo-C₁-C₁₀, alquilo-O-C₁-C₃, -metil-N-tetrahidro-oxazinilo, -COOH, -COO-alquilo-C₁-C₄, fenilo, heteroarilo, -CONH-alquilo-C₁-C₁₀, -CONH-cicloalquilo-C₃-C₆, -CONH-

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heteroarilo, -CONH-arilo, -CONMealquilo-C₁-C₃, benzimidazol y un grupo de la fórmula



Los sustituyentes opcionales de los grupos cicloalquilo mencionados anteriormente se seleccionan del grupo que consiste de =O, o los grupos cicloalquilo se pueden hibridar a un anillo de benceno,

y en donde, a menos que se establezca otra cosa,

el término arilo denota un sistema de anillo aromático con 6 a 14 átomos de carbono,

el término heteroarilo denota un sistema de anillo mono o bicíclico de 5-10 miembros en donde hasta tres átomos C se pueden reemplazar por uno o más heteroátomos seleccionados de entre oxígeno, nitrógeno o azufre,

el término cicloalquilo denota grupos cicloalquilo saturados o insaturados con 3 – 8 átomos de carbono,

el término heterocicloalquilo denota heterociclos saturados o insaturados de 5, 6 o 7 miembros, que pueden contener nitrógeno, oxígeno o azufre como heteroátomos,

mientras cada uno de los heterociclos mencionados anteriormente también puede opcionalmente ser hibridado en un anillo de benceno,

opcionalmente en la forma de los tautómeros, los racematos, los enantiómeros, los diastereoisómeros, y opcionalmente las sales de adición ácida farmacológicamente aceptables de estos.

2) Compuestos de acuerdo con la reivindicación 1, en donde

X y R⁶ tienen el significado indicado, y

R¹ denota hidrógeno,

R² denota un grupo seleccionado entre un grupo CHO, OH, y CH₃,

R³, R⁴ que pueden ser idénticos o diferentes denotan un grupo seleccionado de entre alquilo-C₁-C₆ opcionalmente sustituido, alquenilo-C₂-C₆, alquinilo-C₂-C₆, cicloalquilo-C₃-C₇, o

R³ y R⁴ juntos denotan un puente de alquilo C₂-C₅,

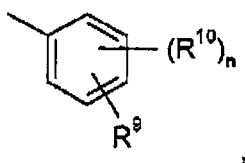
R⁵ denota un grupo seleccionado de entre alquilo-C₁-C₁₀ opcionalmente sustituido alquenilo C₂-C₁₀, alquinilo C₂-C₁₀, y cicloalquilo C₃-C₆, y

R^7 denota hidrógeno,

opcionalmente en la forma de los tautómeros, los racematos, los enantiómeros, los diastereoisómeros, y opcionalmente las sales de adición ácida farmacológicamente aceptables de estos.

3) Compuestos de acuerdo con la reivindicación 1 o 2, en donde R^1 - R^5 , R^7 , R^8 y X tienen el significado indicado y

R^6 denota un grupo de la fórmula general



En donde

n denota 1, 2, 3, o 4,

R^9 denota un grupo seleccionado entre alquilo- C_1 - C_6 opcionalmente sustituido, alqueno- C_2 - C_6 , alquino- C_2 - C_6 , -CONH-alqueno- C_1 - C_{10} , arilo-O-, heteroarilo-O-, cicloalquilo-O-, heterocicloalquilo-O-, arilo, heteroarilo, cicloalquilo, heterocicloalquilo o

un grupo seleccionado entre -O-alquilo- C_1 - C_6 - Q^1 , -CONR⁸-alquilo- C_1 - C_{10} - Q^1 , -CONR⁸-alqueno- C_2 - C_{10} - Q^1 , -CONR⁸- Q^2 , halógeno, OH, -SO₂R⁸, -

$\text{SO}_2\text{N}(\text{R}^8)_2$, COR^8 , COOR^8 , $-\text{N}(\text{R}^8)_2$, NHCOR^8 , CONR^8O -alquilo- $\text{C}_1\text{-C}_{10}$ - Q^1 y CONR^8OQ^2 ,

Q^1 denota hidrógeno, $-\text{NHCOR}^8$, o un grupo seleccionado entre -arilo-NH- opcionalmente sustituido, heteroarilo-NH-, arilo, heteroarilo, cicloalquilo- $\text{C}_3\text{-C}_8$, y grupo heterocicloalquilo,

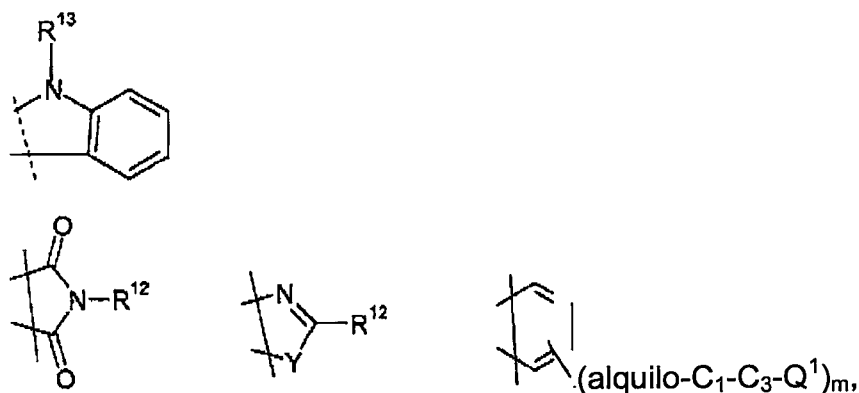
Q^2 denota hidrógeno o un grupo seleccionado entre un arilo opcionalmente sustituido, heteroarilo y grupo cicloalquilo- $\text{C}_3\text{-C}_8$,

R^{10} que puede ser idéntico o diferente denota un grupo seleccionado entre alquilo- $\text{C}_1\text{-C}_6$ opcionalmente sustituido, alquenilo- $\text{C}_2\text{-C}_6$, y alquinilo- $\text{C}_2\text{-C}_6$, $-\text{O}$ -alquilo- $\text{C}_1\text{-C}_6$, $-\text{O}$ -alquenilo- $\text{C}_2\text{-C}_6$, $-\text{O}$ -alquinilo- $\text{C}_2\text{-C}_6$, heterocicloalquilo- $\text{C}_3\text{-C}_6$, y cicloalquilo- $\text{C}_3\text{-C}_6$, o

un grupo seleccionado entre hidrógeno, $-\text{CONH}_2$ -, $-\text{COOR}^8$, $\text{OCON}(\text{R}^8)_2$ -, $-\text{N}(\text{R}^8)_2$, NHCOR^8 , $-\text{NHCON}(\text{R}^8)_2$ -, $-\text{NO}_2$ y halógeno,

o

grupos adyacentes R^9 y R^{10} denotan un puente de fórmula general



Y denota O, S, o NR^{11} ,

m denota 0, 1 o 2

R^{11} denota hidrógeno o alquilo- $\text{C}_1\text{-C}_2$, y

R^{12} denota hidrógeno o un grupo seleccionado entre fenilo opcionalmente sustituido, piridilo, pirazinilo, pirimidinilo, piridazinilo, fenil-alquilo- $\text{C}_1\text{-C}_3$, piridil-alquilo- $\text{C}_1\text{-C}_3$, pirazinil-alquilo- $\text{C}_1\text{-C}_3$, pirimidinil-alquilo- $\text{C}_1\text{-C}_3$ y piridazinil-alquilo- $\text{C}_1\text{-C}_3$,

R^{13} denota alquilo $\text{C}_1\text{-C}_6$

opcionalmente en la forma de los tautómeros, los racematos, los enantiómeros, los diastereoisómeros, y opcionalmente las sales de adición ácida farmacológicamente aceptables de estos.

4) Compuestos de acuerdo con una de las reivindicaciones 1 a 3, en donde $\text{R}^3\text{-R}^6$, R^8 y X tienen el significado indicado, y

R^1 denota hidrógeno,

R^2 denota CH_3 , y

R^7 denota hidrógeno,

331 338

opcionalmente en la forma de los tautómeros, los racematos, los enantiómeros, los diastereoisómeros, y opcionalmente las sales de adición ácida farmacológicamente aceptable de estos.

- 5) Preparaciones farmacéuticas, que contienen como sustancia activa uno o más compuestos de la fórmula general (I) de acuerdo con una de las reivindicaciones 1 a 4 o las sales fisiológicamente aceptables de este, combinadas opcionalmente con excipientes y/o portadores convencionales.

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(54) NEUE DIHYDROPTERIDINONE, VERFAHREN ZU DEREN HERSTELLUNG UND DEREN VERWENDUNG ALS ARZNEIMITTEL

NOVEL DIHYDROPTERIDINONES, METHOD FOR PRODUCING THE SAME AND THE USE
THEREOF AS MEDICAMENTS

NOUVELLES DIHYDROPTERIDINONES, PROCEDES POUR LES PRODUIRE ET LEUR
UTILISATION EN TANT QUE MEDICAMENTS

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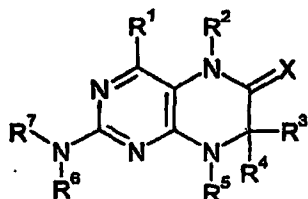
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Beschreibung

[0001] Die vorliegende Erfindung betrifft neue Dihydropteridinone der allgemeinen Formel (I)

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wobei die Reste X, R¹, R², R³, R⁴, R⁵, R⁶ und R⁷ die in den Ansprüchen und der Beschreibung genannten Bedeutungen haben, deren Isomere,

Verfahren zur Herstellung dieser Dihydropteridinone sowie deren Verwendung als Arzneimittel.

Hintergrund der Erfindung

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[0002] Pteridinon-Derivate sind als Wirkstoffe mit antiproliferativer Wirkung aus dem Stand der Technik bekannt. WO 01/019825 beschreibt die Verwendung von Pteridinonderivaten zur Behandlung von Tumor- und Viruserkrankungen. Die Resistenz vieler Tumorarten erfordert die Entwicklung neuer Arzneimittel zur Tumorbekämpfung.

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Es ist die Aufgabe der vorliegenden Erfindung neue Verbindungen mit antientzündlicher und antiproliferativer Wirkung bereitzustellen.

Detaillierte Beschreibung der Erfindung

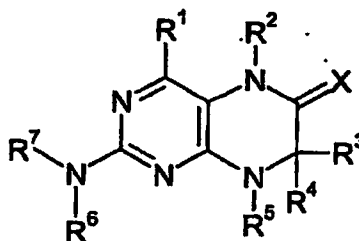
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[0003] Überraschenderweise wurde gefunden, daß Verbindungen der allgemeinen Formel (I), worin die Reste X und R¹ bis R⁷ die nachstehend genannten Bedeutungen haben, als Inhibitoren spezifischer Zellzyklusinasen wirken. Somit können die erfindungsgemäßen Verbindungen beispielsweise zur Behandlung von Erkrankungen, die mit der Aktivität spezifischer Zellzyklusinasen in Zusammenhang stehen und durch exzessive oder anomale Zellproliferation charakterisiert sind, verwendet werden.

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[0004] Die vorliegende Erfindung betrifft daher Verbindungen der allgemeinen Formel (I)

40



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(I)

worin

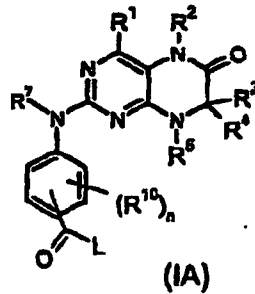
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R¹ ein Rest ausgewählt aus der Gruppe bestehend aus Wasserstoff, NH₂, XH, Halogen und einer gegebenenfalls durch ein oder mehrere Halogenatome substituierten C₁-C₃-Alkyl- Gruppe,

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R² ein Rest ausgewählt aus der Gruppe bestehend aus Wasserstoff, CHO, XH, -X-C₁-C₂-Alkyl und einer gegebenenfalls substituierten C₁-C₃-Alkyl- Gruppe,

R³, R⁴ gleich oder verschieden, ein Rest ausgewählt aus der Gruppe bestehend aus gegebenenfalls substituiertem C₁-C₁₀-Alkyl, C₂-C₁₀-Alkenyl, C₂-C₁₀-Alkynyl, Aryl, Heteroaryl, C₃-C₈-Cycloalkyl, C₃-C₈-Heterocycloalkyl, -X-Aryl,

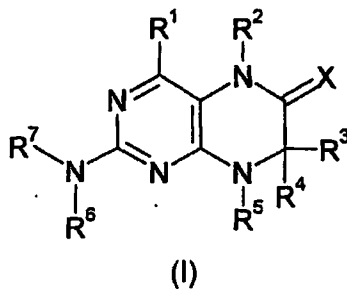
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worin

R¹ bis R⁵, R⁷, R¹⁰ und n die in den Ansprüchen 1 bis 4 angegebene Bedeutung aufweisen, und L eine Abgangsgruppe bedeutet, mit einem primären oder sekundären Amin zu dem entsprechenden Amid oder mit einem Alkohol zu dem entsprechenden Ester umgesetzt wird.

Claims

1. Compounds of general formula (I),



wherein

R¹ denotes a group selected from among hydrogen, NH₂, XH, halogen and a C₁-C₃-alkyl group optionally substituted by one or more halogen atoms,

R² denotes a group selected from among hydrogen, CHO, XH, -X-C₁-C₂-alkyl and an optionally substituted C₁-C₃-alkyl group,

R³, R⁴ which may be identical or different denote a group selected from among optionally substituted C₁-C₁₀-alkyl, C₂-C₁₀-alkenyl, C₂-C₁₀-alkynyl, aryl, heteroaryl, C₃-C₈-cycloalkyl, -X-aryl, -X-heteroaryl, -X-cycloalkyl, -NR⁸-aryl, -NR⁸-heteroaryl, -NR⁸-cycloalkyl, or -NR⁸-heterocycloalkyl, X-heterocycloalkyl, C₃-C₈-heterocycloalkyl, or a group selected from among hydrogen, halogen, COXR⁸, CON(R⁸)₂, COR⁸ and XR⁸, or R³ and R⁴ together denote a 2- to 5-membered alkyl bridge which may contain 1 to 2 heteroatoms,

R⁵ denotes hydrogen or a group selected from among optionally substituted C₁-C₁₀-alkyl, C₂-C₁₀-alkenyl, C₂-C₁₀-alkynyl, aryl, heteroaryl and -C₃-C₆-cycloalkyl, or

R³ and R⁵ or R⁴ and R⁵ together denote a saturated or unsaturated C₃-C₄-alkyl bridge which may contain 1 to 2 heteroatoms,

R⁶ denotes optionally substituted aryl or heteroaryl,

R⁷ denotes hydrogen or -CO-X-C₁-C₄-alkyl, and

X in each case independently of one another denotes O or S,

R⁸ in each case independently of one another denotes hydrogen or a group selected from among optionally

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substituted C₁-C₄-alkyl, C₂-C₄-alkenyl, C₂-C₄-alkynyl and phenyl,

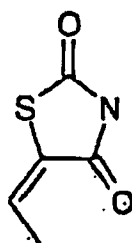
wherein, unless stated otherwise,

the substituents of the optionally substituted alkyl groups are selected from among the halogen atoms fluorine, chlorine, bromine or iodine, a group selected from among -CN, -OCOCH₃, aryl, heteroaryl, saturated or unsaturated heterocycloalkyl, an amine group, a saturated or unsaturated bicyclic ring system,

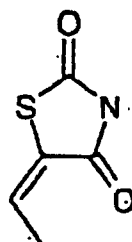
the substituents of the optionally substituted alkenyl groups are selected from among the halogen atoms fluorine, chlorine, bromine or iodine,

the substituents of the optionally substituted alkynyl groups are selected from among the halogen atoms fluorine, chlorine, bromine or iodine,

the substituents of the optionally substituted aryl groups are selected from among -OH, -NO₂, -CN, -OCHF₂, -OCF₃, -NH₂, halogen, -C₁-C₁₀-alkyl, -O-C₁-C₃-alkyl, -N-methyl-tetrahydrooxaziny, -COOH, -COO-C₁-C₄-alkyl, -CONH₂, -CONH-C₁-C₁₀-alkyl, -CONH-C₃-C₈-cycloalkyl, -CONH-heterocycloalkyl, -CONH-heteroaryl, -CONH-aryl, -CONHMeC₁-C₃-alkyl, benzimidazole or a group of the formula



the substituents of the optionally substituted heteroaryl group are selected from among -OH, -NO₂, -CN, -OCHF₂, -OCF₃, -NH₂, halogen, -C₁-C₁₀-alkyl, -O-C₁-C₃-alkyl, -N-methyl-tetrahydrooxaziny, -COOH, -COO-C₁-C₄-alkyl, -CONH₂, phenyl, heteroaryl, -CONH-C₁-C₁₀-alkyl, -CONH-C₃-C₈-cycloalkyl, -CONH-heteroaryl, -CONH-aryl, -CONHMeC₁-C₃-alkyl, benzimidazole or a group of the formula



the substituents of the optionally substituted cycloalkyl group are selected from among one or more oxygen atoms linked via a double bond, wherein the cycloalkyl group may also be anellated to a benzene ring, and, unless stated otherwise,

by the term "aryl" used in the definitions hereinbefore is meant an aromatic ring system with 6 to 14 carbon atoms, by the term "heteroaryl" used in the definitions hereinbefore is meant a 5-10-membered mono- or bicyclic heteroaryl ring in which up to three carbon atoms may be replaced by one or more heteroatoms selected from among oxygen, nitrogen or sulphur,

by the term "cycloalkyl" used in the definitions hereinbefore is meant a saturated or unsaturated cycloalkyl group having 3 to 8 carbon atoms,

by the term "cycloalkyl" used in the definitions hereinbefore is meant a 5-, 6- or 7-membered, saturated or unsaturated, heterocyclic group which may contain nitrogen, oxygen or sulphur as the heteroatom, while each of the above-mentioned heterocyclic groups may optionally also be anellated to a benzene ring,

optionally in the form of the tautomers, the racemates, the enantiomers, the diastereomers and the mixtures thereof, and optionally the pharmacologically acceptable acid addition salts thereof.

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2. Compounds according to claim 1, wherein

X and R⁶ have the meaning indicated, and

R¹ denotes hydrogen,

R² denotes a group selected from among a CHO, OH, and CH₃ group,

R³, R⁴ which may be identical or different denote a group selected from among hydrogen, optionally substituted C₁-C₆-alkyl, C₂-C₆-alkenyl, C₂-C₆-alkynyl, C₃-C₇-cycloalkyl, or

R³ and R⁴ together denote a C₂-C₅-alkyl bridge,

R⁵ denotes a group selected from among optionally substituted C₁-C₁₀-alkyl, C₂-C₁₀-alkenyl, C₂-C₁₀-alkynyl and C₃-C₆-cycloalkyl, or

R³ and R⁵ or R⁴ and R⁵ together denote a saturated or unsaturated C₃-C₄-alkyl bridge which may contain 1 to 2 heteroatoms, and

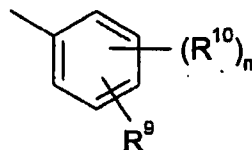
R⁷ denotes hydrogen,

optionally in the form of the tautomers, the racemates, the enantiomers, the diastereomers and the mixtures thereof, and optionally the pharmacologically acceptable acid addition salts thereof.

3. Compounds according to claim 1 or 2, wherein

R¹-R⁵, R⁷, R⁸ and X have the meaning indicated, and

R⁶ denotes a group of general formula



wherein

n denotes 1, 2, 3 or 4,

R⁹ denotes a group selected from among optionally substituted C₁-C₆-alkyl, C₂-C₆-alkenyl, C₂-C₆-alkynyl, -CONH-C₁-C₁₀-alkylene, -O-aryl, -O-heteroaryl, -O-cycloalkyl, -O-heterocycloalkyl, aryl, heteroaryl, cycloalkyl and heterocycloalkyl or

a group selected from among -O-C₁-C₆-alkyl-Q¹, -CONR⁸-C₁-C₁₀-alkyl-Q¹, -CONR⁸-C₂-C₁₀-alkenyl-Q¹, -CONR⁸-Q², halogen, OH, -SO₂R⁸, -SO₂N(R⁸)₂, -COR⁸, -COOR⁸, -N(R⁸)₂, -NHCOR⁸, CONR⁸OC₁-C₁₀ alkylQ¹ and CONR⁸OQ²,

Q¹ denotes hydrogen, -NHCOR⁸, or a group selected from among an optionally substituted -NH-aryl, -NH-heteroaryl, aryl, heteroaryl, C₃-C₈-cycloalkyl and heterocycloalkyl group,

Q² denotes hydrogen or a group selected from among an optionally substituted aryl, heteroaryl, C₃-C₈-heterocycloalkyl, C₃-C₈-cycloalkyl and C₁-C₄-alkyl-C₃-C₈-cycloalkyl group,

R¹⁰ which may be identical or different denotes a group selected from among optionally substituted C₁-C₆-alkyl, C₂-C₆-alkenyl and C₂-C₆-alkynyl, -O-C₁-C₆-alkyl, -O-C₂-C₆-alkenyl, -O-C₂-C₆-alkynyl, C₃-C₆-heterocycloalkyl and C₃-C₆-cycloalkyl, or

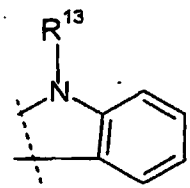
a group selected from among hydrogen, -CONH₂, -COOR⁸, -OCON(R⁸)₂, -N(R⁸)₂, -NHCOR⁸, -NHCON(R⁸)₂, -NO₂ and halogen,

or

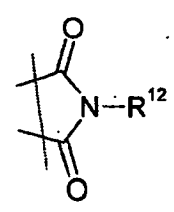
adjacent groups R⁹ and R¹⁰ together denote a bridge of general formula

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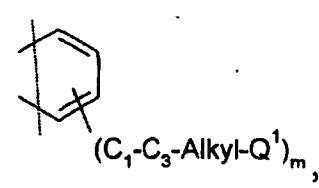
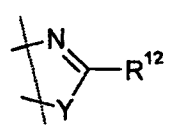
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Y denotes O, S or NR¹¹,
 m denotes 0, 1 or 2
 R¹¹ denotes hydrogen or C₁-C₂-alkyl, and
 R¹² denotes hydrogen or a group selected from among optionally substituted phenyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, -C₁-C₃-alkyl-phenyl, -C₁-C₃-alkyl-pyridyl, -C₁-C₃-alkyl-pyrazinyl, -C₁-C₃-alkyl-pyrimidinyl and -C₁-C₃-alkyl-pyridazinyl,
 R¹³ denotes C₁-C₈-alkyl

optionally in the form of the tautomers, the racemates, the enantiomers, the diastereomers and the mixtures thereof, and optionally the pharmacologically acceptable acid addition salts thereof.

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4. Compounds according to one of claims 1 to 3, wherein

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R³-R⁶, R⁸ and X have the meaning indicated, and
 R¹ denotes hydrogen,
 R² denotes CH₃, and
 R⁷ denotes hydrogen,

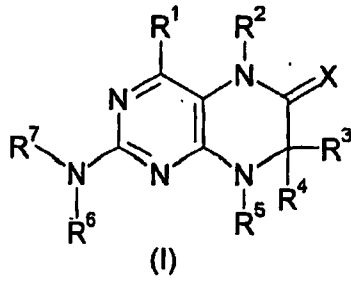
optionally in the form of the tautomers, the racemates, the enantiomers, the diastereomers and the mixtures thereof, and optionally the pharmacologically acceptable acid addition salts thereof.

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5. Compound of formula I according to one of claims 1 to 4 for use as a pharmaceutical composition.
6. Compound of formula I according to one of claims 1 to 4 for use as a pharmaceutical composition with an antiproliferative activity.
7. Use of a compound of formula I for preparing a pharmaceutical composition for the treatment and/or prevention of cancer, infections, inflammatory and autoimmune diseases.
8. Pharmaceutical preparations, containing as active substance one or more compounds of general formula (I) according to one of claims 1 to 4 or the physiologically acceptable salts thereof, optionally combined with conventional excipients and/or carriers.
9. Process for preparing a compound of general formula (I),

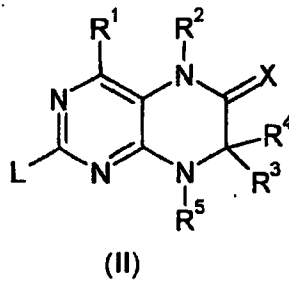
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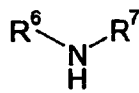
wherein

R¹-R⁷ and X have the meanings given in claims 1 to 4,
characterised in that a compound of general formula (II)



wherein

R¹-R⁵ and X have the meanings given in claims 1 to 4 and L is a leaving group,
is reacted with an optionally substituted compound of general formula (III)



wherein

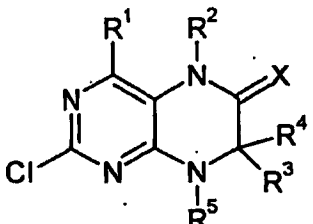
R⁶ and R⁷ have the meanings given in claims 1 to 4.

10. Compound of formula (II),

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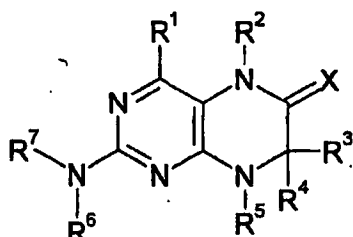
(II)

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wherein
R¹-R⁵ and X have the meanings given in claims 1 to 4.

11. Process for preparing a compound of general formula (I),

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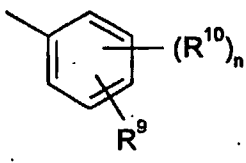
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(I)

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wherein
R⁶ denotes a group of general formula,

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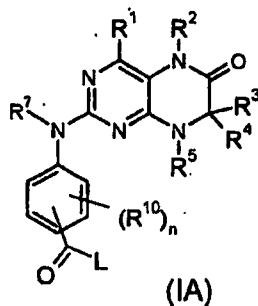
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R⁹ denotes an optionally substituted group -CONH-C₁-C₁₀-alkylene or a group selected from among
-CONR⁸-C₁-C₁₀-alkyl-Q¹, -CONR⁸-C₂-C₁₀-alkenyl-Q¹, -CONR⁸-Q², and -COOR⁸,
R¹-R⁵, R⁷, R¹⁰, n and X are as defined as in claims 1 to 4, and R⁸ is as defined in claim 1,
characterised in that a compound of general formula (IA)

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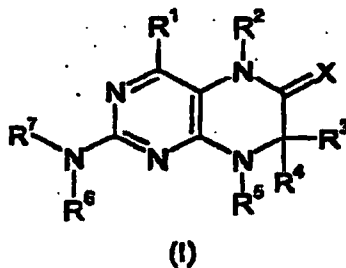
336 343



wherein
 R^1 to R^5 , R^7 , R^{10} and n are as defined as in claims 1 to 4, and
 L denotes a leaving group,
 is reacted with a primary or secondary amine to form the corresponding amide or is reacted with an alcohol to form the corresponding ester.

Revendications

1. Composés de formule générale (I)



où

R^1 représente un groupement choisi dans le groupe consistant en l'hydrogène, NH_2 , XH , halogène et un groupe C_1 - C_3 -alkyle éventuellement substitué par un ou plusieurs atomes d'halogène,
 R^2 représente un groupement choisi dans le groupe consistant en l'hydrogène, CHO , XH , $-X-C_1-C_2$ -alkyle et un groupe C_1 - C_3 -alkyle éventuellement substitué,
 R^3 , R^4 , identiques ou différents, représentent un groupement choisi dans le groupe consistant en C_1 - C_{10} -alkyle, C_2 - C_{10} -alcényle, C_2 - C_{10} -alcynyle, aryle, hétéroaryle, C_3 - C_8 -cycloalkyle, $-X$ -aryle, $-X$ -hétéroaryle, $-X$ -cycloalkyle, $-NR^8$ -aryle, $-NR^8$ -hétéroaryle, $-NR^8$ -cycloalkyle ou $-NR^8$ -hétérocycloalkyle, X -hétérocycloalkyle, C_3 - C_8 -hétérocycloalkyle éventuellement substitué ou un groupement choisi dans le groupe consistant en l'hydrogène, halogène, $COXR^8$, $CON(R^8)_2$, COR^8 et XR^8 , ou
 R^3 et R^4 représentent ensemble un pont alkyle à 2 à 5 membres qui peut contenir 1 à 2 hétéroatomes,
 R^5 représente l'hydrogène ou un groupement choisi dans le groupe consistant en C_1 - C_{10} -alkyle, C_2 - C_{10} -alcényle, C_2 - C_{10} -alcynyle, aryle, hétéroaryle et C_3 - C_6 -cycloalkyle éventuellement substitué, ou
 R^3 et R^5 ou R^4 et R^5 représentent ensemble un pont C_3 - C_4 -alkyle saturé ou insaturé qui peut contenir 1 à 2 hétéroatomes,
 R^6 représente aryle ou hétéroaryle éventuellement substitué,
 R^7 représente l'hydrogène ou $-CO-X-C_1-C_4$ -alkyle, et
 X représente dans chaque cas indépendamment O ou S ,
 R^8 représente à chaque fois indépendamment l'hydrogène ou un groupement choisi dans le groupe consistant

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en C₁-C₄-alkyle, C₂-C₄-alcényle, C₂-C₄-alcynyle et phényle éventuellement substitué,

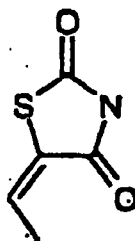
où, sauf indication contraire,

les substituants des groupes alkyle éventuellement substitués sont choisis dans le groupe consistant en les atomes d'halogène fluor, chlore, brome ou iode, un groupement choisi dans le groupe consistant en -CN, -OCOCH₃, aryle, hétéroaryle, hétérocycloalkyle saturé ou insaturé, un groupement amine, un système cyclique bicyclique saturé ou insaturé,

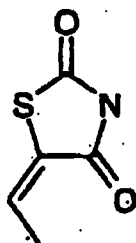
les substituants des groupes alcényle éventuellement substitués sont choisis dans le groupe consistant en les atomes d'halogène fluor, chlore, brome ou iode,

les substituants des groupes alcynyle éventuellement substitués sont choisis dans le groupe consistant en les atomes d'halogène fluor, chlore, brome ou iode,

les substituants des groupes aryle éventuellement substitués sont choisis dans le groupe consistant en -OH, -NO₂, -CN, -OCHF₂, -OCF₃, -NH₂, halogène, -C₁-C₁₀-alkyle, -O-C₁-C₃-alkyle, -N-méthyl-tétrahydrooxazinyne, -COOH, -COO-C₁-C₄-alkyle, -CONH₂, -CONH-C₁-C₁₀-alkyle, -CONH-C₃-C₆-cycloalkyle, -CONH-hétérocycloalkyle, -CONH-hétéroaryle, -CONH-aryle, -CONMe-C₁-C₃-alkyle, benzimidazole ou un groupement de formule



les substituants du groupe hétéroaryle éventuellement substitué sont choisis dans le groupe consistant en -OH, -NO₂, -CN, -OCHF₂, -OCF₃, -NH₂, halogène, -C₁-C₁₀-alkyle, -O-C₁-C₃-alkyle, -N-méthyl-tétrahydrooxazinyne, -COOH, -COO-C₁-C₄-alkyle, -CONH₂, phényle, hétéroaryle, -CONH-C₁-C₁₀-alkyle, -CONH-C₃-C₆-cycloalkyle, -CONH-hétéroaryle, -CONH-aryle, -CONMe-C₁-C₃-alkyle, benzimidazole ou un groupement de formule



les substituants du groupe cycloalkyle éventuellement substitué sont choisis dans le groupe consistant en un ou plusieurs atomes d'oxygène liés par le biais d'une double liaison, où le groupe cycloalkyle peut aussi être condensé à un cycle benzénique,

et où, sauf indication contraire,

par l'expression « aryle » citée précédemment dans les définitions, on doit comprendre un système cyclique aromatique ayant 6 à 14 atomes de carbone,

par l'expression « hétéroaryle » citée précédemment dans les définitions, on doit comprendre un cycle hétéroaryle mono- ou bicyclique à 5-10 membres dans lequel jusqu'à trois atomes C peuvent être remplacés par un ou plusieurs hétéroatomes choisis dans le groupe oxygène, azote ou soufre,

par l'expression « cycloalkyle » citée précédemment dans les définitions, on doit comprendre un groupement cycloalkyle saturé ou insaturé ayant 3-8 atomes de carbone,

par l'expression « hétérocycloalkyle » citée précédemment dans les définitions, on doit comprendre un hétérocycle



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(12) **United States Patent**
Bauer et al.

(10) **Patent No.:** **US 6,806,272 B2**

(45) **Date of Patent:** **Oct. 19, 2004**

(54) **DIHYDROPTERIDINONES, PROCESSES FOR PREPARING THEM AND THEIR USE AS PHARMACEUTICAL COMPOSITIONS**

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(*) **Notice:** Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 89 days.

(21) **Appl. No.:** **10/226,710**

(22) **Filed:** **Aug. 23, 2002**

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Related U.S. Application Data

(60) **Provisional application No. 60/332,681, filed on Nov. 14, 2001.**

(30) **Foreign Application Priority Data**

Sep. 4, 2001 (DE) 101 43 272

(51) **Int. Cl.⁷** **C07D 487/04; A61K 31/4985**

(52) **U.S. Cl.** **514/250; 544/257**

(58) **Field of Search** **544/257; 514/250**

(56) **References Cited**

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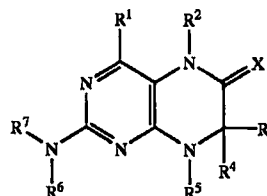
Primary Examiner—Richard L. Raymond

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(57) **ABSTRACT**

The present invention relates to new dihydropteridinones of the formula (I)



wherein the groups X, R¹, R², R³, R⁴, R⁵ and R⁷ have the meanings given in the claims and the specification, the isomers thereof, processes and intermediates for preparing these dihydropteridinones as well as the use thereof as pharmaceutical compositions.

10 Claims, No Drawings

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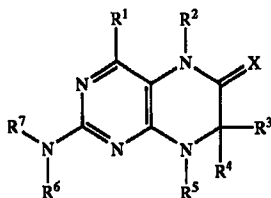
DIHYDROPTERIDINONES, PROCESSES FOR PREPARING THEM AND THEIR USE AS PHARMACEUTICAL COMPOSITIONS

APPLICATION DATA

This application claims benefit to DE 101 43 272.0 filed Sep. 4, 2001 and U.S. provisional application No. 60/332681 filed Nov. 14, 2001.

FIELD OF THE INVENTION

The present invention relates to new dihydropteridinones of general formula (I)



wherein the groups X, R¹, R², R³, R⁴, R⁵, R⁶ and R⁷ have the meanings given in the claims and specification, the isomers thereof, processes for preparing these dihydropteridinones and the use thereof as pharmaceutical compositions.

BACKGROUND OF THE INVENTION

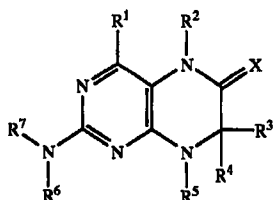
Pteridinone derivatives are known from the prior art as active substances with an antiproliferative activity. WO 01/019825 describes the use of pteridinone derivatives for the treatment of neoplastic and viral diseases. The resistance of many types of tumours calls for the development of new pharmaceutical compositions for combating tumours.

The aim of the present invention is to prepare new compounds with an antiinflammatory and antiproliferative activity.

DETAILED DESCRIPTION OF THE INVENTION

Surprisingly it has been found that compounds of general formula (I) wherein the groups X and R¹ to R⁷ have the meanings given hereinafter act as inhibitors of specific cell cycle kinases. Thus, the compounds according to the invention may be used for example to treat diseases connected with the activity of specific cell cycle kinases and characterised by excessive or abnormal cell proliferation.

The present invention therefore relates to compounds of general formula (I)



wherein

R¹ denotes a group selected from among hydrogen, NH₂, XH, halogen and a C₁-C₃-alkyl group optionally substituted by one or more halogen atoms,

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R² denotes a group selected from among hydrogen, CHO, XH, —X—C₁-C₂-alkyl and an optionally substituted C₁-C₃-alkyl group,

R³, R⁴ which may be identical or different denote a group selected from among optionally substituted C₁-C₁₀-alkyl, C₂-C₁₀-alkenyl, C₂-C₁₀-alkynyl, aryl, heteroaryl, C₃-C₈-cycloalkyl, C₃-C₈-heterocycloalkyl, —X-aryl, —X-heteroaryl, —X-cycloalkyl, —X-heterocycloalkyl, —NR⁸-aryl, —NR⁸-heteroaryl, —NR⁸-cycloalkyl and —NR⁸-heterocycloalkyl, or a group selected from among hydrogen, halogen, COXR⁸, CON(R⁸)₂, COR⁸ and XR⁸, or

R³ and R⁴ together denote a 2- to 5-membered alkyl bridge which may contain 1 to 2 heteroatoms,

R⁵ denotes hydrogen or a group selected from among optionally substituted C₁-C₁₀-alkyl, C₂-C₁₀-alkenyl, C₂-C₁₀-alkynyl, aryl, heteroaryl and —C₃-C₆-cycloalkyl, or

R³ and R⁵ or R⁴ and R⁵ together denote a saturated or unsaturated C₃-C₄-alkyl bridge which may contain 1 to 2 heteroatoms,

R⁶ denotes optionally substituted aryl or heteroaryl,

R⁷ denotes hydrogen or —CO—X—C₁-C₄-alkyl, and

X in each case independently of one another denotes O or S,

R⁸ in each case independently of one another denotes hydrogen or a group selected from among optionally substituted C₁-C₄-alkyl, C₂-C₄-alkenyl, C₂-C₄-alkynyl and phenyl,

optionally in the form of the tautomers, the racemates, the enantiomers, the diastereomers and the mixtures thereof, and optionally the pharmacologically acceptable acid addition salts thereof.

Preferred compounds of formula (I) are those wherein

X and R⁶ have the meaning indicated, and

R¹ denotes hydrogen,

R² denotes a group selected from among a CHO, OH, and CH₃ group,

R³, R⁴ which may be identical or different denote a group selected from among hydrogen, optionally substituted C₁-C₆-alkyl, C₂-C₆-alkenyl, C₂-C₆-alkynyl, C₃-C₇-cycloalkyl, or

R³ and R⁴ together denote a C₂-C₅-alkyl bridge,

R⁵ denotes a group selected from among optionally substituted C₁-C₁₀-alkyl, C₂-C₁₀-alkenyl, C₂-C₁₀-alkynyl, C₃-C₆-cycloalkyl and C₃-C₆-cycloalkenyl, or

R³ and R⁵ or R⁴ and R⁵ together denote a saturated or unsaturated C₃-C₄-alkyl bridge which may contain 1 to 2 heteroatoms, and

R⁷ denotes hydrogen,

optionally in the form of the tautomers, the racemates, the enantiomers, the diastereomers and the mixtures thereof, and optionally the pharmacologically acceptable acid addition salts thereof.

Solutions for injection and infusion are prepared in the usual way, e.g. with the addition of preservatives such as p-hydroxybenzoates, or stabilisers such as alkali metal salts of ethylenediamine tetraacetic acid, optionally using emulsifiers and/or dispersants, while if water is used as the diluent organic solvents may optionally be used as solubilisers or auxiliary solvents, and transferred into injection vials or ampoules or infusion bottles.

Capsules containing one or more active substances or combinations of active substances may for example be prepared by mixing the active substances with inert carriers such as lactose or sorbitol and packing them into gelatine capsules.

Suitable suppositories may be made for example by mixing with carriers provided for this purpose, such as neutral fats or polyethyleneglycol or the derivatives thereof.

Suitable excipients may be, for example, water, pharmaceutically acceptable organic solvents, such as paraffins (e.g. petroleum fractions), oils of vegetable origin (e.g. groundnut or sesame oil), mono- or polyfunctional alcohols (e.g. ethanol or glycerol), carriers such as e.g. natural mineral powders (e.g. kaolin, clays, talc, chalk), synthetic mineral powders (e.g. highly dispersed silica and silicates), sugar (e.g. glucose, lactose and dextrose), emulsifiers (e.g. lignin, spent sulphite liquors, methylcellulose, starch and polyvinylpyrrolidone) and lubricants (e.g. magnesium stearate, talc, stearic acid and sodium lauryl sulphate).

The preparations are administered in the usual way, preferably by oral or transdermal route, particularly preferably by oral route. When administered orally the tablets may, of course, contain additives, such as e.g. sodium citrate, calcium carbonate and dicalcium phosphate together with various additives, such as starch, preferably potato starch, gelatine and the like, in addition to the abovementioned carriers. Lubricants such as magnesium stearate, sodium laurylsulphate and talc may also be used to form tablets. In the case of aqueous suspensions the active substances may be combined with various flavour enhancers or colourings in addition to the abovementioned excipients.

For parenteral use, solutions of the active substances may be prepared using suitable liquid carrier materials.

The dosage for intravenous use is 1-1000 mg per hour, preferably between 5-500 mg per hour.

However, it may optionally be necessary to deviate from the amounts specified, depending on the body weight or method of administration, the individual response to the medication, the nature of the formulation used and the time or interval over which it is administered. Thus, in some cases, it may be sufficient to use less than the minimum quantity specified above, while in other cases the upper limit specified will have to be exceeded. When large amounts are administered it may be advisable to spread them over the day in a number of single doses.

The formulation examples that follow illustrate the present invention without restricting its scope:

Examples of Pharmaceutical Formulations

A)	Tablets	per tablet
	active substance	100 mg
	lactose	140 mg
	corn starch	240 mg

-continued

A)	Tablets	per tablet
	polyvinylpyrrolidone	15 mg
	magnesium stearate	5 mg
		500 mg

The finely ground active substance, lactose and some of the corn starch are mixed together. The mixture is screened, then moistened with a solution of polyvinylpyrrolidone in water, kneaded, wet-granulated and dried. The granules, the remaining corn starch and the magnesium stearate are screened and mixed together. The mixture is compressed to produce tablets of suitable shape and size.

B)	Tablets	per tablet
	active substance	80 mg
	lactose	55 mg
	corn starch	190 mg
	microcrystalline cellulose	35 mg
	polyvinylpyrrolidone	15 mg
	sodium-carboxymethyl starch	23 mg
	magnesium stearate	2 mg
		400 mg

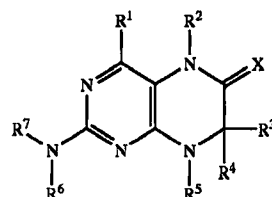
The finely ground active substance, some of the corn starch, lactose, microcrystalline cellulose and polyvinylpyrrolidone are mixed together, the mixture is screened and worked with the remaining corn starch and water to form a granulate which is dried and screened. The sodiumcarboxymethyl starch and the magnesium stearate are added and mixed in and the mixture is compressed to form tablets of a suitable size.

C)	Ampoule solution	
	active substance	50 mg
	sodium chloride	50 mg
	water for inj.	5 ml

The active substance is dissolved in water at its own pH or optionally at pH 5.5 to 6.5 and sodium chloride is added to make it isotonic. The solution obtained is filtered free from pyrogens and the filtrate is transferred under aseptic conditions into ampoules which are then sterilised and sealed by fusion. The ampoules contain 5 mg, 25 mg and 50 mg of active substance.

What is claimed is:

1. A compound of the formula (I),



wherein

R¹ denotes a group selected from among hydrogen, NH₂, XH, halogen and a C₁-C₃-alkyl group optionally substituted by one or more halogen atoms,

In view of their biological properties the compounds of general formula I according to the invention, their isomers and their physiologically acceptable salts are suitable for the treatment of diseases characterised by excessive or abnormal cell proliferation.

Such diseases include, for example: viral infections (e.g. HIV and Kaposi's sarcoma); inflammatory and autoimmune diseases (e.g. colitis, arthritis, Alzheimer's disease, glomerulonephritis and wound healing); bacterial, fungal and/or parasitic infections; leukaemias, lymphoma and solid tumours; skin diseases (e.g. psoriasis); bone diseases; cardiovascular diseases (e.g. restenosis and hypertrophy). They are also suitable for protecting proliferating cells (e.g. hair, intestinal, blood and progenitor cells) from damage to their DNA caused by radiation, UV treatment and/or cytostatic treatment (Davis et al., 2001).

The new compounds may be used for the prevention, short-term or long-term treatment of the abovementioned diseases, also in combination with other active substances used for the same indications, e.g. cytostatics.

The activity of the compounds according to the invention was determined in the cytotoxicity test on cultivated human tumour cells and/or in a FACS analysis, for example on HeLaS3 cells. In both test methods, the compounds exhibited a good to very good activity, i.e. for example an EC_{50} value in the HeLaS3 cytotoxicity test of less than 5 mol, generally less than 1 mol.

Measurement of Cytotoxicity on Cultivated Human Tumour Cells

To measure the cytotoxicity on cultivated human tumour cells, cells of the cervical cancer tumour cell line HeLaS3 (obtained from American Type Culture Collection (ATCC)) in Ham's F12 Medium (Life Technologies) and 10% foetal calf serum (Life Technologies) were cultivated and harvested in the logarithmic growth phase. Then the HeLaS3 cells were placed in 96-well plates (Costar) at a density of 1000 cells per well and incubated overnight in an incubator (at 37° C. and 5% CO₂), while on each plate 6 wells were filled only with medium (3 wells as a control of the medium, 3 wells for incubation with reduced AlamarBlue). The active substances were added to the cells in various concentrations (dissolved in DMSO; final concentration: 1%) (in each case as a triple measurement). After 72 hours' incubation, 20 μ l of AlamarBlue (AccuMed International) were added to each well, and the cells were incubated for a further 7 hours. As a control, 20 μ l of reduced Alamar Blue (AlamarBlue reagent which had been autoclaved for 30 min) were added to 3 wells. After 7 h incubation the colour change of the AlamarBlue reagent in the individual wells was determined in a Perkin Elmer fluorescence spectrophotometer (excitation 530 nm, emission 590 nm, slits 15, integrate time 0.1). The amount of AlamarBlue reagent reacted represents the metabolic activity of the cells. The relative cell activity was calculated as a percentage of the control (HeLa S3 cells without inhibitor) and the active substance concentration which inhibits the cell activity by 50% (IC_{50}) was obtained. The values were calculated from the average of three individual measurements, correcting for the control value (medium control).

FACS Analysis

Propidium iodide (PI) binds stoichiometrically to double-stranded DNA, and is thus suitable for determining the percentage of cells in the G1, S and G2/M phase of the cell cycle on the basis of the cell DNA content. Cells in the G0 and G1 phase have a diploid DNA content (2N), whereas

cells in G2 or mitosis have a 4N DNA content. For PI staining, 0.4 million HeLaS3 cells were seeded, for example, on a 75 cm² cell culture flask, and after 24 h either 1% DMSO was added as control or the substance was added in various concentrations (in 1% DMSO). The cells were incubated for 24 h with the substance or with DMSO, before the cells were washed with 2xPBS and detached with trypsin/EDTA. The cells were centrifuged (1000 rpm, 5 min, 4° C.), and the cell pellet was washed 2x with PBS, before the cells were resuspended in 0.1 ml of PBS. Then the cells were fixed with 80% ethanol for 16 hours at 4° C. or alternatively for 2 hours at -20° C. The fixed cells (10⁶ cells) were centrifuged (1000 rpm, 5 min, 4° C.), washed with PBS and then centrifuged again. The cell pellet was resuspended in 2 ml of Triton X-100 in 0.25% PBS, and incubated for 5 min on ice, before 5 ml of PBS were added and the mixture was centrifuged again. The cell pellet was resuspended in 350 μ l of PI stain solution (0.1 mg/ml of Raze A, 10 μ g/ml of presidium iodide in 1xPBS). The cells were incubated for 20 min in the dark with the stain buffer before being transferred into sample measuring vessels for the FACS scan. The DNA measurement was carried out in a Becton Dickinson FACS Analyzer, with an argon laser (500 mW, emission 488 nm), and the DNA Cell Quest Program (BD). The logarithmic PI fluorescence was determined with a band-pass filter (BP 585/42). The cell populations in the individual phases of the cell cycle were quantified with the ModFit LT program of Becton Dickinson.

The compounds of general formula (I) may be used on their own or combined with other active substances according to the invention, optionally also in conjunction with other pharmacologically active substances. Suitable preparations include for example tablets, capsules, suppositories, solutions, particularly solutions for injection (s.c., i.v., i.m.) and infusion, syrups, emulsions or dispersible powders. The amount of pharmaceutically active compound in each case should be in the range from 0.1–90 wt. %, preferably 0.5–50 wt. % of the total composition, i.e. in amounts which are sufficient to achieve the dosage range given below. The doses specified may, if necessary, be given several times a day.

Suitable tablets may be obtained, for example, by mixing the active substance(s) with known excipients, for example inert diluents such as calcium carbonate, calcium phosphate or lactose, disintegrants such as corn starch or alginic acid, binders such as starch or gelatine, lubricants such as magnesium stearate or talc and/or agents for delaying release, such as carboxymethyl cellulose, cellulose acetate phthalate, or polyvinyl acetate. The tablets may also comprise several layers.

Coated tablets may be prepared accordingly by coating cores produced analogously to the tablets with substances normally used for tablet coatings, for example collidone or shellac, gum arabic, talc, titanium dioxide or sugar. To achieve delayed release or prevent incompatibilities the core may also consist of a number of layers. Similarly the tablet coating may consist of a number of layers to achieve delayed release, possibly using the excipients mentioned above for the tablets.

Syrups or elixirs containing the active substances or combinations thereof according to the invention may additionally contain a sweetener such as saccharin, cyclamate, glycerol or sugar and a flavour enhancer, e.g. a flavouring such as vanillin or orange extract. They may also contain suspension adjuvants or thickeners such as sodium carboxymethyl cellulose, wetting agents such as, for example, condensation products of fatty alcohols with ethylene oxide, or preservatives such as phydroxybenzoates.

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R^2 denotes a group selected from among hydrogen, CHO, XH, $-X-C_1-C_2$ -alkyl and an optionally substituted C_1-C_3 -alkyl group,

R^3 , R^4 are identical or different and denote a group selected from among optionally substituted C_1-C_{10} -alkyl, C_2-C_{10} -alkenyl, C_2-C_{10} -alkynyl, aryl, heteroaryl, C_3-C_8 -cycloalkyl, C_3-C_8 -heterocycloalkyl, $-X$ -aryl, $-X$ -heteroaryl, $-X$ -cycloalkyl, $-X$ -heterocycloalkyl, $-NR^8$ -aryl, $-NR^8$ -heteroaryl, $-NR^8$ -cycloalkyl, and $-NR^8$ -heterocycloalkyl, or

a group selected from among hydrogen, halogen, $COXR^8$, $CON(R^8)_2$, COR^8 and XR^8 , or

R^3 and R^4 together denote a 2- to 5-membered alkyl bridge which may contain 1 to 2 heteroatoms,

R^5 denotes hydrogen or a group selected from among optionally substituted C_1-C_{10} -alkyl, C_2-C_{10} -alkenyl, C_2-C_{10} -alkynyl, aryl, heteroaryl and $-C_3-C_6$ -cycloalkyl, or

R^3 and R^5 or R^4 and R^5 together denote a saturated or unsaturated C_3-C_4 -alkyl bridge which may contain 1 to 2 heteroatoms,

R^6 denotes optionally substituted aryl or heteroaryl,

R^7 denotes hydrogen or $-CO-X-C_1-C_4$ -alkyl, and X in each case independently of one another denotes O or S, and

R^8 in each case independently of one another denotes hydrogen or a group selected from among optionally substituted C_1-C_4 -alkyl, C_2-C_4 -alkenyl, C_2-C_4 -alkynyl and phenyl,

or the tautomers, the racemates, the enantiomers, the diastereomers and the mixtures thereof, and optionally the pharmacologically acceptable acid addition salts thereof.

2. The compound according to claim 1, wherein

R^1 denotes hydrogen,

R^2 denotes a group selected from among a CHO, OH, and CH_3 group,

R^3 , R^4 are identical or different and denote a group selected from among hydrogen, optionally substituted C_1-C_6 -alkyl, C_2-C_6 -alkenyl, C_2-C_6 -alkynyl, C_3-C_7 -cycloalkyl, or R^3 and R^4 together denote a C_2-C_5 -alkyl bridge,

R^5 denotes a group selected from among optionally substituted C_1-C_{10} -alkyl, C_2-C_{10} -alkenyl, C_2-C_{10} -alkynyl, C_3-C_6 -cycloalkyl and C_3-C_6 -cycloalkenyl, or

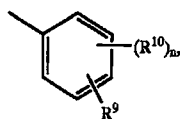
R^3 and R^5 or R^4 and R^5 together denote a saturated or unsaturated C_3-C_4 -alkyl bridge which may contain 1 to 2 heteroatoms, and

R^7 denotes hydrogen.

3. The compound according to claim 2, wherein

R^1 - R^5 , R^7 , R^8 and X have the meaning indicated, and

R^6 denotes a group of general formula



wherein

n denotes 1, 2, 3 or 4,

R^9 denotes a group selected from among optionally substituted C_1-C_6 -alkyl, C_2-C_6 -alkenyl, C_2-C_6 -

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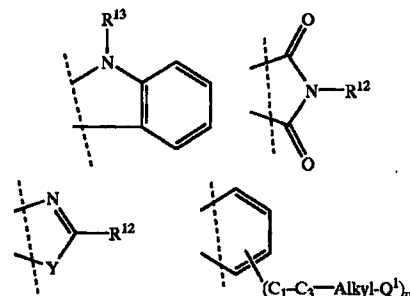
alkynyl, $-CONH-C_1-C_{10}$ -alkylene, $-O$ -aryl, $-O$ -heteroaryl, $-O$ -cycloalkyl, $-O$ -heterocycloalkyl, aryl, heteroaryl, cycloalkyl and heterocycloalkyl or a group selected from among $-O-C_1-C_6$ -alkyl- Q^1 , $-CONR^8-C_1-C_{10}$ -alkyl- Q^1 , $-CONR^8-C_2-C_{10}$ -alkenyl- Q^1 , $-CONR^8-Q^2$, halogen, OH, $-SO_2R^8$, $-SO_2N(R^8)_2$, $-COR^8$, $-COOR^8$, $-N(R^8)_2$, $-NHCOR^8$, $CONR^8OC_1-C_{10}$ alkyl Q^1 and $CONR^8OQ^2$,

Q^1 denotes hydrogen, $-NHCOR^8$, or a group selected from among an optionally substituted $-NH$ -aryl, $-NH$ -heteroaryl, aryl, heteroaryl, C_3-C_8 -cycloalkyl- and heterocycloalkyl group,

Q^2 denotes hydrogen or a group selected from among an optionally substituted aryl, heteroaryl, C_3-C_8 -heterocycloalkyl, C_3-C_8 -cycloalkyl- and C_1-C_4 -alkyl- C_3-C_8 -cycloalkyl group,

R^{10} is identical or different and denotes a group selected from among optionally substituted C_1-C_6 -alkyl, C_2-C_6 -alkenyl and C_2-C_6 -alkynyl, $-O-C_1-C_6$ -alkyl, $-O-C_2-C_6$ -alkenyl, $-O-C_2-C_6$ -alkynyl, C_3-C_6 -heterocycloalkyl and $C_3-C_3-C_6$ -cycloalkyl, or a group selected from among hydrogen, $-CONH_2$, $-COOR^8$, $-OCON(R^8)_2$, $-N(R^8)_2$, $-NHCOR^8$, $-NHCON(R^8)_2$, $-NO_2$ and halogen, or

adjacent groups R^9 and R^{10} together denote a bridge of the formula



Y denotes O, S or NR^{11} ,

m denotes 0, 1 or 2

R^{11} denotes hydrogen or C_1-C_2 -alkyl, and

R^{12} denotes hydrogen or a group selected from among optionally substituted phenyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, $-C_1-C_3$ -alkyl-phenyl, $-C_1-C_3$ -alkyl-pyridyl, $-C_1-C_3$ -alkyl-pyrazinyl, $-C_1-C_3$ -alkyl-pyrimidinyl and $-C_1-C_3$ -alkyl-pyridazinyl, and

R^{13} denotes C_1-C_6 -alkyl.

4. The compounds according to claim 3, wherein

R^1 denotes hydrogen,

R^2 denotes CH_3 , and

R^7 denotes hydrogen.

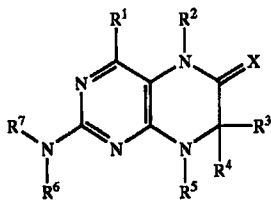
5. A pharmaceutical composition comprising a pharmaceutically effective amount of a compound of formula I according to claim 1 optionally combined with conventional excipients and/or carriers.

6. A method of inhibiting proliferation of cells in a patient in need thereof, said method comprising administering to a patient in need thereof a therapeutically effective amount of a compound of formula I according to claim 1.

7. The method according to claim 6 wherein the cells are tumour cells, endothelial, hair, intestinal, blood or progenitor cells.

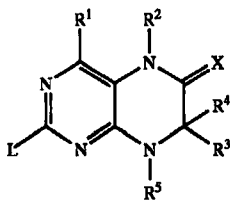
181

8. A process for preparing a compound of the formula (I) according to claim 1,



wherein

R¹-R⁷ and X are as defined in claim 1, comprising 15
reacting a compound of the formula (II)



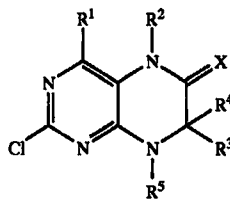
wherein

L is a leaving group, 30
with an optionally substituted compound of the formula (III)



wherein

R⁶ and R⁷ are as defined in claim 1, and subsequently 35
isolating the product compound.
9. A compound of the formula (II),

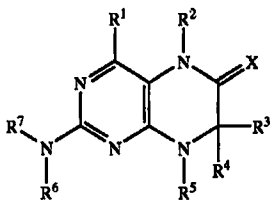


wherein

R¹-R⁵ and X have the meanings given in claims 1 to 4.

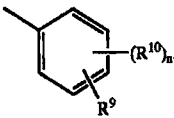
182

10. A process for preparing a compound of the formula (I), 5
(I)

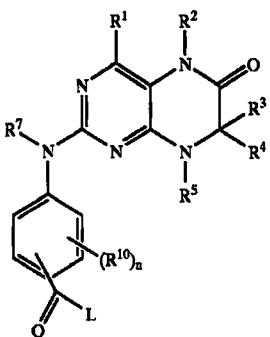


wherein

R⁶ denotes a group of the formula:



R⁹ denotes an optionally substituted group —CONH— 25
C₁-C₁₀-alkylene or a group selected from among
—CONR⁸—C₁-C₁₀-alkyl-Q¹, —CONR⁸—C₂-C₁₀-
alkenyl-Q¹,
—CONR⁸—Q², and —COOR⁸, and
R¹-R⁵, R⁷, R¹⁰, n and X are as defined as in claim 1,
comprising reacting a compound of the formula (IA),



wherein

R¹ to R⁵, R⁷, R¹⁰ and n are as defined as in claim 1, and 40
L denotes a leaving group
with a primary or secondary amine to form the corre-
sponding amide; or
reaching a compound of the formula (IA) with an alcohol
to form the corresponding ester;
and subsequently isolating the product compound. 45

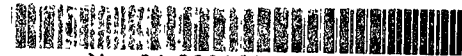
* * * * *

347 347

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



Nº 04-020069-00007-0000

RECIBO OFICIAL DE CAJA : 07 - 105,453
FECHA : DICIEMBRE 28 DE 2007

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CANT RESPUESTARQUE Folia 31

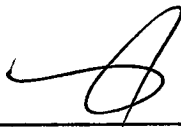
***** CONSIGNACION *****

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CAVELIER ABOGADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	63768293	28/12/2007	5,651,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-03	CAMBIO DE MODALIDAD Y MODIFICA	
12		MARCAS Y LEHAS COMERCIALES	99,000.00
		TOTAL :	\$ 99,000.00

: NOVENTA Y NUEVE MIL PESOS

RESPONSABLE : 

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

010 13736-841-025-4

348

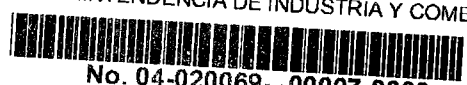
344

 SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

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RECIBO OFICIAL DE CAJA : 08 - 204
FECHA : ENERO 2 DE 2008

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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Tra: 11 PATLNIEIYII Ene 379 FASENACIONALII
Act 444 KLSPULSTARLOUL Folios: 31

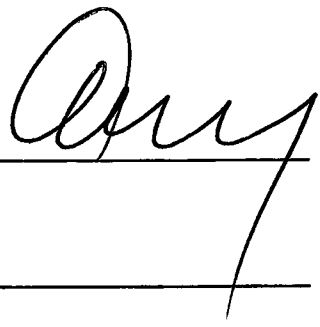
***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CAVELIER ABOGADOS	CONSIGNACION	BANCO DE BOGOTA	062754387	2808637	02/01/2008	42,278,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-09	OTROS SERVICIOS DE PROPIEDAD I	
		998 VALOR COMPLEMENTO TARIFA A#D ANTR	4,000.00
		TOTAL :	\$ 4,000.00

SON: CUATRO MIL PESOS

RESPONSABLE : 

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

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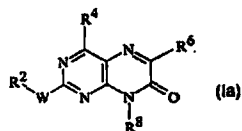
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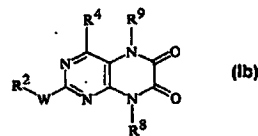
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60/154,095 15 September 1999 (15.09.1999) US(71) Applicant (for all designated States except US):
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201 Taber Road, Morris Plains, NJ 07950 et al. (US).(81) Designated States (national): AE, AG, AL, AU, BA, BB,
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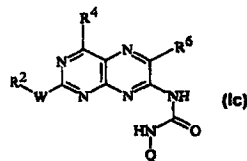
(54) Title: PTERIDINONES AS KINASE INHIBITORS



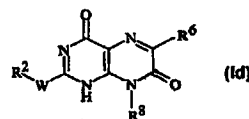
(Ia)



(Ib)



(Ic)



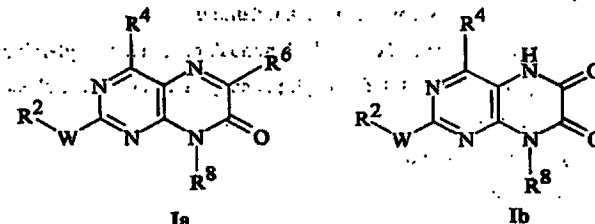
(Id)

(57) Abstract: Disclosed are compounds of Formulae (Ia), (Ib), (Ic), (Id) wherein: W is NH, S, SO, or SO₂; R² is (un)substituted aryl, (un)substituted heteroaryl, or (un)substituted carbocycle or heterocycle; Q is hydrogen or lower alkyl; R⁴ and R⁶ are the same or different and represent hydrogen, halogen, lower alkyl, lower alkoxy, (un)substituted aryl, (un)substituted heteroaryl, (un)substituted arylalkyl or (un)substituted heteroarylalkyl; and R⁸ is hydrogen, lower alkyl or an (un)substituted carbocyclic group containing from 3-7 members, up to two of which members are optionally hetero atoms selected from oxygen and nitrogen; or R⁸ is (un)substituted aryl, (un)substituted heteroaryl, (un)substituted arylalkyl or (un)substituted heteroarylalkyl. These compounds are useful for treating cell proliferative disorders, such as cancer and restenosis. These compounds are potent inhibitors of cyclin-dependent kinases (cdks) and growth factor-mediated kinases. The present invention also provides a method of treating cell proliferative disorders. Also provided by the present invention is a pharmaceutically acceptable composition containing a compound of Formula (I).

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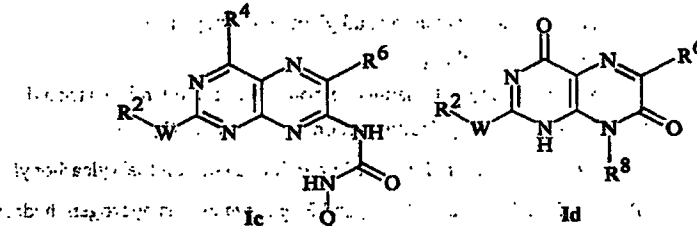
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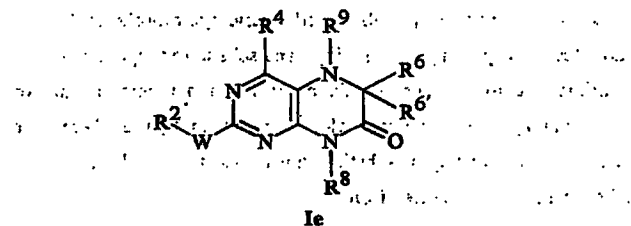
Ia

Ib



Ic

Id



Ie

and pharmaceutically acceptable salts, esters, amides and prodrugs thereof,
wherein:

W is NH, O, S, SO, or SO₂;

R² is:

C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₃-C₁₀ cycloalkyl, (CH₂)_n-aryl,

COR⁴, (CH₂)_n-heteroaryl, and (CH₂)_n-heterocyclyl, wherein each of the

foregoing alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and

heterocyclyl groups can be unsubstituted or substituted with from 1 to

5 substituent groups selected from:

(a) halogen

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- (b) amino, alkylamino, and dialkylamino
 (c) alkoxy, aminoalkoxy, alkylaminoalkoxy, and dialkylaminoalkoxy
 (d) phenyl, substituted phenyl, phenoxy, and substituted phenoxy
 (e) hydroxy
 (f) thio, alkylthio
 (g) cyano
 (h) nitro
 (i) alkanoyl, aminoalkanoyl, alkylaminoalkanoyl, and dialkylaminoalkanoyl
 (j) aminocarbonyl, alkylaminocarbonyl, and dialkylaminocarbonyl
 (k) amino-C₃-C₇ cycloalkylcarbonyl, alkylamino-C₃-C₇ cycloalkylcarbonyl, and dialkylamino-C₃-C₇ cycloalkylcarbonyl
 (l) CO₂Z, CO₂Z, SO₂Z, SO₂Z, and PO₃Z, where Z is hydrogen, hydroxy, alkoxy, lower alkyl, substituted alkyl, amino, alkylamino, dialkylamino, piperidinyl, substituted piperidinyl, morpholinyl, substituted morpholinyl, piperazinyl, and substituted piperazinyl
 (m) a carbocyclic group containing from 3 to 7 ring members, one or two of which may be a heteroatom selected from O or N, and wherein the carbocyclic group may be substituted with one, two, or three substituent groups selected from:
 (1) halogen
 (2) hydroxy
 (3) alkyl, aminoalkyl, alkyl and dialkylaminoalkyl
 (4) trifluoromethyl
 (5) alkoxy
 (6) amino, alkylamino, dialkylamino, alkanoylamino
 (7) CO₂Z, CO₂Z, SO₂Z, SO₂Z, or PO₃Z
 (8) aryl
 (9) heteroaryl
 (10) (CH₂)_n morpholino
 (11) (CH₂)_n piperazinyl
 (12) (CH₂)_n piperidinyl

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- (13) (CH₂)_n tetrazolyl
 (n) trifluoromethyl;
 R⁴, R⁶, R^{6'}, and R⁹ are:
 (a) the same or different and are independently hydrogen, halogen, lower alkyl, or lower alkoxy, substituted alkyl, (CH₂)_n-alkenyl, (CH₂)_n-alkynyl, (CH₂)_n-cyano, amino, aminoalkoxy, phenoxy, hydroxy, trifluoromethyl, mono- or dialkylamino, mono- or dialkylaminoalkoxy, thiol, thioalkyl, nitrile, nitro, carboxylic acid, carboxylic acid esters, carboxamides, SO₃Z, PO₃Z, aminoalkanoyl, aminocarbonyl, amino-C₃-C₇-cycloalkylcarbonyl, and N-mono- or N,N-dialkylaminocarbonyl;
 (b) the same or different and are independently (CH₂)_n-aryl, (CH₂)_n-heteroaryl, arylalkyl, or heteroarylalkyl, wherein each aryl and heteroaryl is unsubstituted or substituted with up to five groups selected from halogen, hydroxy, lower alkyl, trifluoromethyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, lower alkoxy, amino, mono- or dialkylamino, trifluoromethyl, thiol, thioalkyl, nitrile, nitro, carboxylic acid, carboxylic acid esters, carboxamide, SO₃Z, and PO₃Z;
 R⁸ is:
 (a) hydrogen, lower alkyl, substituted alkyl, (CH₂)_n-alkenyl, (CH₂)_n-alkynyl, or a (CH₂)_n-carbocyclic group containing from 3-7 members, up to two of which members are heteroatoms selected from oxygen and nitrogen, wherein the carbocyclic group is unsubstituted or substituted with one, two or three groups selected from the group consisting of halogen, hydroxy, lower alkyl, lower alkoxy, acetoxy, mono- or dialkylamino, aryl and heteroaryl;
 (b) (CH₂)_n-aryl, (CH₂)_n-heteroaryl, arylalkyl, or heteroarylalkyl, wherein each aryl or heteroaryl is unsubstituted or substituted with up to five groups selected from the group consisting of halogen, hydroxy, lower alkyl, substituted alkyl, lower alkoxy, amino, mono- or dialkylamino and trifluoromethyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl,

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thiol, thioalkyl, nitrile, nitro, carboxylic acid, carboxylic acid esters, carboxamides, SO₃Z, and PO₃Z; and

n is an integer from 0 to 6;

provided that R⁸ is other than hydrogen or C₁-C₃ alkyl when R² is methyl, ethyl, or acetyl.

It is noted that when R⁴ in Formula Ia is OH, then Ia is the tautomer of Id.

It will also be noted that R⁶ and R⁷ can be taken together to form 6-keto compounds such as Formula Ib:

The present invention also provides a pharmaceutically acceptable composition that comprises a compound of Formulas Ia, Ib, Ic, Id, and Ie together with a pharmaceutically acceptable carrier, diluent, or excipient.

The present invention also provides methods for inhibiting cell cycle regulatory kinases such as cyclin-dependent kinase, Wee 1 and growth factor-mediated tyrosine kinase enzymes comprising administering a pteridine of the above formulas to a mammal.

The present invention also provides a method of treating subjects suffering from diseases caused by cellular proliferation. The method comprises inhibiting proliferation of tumorigenic cells of epithelial origin and vascular smooth muscle proliferation, and/or cellular migration, by administering a therapeutically effective amount of a compound of Formulas Ia, Ib, Ic, Id, and Ie to a subject in need of treatment.

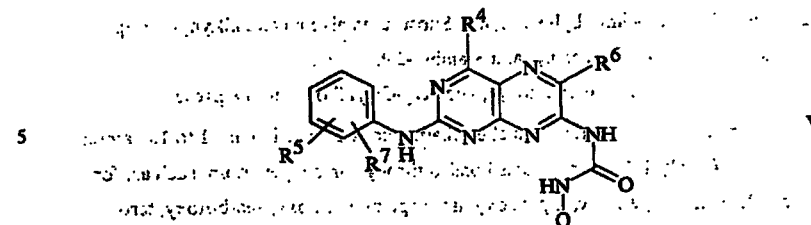
The invention also provides the above compounds useful in the diagnosis and treatment of cancer, psoriasis, vascular smooth muscle cell proliferation associated with atherosclerosis and postsurgical vascular stenosis and restenosis in mammals.

The present invention also provides a method of treating subjects suffering from diseases caused by DNA tumor viruses such as herpes viruses comprising administering a pteridine of the above formulas.

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More preferred compounds of Formula IVc are those wherein R⁸ is cyclopentyl and R⁵ is in the 4-position and represents morpholin-4-yl, 4-piperazin-1-yl, or 4-methylpiperazin-1-yl.

In addition, the present invention also provides compounds of Formula V:



wherein R⁴, R⁶, and Q are as defined above for Formulas Ia, Ib, Ic, Id, and Ie, and R⁵ and R⁷ are defined as defined above for Formula II.

Preferred compounds of Formula V are those wherein R⁴ is hydrogen, R⁶ is aryl, pyridyl, hydrogen or lower alkyl, Q is lower alkyl, R⁵ is halogen or

hydrogen and R⁷ is lower alkyl, unsubstituted or substituted with a carbocyclic group containing from 3-7 members, up to two of which members are hetero atoms selected from oxygen and nitrogen, wherein the carbocyclic group is unsubstituted or substituted with lower alkyl, acyl, amino, or mono- or dialkylamino.

More preferred compounds of Formula V are those wherein R⁷ is lower alkyl unsubstituted or substituted with morpholine, piperidine, piperazine, or pyrrolidine, each of which is unsubstituted or independently substituted with lower alkyl, amino or mono- or dialkylamino.

By "alkyl", "lower alkyl", and "C₁-C₁₀ alkyl" in the present invention is meant straight or branched chain alkyl groups having 1-10 carbon atoms, such as preferably C₁-C₆, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, pentyl, 2-pentyl, isopentyl, neopentyl, hexyl, 2-hexyl, 3-hexyl, decyl, octyl, and 3-methylpentyl. These groups may be substituted, for instance with halo, amino,

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alkyl, and dialkylamino, hydroxy and the like. Examples include chloromethyl, 2-amino ethyl, and 3-dimethyl-aminopropyl.

"Alkenyl" and "alkynyl" mean C₂-C₁₀ carbon chains having one or two nonadjacent double or triple bonds, respectively. Preferred are C₂-C₆ alkenyl such as 3-butenyl and 1-methyl-3-pentenyl. Typical C₂-C₆ alkynyl groups include 2-propynyl and 1,1-dimethyl-3-butyne. Substituted alkenyl and alkynyl groups include 4,4-dibromo-2-pentenyl and 3-amino-5-hexynyl.

By "alkoxy", "lower alkoxy", and "C₁-C₁₀ alkoxy" in the present invention is meant straight or branched chain alkoxy groups having 1 to 10 carbon atoms, preferably 1-6 carbon atoms bonded through an oxygen atom, such as, for example, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, sec-butoxy, tert-butoxy, pentoxy, 2-pentyloxy, isopentoxy, neopentoxy, hexoxy, 2-hexoxy, 3-hexoxy, and 3-methylpentoxy. These alkoxy groups may be substituted, for example with amino, alkylamino, and dialkylamino groups. Examples include aminomethoxy, 2-(methylamino)ethoxy, and 4-(dimethylamino)butoxy.

The term "alkanoyl" means an alkyl group bonded through a carbonyl moiety. Examples include acetyl and pentanoyl. "Aminoalkanoyl" means the alkyl group is substituted with an amino group. Examples include aminoacetyl and 3-aminohexanoyl. "Alkylaminoalkanoyl" means an aminoalkanoyl group wherein the amine is substituted with a C₁-C₁₀ alkyl group, and includes methylaminoacetyl and 4-(isobutylamino)octanoyl. "Dialkylaminoalkanoyl" means an N,N-di-substituted aminoalkanoyl group such as diisopropylaminoacetyl.

The term "aminocarbonyl" means an amino group bonded through a carbonyl group, for example aminoformyl. "Alkylaminocarbonyl" includes groups such as methylaminoformyl, and "dialkylaminocarbonyl" includes groups such as diethylaminoformyl.

By the term "halogen" in the present invention is meant fluorine, bromine, chlorine, and iodine.

"Alkylthio" means the above C₁-C₁₀ alkyl groups bonded through a sulfur atom. Examples include methylthio, isopropylthio, decylthio, and 1,1-dimethylbutylthio.

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By "aryl" is meant an aromatic carbocyclic group having a single ring (e.g., phenyl), multiple rings (e.g., biphenyl), or multiple condensed rings in which at least one is aromatic (e.g., 1,2,3,4-tetrahydronaphthyl, naphthyl, anthryl, or phenanthryl), which can be mono-, di-, trisubstituted or tetrasubstituted with, e.g., halogen, lower alkyl, lower alkoxy, lower alkylthio, trifluoromethyl, lower acyloxy, aryl, heteroaryl, amino, and hydroxy. A preferred aryl is phenyl and substituted phenyl, including 2,6-dichlorophenyl, 3-methoxyphenyl, 2,3-difluoro-4-methoxy-5-trifluoromethylphenyl, 2-chloro-6-bromophenyl, 3,5-diethoxyphenyl, 2,6-dimethylphenyl, 2,6-dichloro-3-hydroxyphenyl, 2,6-dichloro-4-hydroxyphenyl, 3-aminophenyl, 4-aminophenyl, 2-chloro-6-methoxyphenyl, 2-chloro-6-hydroxyphenyl, 2,6-dichloro-4-aminophenyl, and 2,6-dichloro-3-aminophenyl.

By "heteroaryl" is meant one or more aromatic ring systems of 5-, 6-, or 7-members containing at least one and up to four heteroatoms selected from nitrogen, oxygen, or sulfur. Such heteroaryl groups include, for example, thienyl, furanyl, thiazolyl, imidazolyl, (is)oxazolyl, tetrazolyl, pyridyl, pyridonyl, pyrimidinyl, pyrazole, (iso)quinolinyl, naphthyridinyl, phthalimidyl, benzimidazolyl, benzoxazolyl. Preferred heteroaryls of the present invention are pyridyl, phthalimidyl and tetrazolyl. The heteroaryl group can be substituted with one, two, three, or four of the groups mentioned above for aryl, such as 2,3,4,6-tetrachloropyridyl and 2-methoxy-3-trifluoromethylthien-4-yl.

A "carbocyclic group" means a nonaromatic cyclic ring or fused rings having from 3 to 7 ring carbon members. Examples include cyclopropyl, cyclobutyl, and cycloheptyl. These rings may be substituted with one or more of the substituent groups mentioned above for aryl, for example alkyl, halo, amino, hydroxy, and alkoxy. Typical substituted carbocyclic groups include 2-chlorocyclopropyl, 2,3-diethoxycyclopentyl, and 2,2,4,4-tetrafluorocyclohexyl. The carbocyclic group may contain one or two heteroatoms selected from oxygen, sulfur, and nitrogen, and such ring systems are referred to as "heterocyclic". Examples include pyranyl, tetrahydrofuranyl, and dioxanyl. These heterocyclic groups may be substituted with up to four of the substituent groups mentioned for aryl to give groups such as 3-chloro-2-dioxanyl, and 3,5-dihydroxymorpholino.

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The pharmaceutical preparations of the invention are preferably in unit dosage form. In such form, the preparation is subdivided into unit doses, containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

The therapeutically effective dose of a compound of Formulas Ia, Ib, Ic, and Id will generally be from about 1 mg to about 100 mg/kg of body weight per day. Typical adult doses will be about 50 mg to about 800 mg per day. The quantity of active component in a unit dose preparation may be varied or adjusted from about 0.1 mg to about 500 mg, preferably about 0.5 mg to 100 mg according to the particular application and the potency of the active component. The composition can, if desired, also contain other compatible therapeutic agents. A subject in need of treatment with a compound of Formulas Ia, Ib, Ic, and Id is administered a dosage of about 1 to about 500 mg per day, either singly or in multiple doses over a 24-hour period.

The compounds of the present invention are capable of binding to and inhibiting the activity of protein kinases, such as *cdks*, Wee 1, PDGFR, EGFR, c-arc, and EGFR-FL. Cdk's form complexes with cyclins, and these complexes phosphorylate key proteins that regulate the progression of cells through the cell cycle (Meijer L., *Progress in Cell Cycle Research*, 1995;1:351-363). The compounds of this invention inhibit this phosphorylation and therefore can be used as anti-proliferative agents for the treatment of cancer and/or restenosis and other proliferative diseases.

Because of their inhibitory activity against *cdks* and other kinases, the compounds of the present invention are also useful research tools for studying the mechanism of action of those kinases, both in vitro and in vivo.

The pteridines of this invention can be prepared by any of several standard synthetic processes commonly utilized by those skilled in the art of organic chemistry. An illustration of a typical preparation of compounds of the present invention is shown in Scheme I. Although these schemes often indicate exact structures, those with ordinary skill in the art will appreciate that the methods

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8-cyclopentyl-2-[4-[4-(2-hydroxy-ethyl)-3,5-dimethyl-piperazin-1-yl]-phenylamino]-5-methyl-5,8-dihydro-6H-pteridin-7-one;
1-[4-(8-Isopropyl-5-methyl-7-oxo-5,6,7,8-tetrahydro-pteridin-2-ylamino)-phenyl]-pyrrolidine-3-carboxylic acid butylamide;
[4-[4-(8-Cyclopentyl-5-methyl-7-oxo-5,6,7,8-tetrahydro-pteridin-2-ylamino)-phenyl]-piperazin-1-yl]-acetic acid; and
6-(2,6-Dichloro-3-hydroxy-phenyl)-8-methyl-2-(4-morpholin-4-yl-phenylamino)-8H-pteridin-7-one.

EXAMPLE 6

The pharmaceutical utilities of pteridines of this invention are established by the following assays for kinase inhibition.

1. Wee 1 OY assay

These kinase assays are carried out on 96-well filter plates (Millipore, Cat. MADPNOB50) in 50 μ L kinase assay buffer (50 mM Tris, pH 8.0, 10 mM NaCl, 10 mM $MgCl_2$, 10 μ M ATP with 0.25 μ Ci [γ - ^{32} P]ATP, 1 mM DTT) with 0.1 μ g purified N-terminal truncated Wee 1 and 6 μ g poly(Orn, Tyr)4:1 (Sigma, P4534). The assay is started by adding ATP and incubating at room temperature for 20 minutes with shaking. The reactions are terminated by adding 50 μ L ice-cold 20% TCA (trichloroacetic acid) with 0.1 M sodium pyrophosphate and shaking the resultant mixture for 1 minute. The plate is then incubated at 4°C for 1 hour to allow protein to precipitate. These plates are then washed 5 times with 200 μ L ice-cold 10% TCA and with 0.1 M sodium pyrophosphate per wash. Twenty-five microliters scintillation liquid is then added to each well, and the plate is counted in Wallac's MicroBeta counter 1450. Results for several of the pteridines of the invention are shown in Table 2.

2. Cyclin-Dependent Kinase 4 (CDK4) Assay

Enzyme assays for IC₅₀ determinations (Table 1) and kinetic evaluation were performed in 96-well filter plates (Millipore MADVN6550). The total volume was 0.1 mL containing a final concentration of 20 mM TRIS

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(tris[hydroxymethyl]aminomethane); at pH 7.4, 50 mM NaCl, 1 mM dithiothreitol, 10 mM MgCl_2 , 25 μM ATP containing 0.25 μCi of ^{32}P ATP, 20 ng of cdk4/cyclin D₁ complex, 1 μg of retinoblastoma and appropriate dilutions of a compound of the present invention. All components except the ATP were added to the wells, and the plate was placed on a plate mixer for 2 minutes. The reaction was started by adding ^{32}P ATP and the plate incubated at 25°C for 15 minutes. The reaction was terminated by addition of 0.1 mL of 20% TCA. The plate was kept at 4°C for at least 1 hour to allow the substrate to precipitate. The wells were then washed five times with 0.2 mL of 10% TCA and ^{32}P incorporation determined with a beta plate counter (Wallac Inc., Gaithersburg, Maryland).

3. PDGF and FGF Receptor Tyrosine Kinase Assays

Full-length cDNAs for the mouse PDGF- β and human FGF-1 (fgf) receptor tyrosine kinases were obtained from J. Escobedo and prepared as described in *J. Biol. Chem.*, 1991;262:1482-1487. PCR primers were designed to amplify a fragment of DNA that codes for the intracellular tyrosine kinase domain. The fragment was inserted into a baculovirus vector, cotransfected with AcMNPV DNA, and the recombinant virus isolated. SF9 insect cells were infected with the virus to overexpress the protein, and the cell lysate was used for the assay. Assays were performed in 96-well plates (100 μL /incubation/well), and conditions were optimized to measure the incorporation of ^{32}P from γ - ^{32}P -ATP into a glutamate-tyrosine co-polymer substrate. Briefly, to each well was added 82.5 μL of incubation buffer containing 25 mM Hepes (pH 7.0), 150 mM NaCl, 0.1% Triton X-100, 0.2 mM PMSF, 0.2 mM Na_3VO_4 , 10 mM MnCl_2 , and 750 $\mu\text{g}/\text{mL}$ of Poly (4:1) glutamate-tyrosine followed by 2.5 μL of inhibitor and 5 μL of enzyme lysate (7.5 $\mu\text{g}/\mu\text{L}$ FGF-TK or 6.0 $\mu\text{g}/\mu\text{L}$ PDGF-TK) to initiate the reaction. Following a 10 minute incubation at 25°C, 10 μL of γ - ^{32}P -ATP (0.4 μCi plus 50 μM ATP) was added to each well, and samples were incubated for an additional 10 minutes at 25°C. The reaction was terminated by the addition of 100 μL of 30% TCA containing 20 mM sodium pyrophosphate and precipitation of material onto glass fiber mats (Wallac). Filters were washed three times with

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15% TCA containing 100 mM sodium pyrophosphate, and the radioactivity retained on the filters counted in a Wallac 1250 Betaplate reader. Nonspecific activity was defined as radioactivity retained on the filters following incubation of samples with buffer alone (no enzyme). Specific enzymatic activity (enzyme plus buffer) was defined as total activity minus nonspecific activity. The concentration of a compound that inhibited specific activity by 50% (IC_{50}) was determined based on the inhibition curve.

4. C-src Kinase Assays

C-src kinase was purified from baculovirus infected insect cell lysates using an antipeptide monoclonal antibody directed against the N-terminal amino acids (amino acids 2-17) of c-src. The antibody, covalently linked to 0.65 μm latex beads, was added to a suspension of insect cell lysis buffer comprised of 150 mM NaCl, 50 mM Tris pH 7.5, 1 mM DTT, 1% NP-40, 12 mM EGTA, 1 mM sodium vanadate, 1 mM PMSF, 1 $\mu\text{g}/\text{mL}$ each of leupeptin, pepstatin, and aprotinin. Insect cell lysate containing c-src protein was incubated with these beads for 3 to 4 hours at 4°C with rotation. At the end of the lysate incubation, the beads were rinsed three times in lysis buffer, resuspended in lysis buffer containing 10% glycerol, and frozen. These latex beads were thawed, rinsed three times in assay buffer (40 mM Tris, pH 7.5, 5 mM MgCl_2) and suspended in the same buffer. In a Millipore 96-well plate with a 0.65 μm polyvinylidene membrane bottom were added the reaction components: 10 μL C-src beads, 10 μL of 2.5 mg/mL poly GluTyr substrate, 5 μM ATP containing 0.2 μCi labeled ^{32}P -ATP, 5 μL DMSO containing inhibitors or as a solvent control, and buffer to make the final volume 125 μL . The reaction was started at room temperature by addition of the ATP and quenched 10 minutes later by the addition of 125 μL of 30% TCA, 0.1 M sodium pyrophosphate for 5 minutes on ice. The plate was then filtered and the wells washed with two 250 μL aliquots of 15% TCA, 0.1 M pyrophosphate. The filters were then punched, counted in a liquid scintillation counter, and the data examined for inhibitory activity in comparison to a known inhibitor such as erbstatin. The method is also described in *J. Med. Chem.*, 1994;37:598-609.

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5. Cyclin-Dependent Kinase Assays (cdk2/cyclinE, cdk2/cyclinA, cdc2/cyclinB)

Enzyme assays for IC₅₀ determinations and kinetic evaluation were performed in a 96-well filter-plate (Millipore MADVN6550) in a total volume of 0.1 mL of 20 mM TRIS, pH 7.4, 50 mM NaCl, 1 mM dithiothreitol, 10 mM MgCl₂, 12 μM ATP containing 0.25 μCi of [³²P]ATP, 20 ng of enzyme (either cdk2/cyclinE, cdk2/cyclinA, or cdc2/cyclinB); 1 μg retinoblastoma, and appropriate dilutions of the particular invention compound. All components except the ATP were added to the wells, and the plate was placed on a plate mixer for 2 minutes. The reaction was begun by addition of [³²P]ATP, and the plate was incubated at 25°C for 15 minutes. The reaction was terminated by addition of 0.1 mL of 20% TCA. The plate was kept at 4°C for at least 1 hour to allow the substrate to precipitate. The wells were then washed five times with 0.2 mL of 10% TCA and ³²P incorporation determined using a beta plate counter (Wallac Inc., Gaithersburg, Maryland).

Several of the invention compounds exhibited good inhibitory activity when evaluated in the foregoing assays, as illustrated by the data in Table 2.

In the table, the columns have the following meanings:

C-src means C-src kinase

FGF means full length fibroblast growth factor receptor kinase

PDGF means platelet derived growth factor kinase

CDK4D means cyclin-dependent kinase 4/cyclin D₁ complex

CDK2A means cyclin-dependent kinase 2/cyclin A complex

CDK1B means cyclin dependent kinase 1/cyclin B complex

CDK2E means cyclin dependent kinase 2/cyclin E complex

IC₅₀ means the concentration of test compound in micromoles to inhibit the activity of a specified kinase by 50 percent.

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Table 2

Cmpd No.	WEE1OY IC ₅₀ (μM)	C-src IC ₅₀ (μM)	FGF IC ₅₀ (μM)	PDGF IC ₅₀ (μM)	CDK4D IC ₅₀ (μM)	CDK2A IC ₅₀ (μM)	CDK1B IC ₅₀ (μM)	CDK2E IC ₅₀ (μM)
1	>50	>50	>50	>50				
2	0.1445	0.057	>50	7.7				
3	>50	1.53	54% @ 5	7.55				
4	0.8605	0.015	69% @ 5	0.70				
5	>50	>50	38% @ 5	>50				
6	0.987	0.29	0.05	3.13				
7	>50	8.47	33% @ 5	11.95	0.06	0.064		0.65
8	>50	3.35	41% @ 0.5	6	0.041	0.26		0.95
9	>50	3	41% @ 0.5	59% @ 5	0.047	2.78		41
10	>50	34	57% @ 50	>50	0.44	1.84		8
11	>50	11	31% @ 5	>50	1.25	0.036	0.354	0.05
12	1.01	0.38		25.4				
13	4.49	0.50	17% @ 5					
14			30					
15								
16		3.3			0.007	0.18	0.75	0.61
17				2.19	0.0435	0.094	0.4	1.9

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Table 2 (cont'd)

Cmpd No.	WEE10Y IC ₅₀ (μ m)	C-src IC ₅₀ (μ m)	FGF IC ₅₀ (μ m)	PDGF IC ₅₀ (μ m)	CDK4D IC ₅₀ (μ m)	CDK2A IC ₅₀ (μ m)	CDK1B IC ₅₀ (μ m)	CDK2E IC ₅₀ (μ m)
18	>50	20	0.23					
19	7.4	1.45						
20	7.07	0.12						
21	>50	6.8	0.054					
22	>50	47	0.16					
23								
24		4.35						
52		>50			1.8	0.53		4.5
53								
62	0.077							

The following examples further illustrate typical pharmaceutical formulations provided by this invention.

Example 7

Preparation of Pharmaceutical Compositions

- 5 1. A pharmaceutical formulation in the form of hard gelatin capsules for oral administration are prepared using the following ingredients:

	Quantity (mg/capsule)
Active compound	250
Starch powder	200
Magnesium stearate	10
Total	460 mg

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES

202075
Bogotá, D.C.,

Abogado
EMILIO FERRERO.

ASUNTO	Radicación	04020069
	Trámite	002
	Evento	001
	Actuación	430
	Oficio	No 5 9 3 6
	Folios	013

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:

Documentos estudiados

Descripción: Folios: 132 a 218 como se radicó inicialmente.

Reivindicaciones: Folios: 219 a 225 como se radicó inicialmente.
Folios: 323 a 331

Respuesta del solicitante: Folios 309 a 321.

Prioridad: Folio 2 (4 de Septiembre de 2001, DE10143272.0).

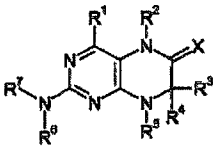
Objeto de la invención

Título de la solicitud:

- Nuevas dihidro-pteridinonas, procedimientos para su preparación y su utilización como medicamentos (original).
- Nuevas dihidro-pteridinonas Folio 332. Modificado

El objeto de la presente solicitud de patente de invención consiste en:
Nuevos compuestos derivados dihidro-pteridinonas.

Reivindicaciones 1—4 : Compuestos de fórmula general (I):



Reivindicación 5 : Preparaciones farmacéuticas que lo contienen.

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El problema planteado en esta solicitud es la necesidad de compuestos que se caracterizan por ser inhibidores de específicas cinasas del ciclo celular . en particular el efecto inhibidor sobre la proliferación de células tumorales excesiva o anómala. Entre estas comprenden las infecciones víricas (VIH), inflamación y enfermedades autoinmunitarias (colitis, artritis, Alzheimer, glomerulonefritis), infecciones bacterianas, fúngicas, parasitarias, leucemias, linfomas y tumores sólidos, psoriasis, enfermedades de los huesos, cardiovasculares (hipertrofia) entre otras.

Para solucionar este problema técnico la solicitud en estudio proporciona compuestos de fórmula (I), y preparaciones farmacéuticas que los contienen.

El objeto de la invención definido anteriormente se clasifico de acuerdo con la Clasificación Internacional de Patentes (IPC) : A61K31/505, C07D487/04, AP61P35/00 y AP61P31/18..

De la solicitud de Patente

Reivindicaciones (artículo 30 D 486)

- Para la reivindicación 1 en R², se refiere a " y opcionalmente un grupo alquilo C1-C3 sustituido". Sin embargo el significado correcto sería "un grupo alquilo C1-C3 opcionalmente sustituido".
- La frase " a menos donde se establezca otra cosa" en los folios 324 y 326 es ambiguo y debe ser eliminado.
- El término " y sistemas de anillos bicíclicos saturados o insaturados" folio 324 último párrafo , no es conciso, ya que no hace referencia a los átomos de carbono que lo conforman y si puede contener heteroátomos o no.
- El término alquilo-O-C₁-C₃- en el folio 325, último párrafo no es correcto. La corrección sería -O-alquilo -C₁-C₃.
- El solicitante define los grupos arilo , heteroarilo, y heterocicloalquilo por el número de miembros o átomos de carbono que los conforman; sin embargo no siguen siendo concisos , ya que dentro de la descripción no hay sustento de que todos los grupos arilos , heteroarilos y heterocicloalquilos definidos de esta manera presenten la misma actividad.

Determinación del Estado de la Técnica

Considerando que la fecha de presentación de la primera solicitud de patente de la cual se reivindica prioridad es 04 de Septiembre de 2001, se consultaron las bases de datos y los archivos con que cuenta la entidad con fecha de publicación anterior y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud :

N°	Documento	Título	Fecha de Publicación*
D2	WO0119825	PTERIDINONES AS KINASE INHIBITORS	22 de Marzo del 2001

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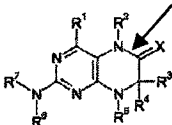
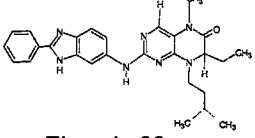
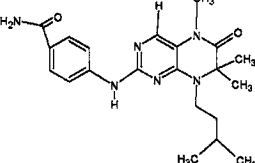
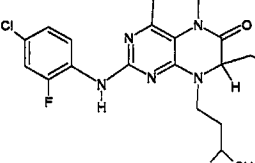
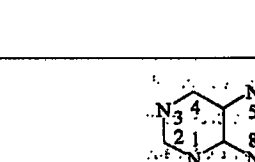
Análisis de patentabilidad (artículo 14 D486)

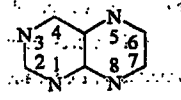
Nivel inventivo (artículo 18 D486)

La reivindicación 1 dice “ Compuestos de fórmula general I ”.

Respecto al estado de la técnica.

D2 (Folios 342-349) , enseña compuestos derivados de pteridinonas, caracterizados por ser inhibidores de las cinasas del ciclo celular, los cuales son útiles en el tratamiento de enfermedades proliferativas celulares tales como cáncer, infecciones virales como el VIH , infecciones fúngicas, Alzheimer, psoriasis, artritis, entre otras.

SOLICITUD		D2
R ¹ es hidrógeno, NH ₂ , XH, halógeno y un grupo alquilo C ₁ -C ₃ opcionalmente sustituido por uno o más átomos de halógeno.		R ⁴ es hidrógeno, amino, hidroxilo, tior, halógeno, alquilo bajo, alquilo sustituido por halógeno
R ² es hidrógeno, CHO, XH, -X-alquilo- C ₁ -C ₂ , un grupo alquilo C ₁ -C ₃ opcionalmente sustituido.		R ⁹ es hidrógeno, hidroxilo, tior, alcoxi bajo, alquilo bajo, alquilo sustituido.
R ³ y R ⁴ son alquilo C ₁ -C ₁₀ opcionalmente sustituido, alqueno C ₂ -C ₁₀ , alquino C ₂ -C ₁₀ , arilo, heteroarilo, X-arilo, hidrógeno, halógeno, COXR ⁸ , CON(R ⁸) ₂ , hidroxilo, tior		R ⁶ y R ⁶ son alquilo bajo o alquilo sustituido, alqueno, alquino, arilo, heteroarilo, fenoxi, hidrógeno, halógeno, ácido carboxílico, ésteres de ácidos carboxílicos, hidroxilo, tior.
R ⁵ es hidrógeno, alquilo C ₁ -C ₁₀ Opcionalmente sustituido, alqueno C ₂ -C ₁₀ , alquino C ₂ -C ₁₀ , arilo, heteroarilo, cicloalquilo C ₃ -C ₆		R ⁸ es hidrógeno, alquilo bajo, alquilo sustituido, alqueno, alquino, arilo, heteroarilo, un grupo carbocíclico de 3-7 miembros.
R ⁶ es arilo o heteroarilo, opcionalmente sustituido.		R ² es (CH ₂) _n -arilo o (CH ₂) _n -heteroarilo, en el cual n es 0. Los cuales pueden estar opcionalmente sustituido.
R ⁷ es hidrógeno, -CO-X- alquilo C ₁ -C ₄ ,		
X es O o S.		W es NH.



La solicitud se diferencia de D1 en que el grupo carbonilo se encuentra en la posición 6 del anillo de la pteridinona.

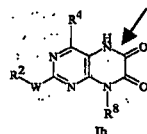
Esta diferencia no parece conceder un efecto técnico inesperado ò una ventaja a las compuestos reclamados en esta solicitud ya que no parecen presentar una mayor actividad inhibitoria de específicas cinasas del ciclo celular (Ver folios 210-214,) en comparación con los compuestos del estado de la técnica más cercano (Ver folios

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346-349, ejemplo 6, páginas 79-84).

El Problema Técnico Objetivo de esta solicitud es la necesidad de compuestos caracterizados por ser inhibidores de específicas cinasas del ciclo celular alternativos a los ya conocidos en el estado del arte.



D2 divulga que dicho grupo carbonilo (Folio 342, página 4, compuesto de fórmula de Ib) puede también estar en la posición 7 de la pteridinona

El Experto en la Materia, enfrentado al Problema Técnico Objetivo y conociendo el Estado de la Técnica (D2) hubiera sugerido sin mucho esfuerzo de su parte modificar la posición del grupo carbonilo en el anillo de la pteridinona (de la posición 7 a la posición 6) de acuerdo a las enseñanzas de D2 para obtener más compuestos con la misma actividad.

De manera que la solución propuesta al problema técnico planteado en esta solicitud en la reivindicación 1 y sus dependientes 2-4, es obvia y no tiene Nivel Inventivo.

La preparación farmacéutica de la Reivindicación 5 no se considera inventiva porque el compuesto que la caracteriza no es inventivo.

Respuesta a los argumentos del solicitante.

- Los argumentos expuestos por el solicitante en cuanto a la claridad de la solicitud, son aceptados por este Despacho en respuesta al primer examen de fondo.
- El solicitante argumenta que el documento EP0429149, en fase internacional fue clasificado como "A", el cual no tiene ninguna relevancia con relación a la solicitud estudiada.
- La solicitud ya fue otorgada en otros países como Estados Unidos y en Europa sin restricción de las reivindicaciones.

En cuanto a que el documento D1 en fase internacional fue citado en el informe de búsqueda internacional como un documento de categoría A, este Despacho demostró que dicho documento demostró en el primer examen de fondo de manera clara e inequívoca que afectaba la novedad de la actual solicitud (Ver folio 306). Sin embargo debido a las restricciones realizadas en el nuevo capítulo reivindicatorio presentado por el solicitante, dicho documento no es tenido en cuenta para el segundo examen de fondo.

Y por último la concesión de una patente en un país no determina su otorgamiento automático en otro, más aún atendiendo al principio de territorialidad mediante el cual los derechos de propiedad industrial se circunscriben al país en el que se concedieron y a su legislación vigente.

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Conclusión:

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

N°	Documento N°	Reivindicaciones Afectadas	Requisito que Afecta
D2	WO0119825	1-5	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.

Notifíquese el presente oficio conforme a lo dispuesto en el artículo 8 de la resolución reglamentaria No. 00210 del 15 de enero de 2001, advirtiéndole que contra él no procede recurso alguno en la vía gubernativa.

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de División de Nuevas Creaciones

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

22 MAYO 2009

CONCEPTO TECNICO No. 1039	EXAMINADOR TECNICO Código No. 202075
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