

Clarke, Modet & C^o

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173 177
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 06-037930-00007-0000

Fecha: 2009-11-18 14:58:41 Dep. 2020 NUECREACIONES
Tra. 11 PATENTE IYI Eve: 378 FASE NACIONAL I
Act 444 RESPUESTA REQUE Folios: 8

P-1939

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
E. S. D.

Re: Expediente No. 06.037.930

Solicitud de patente a nombre de **Ortho-McNeil-Janssen Pharmaceuticals, Inc.**

Yo, DILLA RODRIGUEZ D'ALEMAN, identificada como aparece al pie de mi firma, domiciliada en la carrera 11 No. 86-53, piso 6, obrando como apoderada de la sociedad **Ortho-McNeil-Janssen Pharmaceuticals, Inc.**, domiciliada en Titusville, New Jersey, Estados Unidos de América, solicitante de la patente de la referencia, en respuesta al oficio No. 7673 notificado por fijación en lista el 10 de julio de 2009, relacionado con el concepto técnico de fondo No. 2220, cuyo término fue prorrogado mediante escrito radicado el 5 de octubre de 2009, me permito manifestar:

1. Con fundamento en la facultad que confiere el artículo 34 de la Decisión 486 al solicitante para modificar la solicitud de patente en cualquier momento del trámite, presento junto con este memorial un nuevo capítulo reivindicatorio, el cual consta de 17 reivindicaciones con las cuales se subsanan las objeciones presentadas a la patentabilidad de la solicitud.

En cuanto a estas modificaciones, me permito decir que las mismas no amplían de ninguna manera la materia objeto de la presente solicitud y se realizaron con el ánimo de superar las objeciones de patentabilidad, planteadas por el examinador en su concepto técnico, relacionadas con la unidad de la invención.

2. Claridad de la Invención

El examinador objeta la claridad del capítulo reivindicatorio argumentando que los términos empleados para definir los sustituyentes son demasiado amplios y le restan claridad y concisión al mismo. Al respecto, el solicitante quisiera anotar que el objeto de las reivindicaciones independientes es el de establecer la materia de la invención de la manera más completa y abierta posible, en tanto que el objeto de las reivindicaciones dependientes es el de estrechar el alcance de la reivindicación de la cual dependen hasta su forma más particular.

Con esto en mente, el examinador notará que las reivindicaciones cumplen a cabalidad su objetivo por lo que el solicitante no considera necesario delimitar las definiciones dadas a los sustituyentes en las reivindicaciones 1 a 6.

P-1939

3. Excepciones a la Patentabilidad

El examinador objeta la patentabilidad de las reivindicaciones 19 a 26 por tratarse de métodos de tratamiento. Con el fin de subsanar dicha objeción, el solicitante elimina las reivindicaciones en cuestión.

4. Novedad

El examinador objeta el nivel inventivo de la presente solicitud, argumentando que las anterioridades D1 y D2 ya enseñaban lo mismo que el solicitante desea proteger.

En cuanto al estudio de la novedad, cabe recordar que la novedad solo se ve afectada si todas y cada una de las características de la invención se encuentran contenidas en el estado de la técnica. No basta con que algunas de las características se compartan entre las dos solicitudes, sino que debe ser posible identificar absolutamente todos los elementos reivindicados para poder afirmar que una invención carece de novedad.

En este sentido, me permito manifestar que el artículo 16 de la Decisión 486 de la Comisión de la Comunidad Andina establece que la invención se considera como nueva cuando no está comprendida en el estado de la técnica.

Si de acuerdo con el espíritu de la norma legal indicada anteriormente, la invención no se considera como nueva si está "*comprendida*" en el estado de la técnica, dicha norma se está refiriendo, naturalmente, a la *totalidad del invento y no a alguno o a algunos de los componentes*. Para que la invención pierda su calidad de novedosa, es claro que **TODA ELLA**, ha de estar contenida en el "*conjunto de conocimientos existentes que son aplicables al proceso industrial*" como define el estado de la técnica el Tribunal de justicia del Acuerdo de Cartagena (Proceso No. 6-IP-89, sentencia de 31 de octubre de 1989, publicada en Jurisprudencia del Tribunal de Justicia del Acuerdo de Cartagena, Tomo 11, BID-INTAL, Buenos Aires, 1994, página 60).

Esto se conoce como **NOVEDAD ABSOLUTA**, de conformidad con lo cual para desvirtuar el requisito de novedad de una invención será necesario que lo reivindicado por la invención bajo estudio corresponda de forma total con lo revelado en un documento o anterioridad señalada, conclusión a la que se llega después de un análisis íntegro mediante una comparación entre el capítulo reivindicatorio de la invención en estudio y las anterioridades D1, D7 y D8.

Es necesario resaltar que el examinador esta considerando los aspectos generales de la invención, sin tener en cuenta que son las particularidades las que conceden la novedad.

Ahora bien, si un determinado elemento, condición o circunstancia de la nueva creación ya hace parte del estado de la técnica, no quiere ello decir, desde luego, que la invención deba ser rechazada por carecer del requisito de novedad. No sin razón ha dicho el mencionado Tribunal: *"hay que advertir que toda creación es en cierta forma, producto del estado de la técnica existente, en el sentido de que el inventor ha de tener en cuenta un conjunto de conocimientos técnicos que le permitan crear nuevos procedimientos aplicables a la industria"* (Ibidem, páginas 53 y 54) (el subrayado es mío).

Por lo tanto, como mínimo la novedad debe contemplar los siguientes aspectos:

-Que la invención en estudio esté contenida de forma **TOTAL y ABSOLUTA** en el documento que se menciona como anterioridad o de forma independiente en los documentos que se mencionan, si son varios; y

-Que la invención en estudio puede partir de conocimientos conocidos, caso en el cual habrá que hacer la comparación no de lo conocido sino de lo inédito y novedoso, teniendo que analizarse el valor agregado que aporta la invención con sus nuevas características al campo técnico al cual pertenece la invención en estudio.

Aplicando lo anterior al caso concreto, para que las razones que aduce ese despacho para desvirtuar la novedad fuesen ciertas, sería forzoso que se demostrara que la invención de mi mandante esté comprendida en el estado de la técnica de forma **TOTAL**, lo cual no sucede como se demuestra a continuación.

En primer lugar, el solicitante quisiera anotar que con el fin de subsanar las objeciones presentadas a la novedad de la presente solicitud ha fijado el radical R⁴ como NH₂, lo cual la hace claramente diferente de lo divulgado por la anterioridad D1. A la luz de lo establecido más arriba, dicha diferencia es característica suficiente para reconocer la novedad de la presente solicitud.

En cuanto a la anterioridad D2, al fijar el sustituyente R⁴ como NH₂, también se esta diferenciando la materia del capítulo reivindicatorio en estudio. Como si esto no fuera poco, la materia objeto de la anterioridad D2 se relaciona con compuestos agrícolas en tanto que la presente solicitud se relaciona con medicamentos. Esta diferencia por si misma es suficiente para reconocer la novedad de los compuestos de la presente solicitud por sobre D2, a la luz de lo establecido por la jurisprudencia antes citada.

176/181

Clarke, Modet & C^o

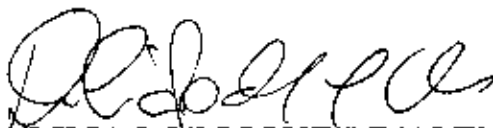
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4

En conclusión, gracias a los argumentos anteriormente mencionados la presente solicitud cumple cabalmente con los requisitos de claridad y novedad respecto a los compuestos divulgados en el capítulo reivindicatorio adjunto. Por lo tanto, solicito comedidamente a ese despacho se sirva reconocer estos requisitos y conceder el privilegio de patente de invención a la solicitud en estudio.

En consecuencia, solicitamos a ese despacho pronunciarse en relación con todos los argumentos presentados en este memorial dando estricta aplicación al principio del debido proceso consagrado en el artículo 29 de la Constitución Nacional. De igual forma, si el examinador considera que subsisten razones para objetar la presente invención ruego expedir otro examen de fondo con los debidos motivos y razones que sustenten su objeción con el fin de que mi mandante tenga la posibilidad de exponer sus argumentos con base en la interpretación de los artículos 45 de la Decisión 486 -el cual otorga la facultad al examinador para emitir los exámenes de fondo-, 35 y 59 del Código Contencioso Administrativo que señala que: *"habiéndose dado oportunidad a los interesados para expresar sus opiniones, y con base en las pruebas e informes disponibles, se tomará la decisión que será motivada al menos en forma sumaria si afecta a particulares"* y *"(..) deberá proferirse la decisión definitiva. Esta se motivará en sus aspectos de hecho y de derecho, y en los de conveniencia si es el caso"*, respectivamente (el subrayado es nuestro).

Señor Superintendente,



DILIA RODRIGUEZ D'ALEMAN

CC. 41.654.882 de Bogotá

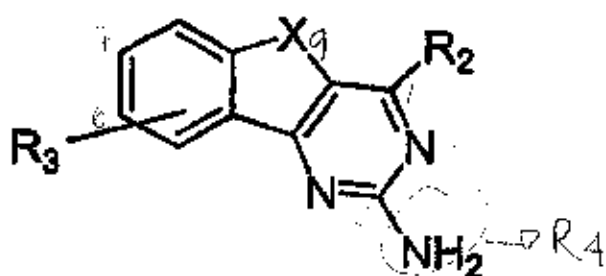
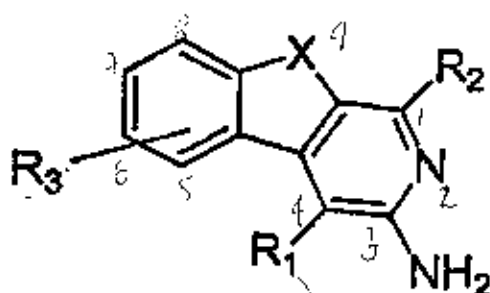
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177
181**REIVINDICACIONES**

1.- Un compuesto que tiene la estructura de la fórmula I o II

**Formula I****Formula II**

o una sal farmacéuticamente aceptable del mismo, en donde

(a) (R_1) se selecciona del grupo que consiste de

(i) $-COR_5$, en donde R_5 se selecciona de H, alquilo de C_{1-8} de cadena recta o ramificada opcionalmente sustituido, arilo opcionalmente sustituido y arilalquilo opcionalmente sustituido; en donde los sustituyentes en el grupo alquilo, arilo y arilalquilo se seleccionan de alcoxi de C_{1-8} , fenilacetiloxi, hidroxil, halógeno, p-tosiloxi, mesiloxi, amino, ciano, carboalcoxi, o NR_7R_8 en donde R_7 y R_8 se seleccionan independientemente del grupo que consiste de hidrógeno, alquilo de C_{1-8} de cadena recta o ramificada, cicloalquilo de C_{3-7} , bencilo, arilo o heteroarilo o NR_7R_8 tomados juntos forman un heterociclo o heteroarilo;

(ii) $COOR_5$, en donde R_5 es como se definió antes;

(iii) ciano;

(iv) $-CONR_9R_{10}$ en donde R_9 y (R_{10}) se seleccionan independientemente de H, alquilo de C_{1-8} de cadena recta o ramificada, cicloalquilo de C_{3-7} , trifluorometilo, hidroxil, alcoxi, acilo, alquilcarbonilo, carboxilo, arilalquilo, arilo, heteroarilo y heterociclilo; en donde los grupos alquilo, cicloalquilo, alcoxi, acilo, alquilcarbonilo, carboxil, arilalquilo, arilo, heteroarilo y heterociclilo pueden ser sustituidos con carboxilo, alquilo, arilo, arilo sustituido, heterociclilo, heterociclilo sustituido, heteroarilo, heteroarilo sustituido, ácido hidroxámico, sulfonamida, sulfonilo, hidroxil, tiol, amino, alcoxi o arilalquilo, o R_9 y R_{10} tomados junto con el nitrógeno al cual están unidos forman un grupo heterociclo o heteroarilo;

(v) alquilo de C_{1-8} de cadena recta o ramificada opcionalmente sustituido; en donde los sustituyentes en el grupo alquilo se seleccionan de alcoxi de C_{1-8} , fenilacetiloxi, hidroxil, halógeno, p-tosiloxi, mesiloxi, amino, ciano, carboalcoxi, carboxil, arilo, heterociclilo, heteroarilo, sulfonilo, tiol, alquiloxi, o NR_7R_8 en donde R_7 y R_8 son como se definió antes;

(b) R_2 se selecciona del grupo que consiste de alquilo opcionalmente sustituido, arilo opcionalmente sustituido, heteroarilo opcionalmente sustituido, heterociclilo opcionalmente sustituido y cicloalquilo de C_{3-7}

→ sólo en anillo de piridina, oxadiazol, pirimidinas.

178
182

opcionalmente sustituido, alcoxi de C_{1-8} , ariloxi, alquilsulfonilo de C_{1-8} , arilsulfonilo, ariltio, o $-NR_{24}R_{25}$.

en donde R_{24} y R_{25} se seleccionan independientemente de H, alquilo de C_{1-8} de cadena recta o ramificada, arilalquilo, cicloalquilo de C_{3-7} , carboxialquilo, arilo, heteroarilo y heterociclilo o R_{24} y R_{25} tomados junto con el nitrógeno forman un grupo heteroarilo o heterociclilo,

- (c) R_3 es de uno a cuatro grupos independientemente seleccionados del grupo que consiste de: hidrógeno, halógeno, alquilo de C_{1-8} de cadena recta o ramificada, arilalquilo, cicloalquilo de C_{3-7} , alcoxi de C_{1-8} , ciano, carboalcoxi de C_{1-4} , trifluorometilo, alquilsulfonilo de C_{1-8} , halógeno, nitro, hidroxilo, trifluorometoxi, carboxilato de C_{1-8} , arilo, heteroarilo y heterociclilo, $-NR_{11}R_{12}$,

en donde R_{11} y R_{12} se seleccionan independientemente de H, alquilo de C_{1-8} de cadena recta o ramificada, arilalquilo, cicloalquilo de C_{3-7} , carboxialquilo, arilo, heteroarilo y heterociclilo, o R_{10} y R_{11} tomados junto con el nitrógeno forman un grupo heteroarilo o heterociclilo,

$-NR_{13}COR_{14}$,

en donde R_{13} se selecciona de hidrógeno o alquilo y R_{14} se selecciona de hidrógeno, alquilo, substituido alquilo, alcoxi de C_{1-3} , carboxialquilo, arilo, arilalquilo, heteroarilo, heterociclilo, $R_{15}R_{16}N(CH_2)_p$, o $R_{15}R_{16}NCO(CH_2)_p$, en donde R_{15} y R_{16} se seleccionan independientemente de H, OH, alquilo y alcoxi, y p es un entero de 1-6, en donde el grupo alquilo pueden ser sustituidos con carboxilo, alquilo, arilo, arilo substituido, heterociclilo, heterociclilo substituido, heteroarilo, heteroarilo substituido, ácido hidroxámico, sulfonamida, sulfonilo, hidroxilo, tiol, alcoxi o arilalquilo, o R_{13} y R_{14} tomados junto con el carbonilo forman un grupo heterociclilo que contiene carbonilo; y

- e) X se selecciona de $C=S$, $C=O$, CH_2 , $CHOH$, $CHOR_{19}$, o $CHNR_{20}R_{21}$ en donde R_{19} , R_{20} , y R_{21} se seleccionan de alquilo de C_{1-8} de cadena recta o ramificada opcionalmente sustituido, en donde los substituentes en el grupo alquilo se seleccionan de alcoxi de C_{1-8} , hidroxilo, halógeno, amino, ciano, o $NR_{22}R_{23}$ en donde R_{22} y R_{23} se seleccionan independientemente del grupo que consiste de hidrógeno, alquilo de C_{1-8} de cadena recta o ramificada, cicloalquilo de C_{3-7} , bencilo, arilo, heteroarilo, o $NR_{22}R_{23}$ tomados juntos forman a heterociclo or heteroarilo;

con la condición de que en un compuesto de la fórmula II cuando R_1 es un ciano, entonces R_2 no es fenilo.

2.- El compuesto de conformidad con la reivindicación 1, fórmula I, caracterizado además porque R_2 es arilo o heteroarilo.

3.- El compuesto de conformidad con la reivindicación 1, fórmula II, caracterizado además porque R_2 es arilo o heteroarilo.

4.- El compuesto de conformidad con la reivindicación 3, caracterizado además porque R_2 es furilo o furilo sustituido.

5.- El compuesto de conformidad con la reivindicación 3, caracterizado además porque R_1 es COOR_5 , en donde R_5 se selecciona de alquilo de C_{1-8} de cadena recta o ramificada opcionalmente sustituido.

6.- El compuesto de conformidad con la reivindicación 1, caracterizado además porque es 2-amino-4-furan-2-il-indeno[1,2-d]pirimidin-5-ona.

7.- El compuesto de conformidad con la reivindicación 1, caracterizado además porque es 2-amino-4-fenil-indeno[1,2-d]pirimidin-5-ona. (1)

8.- El compuesto de conformidad con la reivindicación 1, caracterizado además porque es 2-amino-4-tiofen-2-il-indeno[1,2-d]pirimidin-5-ona. (2)

9.- El compuesto de conformidad con la reivindicación 1, caracterizado además porque es 2-amino-4-(5-metil-furan-2-il)-indeno[1,2-d]pirimidin-5-ona. (3)

10.- El compuesto de conformidad con la reivindicación 1, caracterizado además porque es 2,6-diamino-4-furan-2-il-indeno[1,2-d]pirimidin-5-ona. (4)

11.- El compuesto de conformidad con la reivindicación 1, caracterizado además porque es 3-amino-1-furan-2-il-9-oxo-9H-indeno[2,1-c]piridin-4-carbonitrilo. (1)

12.- El compuesto de conformidad con la reivindicación 1, caracterizado además porque es éster 2-dimetilamino-etílico de ácido 3-amino-1-furan-2-il-9-oxo-9H-indeno[2,1-c]piridin-4-carboxílico. (2)

13.- El compuesto de conformidad con la reivindicación 1, caracterizado además porque es éster 2-dimetilamino-etílico de ácido 3-amino-1-fenil-9-oxo-9H-indeno[2,1-c]piridin-4-carboxílico. (3)

14.- El compuesto de conformidad con la reivindicación 1, caracterizado además porque es (2-dimetilamino-1-metil-etil)-amida de ácido 3-amino-1-furan-2-il-9-oxo-9H-indeno[2,1-c]piridin-4-carboxílico. (4)

15.- El compuesto de conformidad con la reivindicación 1, caracterizado además porque es (2-dimetilamino-etil)-metil-amida de ácido 3-amino-1-furan-2-il-9-oxo-9H-indeno[2,1-c]piridin-4-carboxílico. (5)

United States Patent [19]

Böttcher et al.

[11] Patent Number: 4,740,602

[45] Date of Patent: Apr. 26, 1988

[54] INDOLE DERIVATIVES

[75] Inventors: Heusing Böttcher, Darmstadt;
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Seeheim-Jungenheim; Klaus-Otto
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[21] Appl. No.: 878,539

[22] Filed: Jun. 26, 1986

[30] Foreign Application Priority Data

Jun. 27, 1985 [DE] Fed. Rep. of Germany 3522959

[51] Int. Cl.⁴ C07F 7/19

[52] U.S. Cl. 548/406; 546/80;
546/89; 546/93; 546/101; 546/111

[58] Field of Search 548/406

[56] References Cited

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1, 1982.

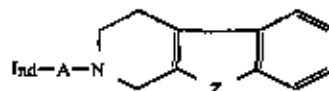
Primary Examiner—Richard A. Schwartz

Assistant Examiner—Zinna Northington

Attorney, Agent, or Firm—Millen & White

[57] ABSTRACT

New indole derivatives of the general formula I



in which

Ind is a 3-indolyl radical which can be substituted by
a hydroxymethyl, methylenedioxy, S-alkyl, SO-
alkyl, SO₂-alkyl, CN or COW group and/or can be
substituted once or twice by alkyl, O-alkyl, OH, F,
Cl or Br,

W is H, OH, O-alkyl, NH₂, NH-alkyl or N(alkyl)₂,
A is —(CH₂)_n—, —CH₂—S—CH₂CH₂—, —CH-
2—SO—CH₂CH₂— or —CH₂—SO₂—CH₂CH₂—,
is —(CH₂)_m—, —CH=CH—, —CHOH—, —CO—,
S, SO, SO₂ or O,

n is 2, 3, 4 or 5 and
m is 1, 2 or 3,

in which the alkyl groups each have 1–4 C atoms, and
their salts, have effects on the central nervous system.

1 Claim, No Drawings

INDOLE DERIVATIVES

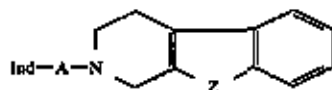
This invention relates to new indole derivatives having pharmacological properties.

SUMMARY OF THE INVENTION

It is an object of this invention to provide new compounds which can be used for the preparation of medicaments.

Upon further study of the specification and appended claims, further objects and advantages of this invention will become apparent to those skilled in the art.

These objects have been achieved by providing new indole derivatives of the general formula I



in which

Ind is a 3-indolyl radical which can be substituted by a hydroxymethyl, methylenedioxy, S-alkyl, SO-alkyl, SO₂-alkyl, CN or CO₂ group and/or can be substituted once or twice by alkyl, O-alkyl, OH, F, Cl or Br,

W is H, OH, O-alkyl, NH₂, NH-alkyl or N(alkyl)₂,

A is $-(CH_2)_n-$, $-CH_2-S-CH_2CH_2-$, $-CH_2-SO-CH_2CH_2-$ or $-CH_2-SO_2-CH_2CH_2-$,

Z is $-(CH_2)_m-$, $-CH=CH-$, $-CHO-$, $-CO-$, S, SO, SO₂ or O,

n is 2, 3, 4 or 5 and

m is 1, 2 or 3, in which the alkyl groups each have 1-4 C atoms, and to their salts.

DETAILED DISCUSSION

It has been found that the compounds of the formula I and their physiologically acceptable salts have valuable pharmacological properties. Thus, they exhibit, in particular, effects on the central nervous system, especially dopamine-stimulating presynaptic (neuroleptic) or postsynaptic (anti-Parkinson) effects. Specifically, the compounds of the formula I induce contralateral pivoting behavior in hemiparkinsonian rats (which can be determined by the method of Ungerstedt et al., Brain Res. 24 (1970), 485-493) and inhibit the binding of tritiated dopamine agonists and antagonists to striatal receptors (which can be determined by the method of Schwarcz et al., J. Neurochemistry 34 (1980), 772-778, and Creese et al., European J. Pharmacol. 46 (1977), 377-381). In addition, the compounds inhibit the linguomandibular reflex of anesthetized rats (which can be determined by a method based on that of Barnett et al., European J. Pharmacol. 21 (1973), 178-182, and of Ilhan et al., European J. Pharmacol. 33 (1975), 61-64).

Furthermore, analgesic and hypotensive effects occur; thus, the blood pressure measured directly in conscious, spontaneously hypertensive rats (strain: SHR/NIH-MO/CHB-EMD; for method, compare Weeks and Jones, Proc. Soc. Exptl. Biol. Med. 104 (1960), 646-648) fitted with catheters is reduced after intragastric administration of the compounds.

Hence, the compounds of the formula I and their physiologically acceptable salts can be used as active compounds in medicaments and as intermediates for the preparation of other active compounds in medicaments.

The invention relates to the indole derivatives of the formula I and to their salts.

Alkyl is the radicals Ind and W is preferably methyl, as well as ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl or tert-butyl. O-Alkyl is preferably methoxy, as well as ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy or tert-butoxy. S-Alkyl is preferably methylthio, as well as ethylthio, propylthio, isopropylthio, butylthio, isobutylthio, sec-butylthio or tert-butylthio. SO-Alkyl is preferably methylsulfinyl, as well as ethyl-, propyl-, isopropyl-, butyl-, isobutyl-, sec-butyl- or tert-butylsulfinyl, and SO₂-alkyl is preferably methylsulfonyl, as well as ethyl-, propyl-, isopropyl-, butyl-, isobutyl-, sec-butyl- or tert-butylsulfonyl.

The radical Ind is, in particular, an unsubstituted or singly substituted 3-indolyl radical. It is preferably substituted in the 5- or 6-position or in the 4- or 7-position. Substitution in the 1- or 2-position is also possible. Preferred disubstituted 3-indolyl radicals are substituted in the 5,6-position; disubstitution is also possible in the 1,2-, 1,4-, 1,5-, 1,6-, 1,7-, 2,4-, 2,5-, 2,6-, 2,7-, 4,5-, 4,6-, 4,7-, 5,7- or 6,7-position. In all these cases, the substituents can be identical or different.

Specifically preferred substituents in the benzene ring of the radical Ind are hydroxyl and methoxy, as well as methyl, ethyl, ethoxy, F, Cl, Br, methylthio, methylsulfinyl, methylsulfonyl, CN, hydroxymethyl, formyl, carboxyl, methoxycarbonyl or ethoxycarbonyl, carbamoyl, N-methyl-, N-ethyl-, N,N-dimethyl- and N,N-diethylcarbamoyl, as well as the other alkyl, O-alkyl, S-alkyl, SO-alkyl or SO₂-alkyl groups indicated above, as well as propoxy-, isopropoxy-, butoxy-, isobutoxy-, sec-butoxy- and tert-butoxycarbonyl, N-propyl-, N-isopropyl-, N-butyl-, N-isobutyl-, N-sec-butyl-, N-tert-butyl-, N-methyl-N-ethyl-, N,N-dipropyl-, N-methyl-N-propyl-, N-ethyl-N-propyl- and N,N-dibutylcarbamoyl. Accordingly, some preferred meanings of the radical Ind are, in particular, 5-hydroxy-3-indolyl, also 2-, 4-, 6- or 7-hydroxy-3-indolyl, unsubstituted 3-indolyl, 2-, 4-, 5-, 6- or 7-methoxy-3-indolyl, furthermore 1-, 2-, 4-, 5-, 6- or 7-methyl-3-indolyl, 1-, 2-, 4-, 5-, 6- or 7-ethyl-3-indolyl, 2-, 4-, 5-, 6- or 7-ethoxy-3-indolyl, 2-, 4-, 5-, 6- or 7-fluoro-3-indolyl, 2-, 4-, 5-, 6- or 7-chloro-3-indolyl, 2-, 4-, 5-, 6- or 7-bromo-3-indolyl, 2-, 4-, 5-, 6- or 7-methylthio-3-indolyl, 2-, 4-, 5-, 6- or 7-methylsulfinyl-3-indolyl, 2-, 4-, 5-, 6- or 7-methylsulfonyl-3-indolyl, 2-, 4-, 5-, 6- or 7-formyl-3-indolyl, 2-, 4-, 5-, 6- or 7-carboxy-3-indolyl, 2-, 4-, 5-, 6- or 7-methoxycarbonyl-3-indolyl, 2-, 4-, 5-, 6- or 7-ethoxycarbonyl-3-indolyl, 2-, 4-, 5-, 6- or 7-carbamoyl-3-indolyl, 2-, 4-, 5-, 6- or 7-N-methylcarbamoyl-3-indolyl, 2-, 4-, 5-, 6- or 7-N-ethylcarbamoyl-3-indolyl, 2-, 4-, 5-, 6- or 7-N,N-dimethylcarbamoyl-3-indolyl, furthermore 5,6-dihydroxy-3-indolyl, 5-hydroxy-6-methoxy-3-indolyl, 5-methoxy-6-hydroxy-3-indolyl, 5,6-dimethoxy-3-indolyl, also 4,5-, 4,6-, 4,7-, 5,7- or 6,7-dihydroxy-3-indolyl, 4-hydroxy-5-, 6- or 7-methoxy-3-indolyl, 5-hydroxy-4- or 7-methoxy-3-indolyl, 6-hydroxy-4- or 7-methoxy-3-indolyl, 7-hydroxy-4-, 5- or 6-methoxy-3-indolyl, 5,6-methylenedioxy-3-indolyl, 4,5-, 4,6-, 4,7-, 5,7- or 6,7-dimethoxy-3-indolyl, 1-methyl-4-, -5-, -6- or -7-hydroxymethyl-3-indolyl, 1-methyl-4-, -5-, -6- or -7-formyl-3-indolyl, 1-methyl-4-, -5-, -6- or -7-carboxy-3-indolyl, 1-methyl-4-, -5-, -6- or -7-carbamoyl-3-indolyl, 2-methyl-4-, -5-, -6- or -7-hydroxymethyl-3-indolyl, 2-methyl-4-, -5-, -6- or -7-formyl-3-indolyl, 2-methyl-4-, -5-, -6- or -7-carboxy-3-indolyl, 2-methyl-4-, -5-, -6- or -7-carbamoyl-3-indolyl, 5-methoxy-4-, -6- or -7-methoxycarbonyl-3-indolyl,

2-[4-(6-bromo-3-indolyl)-3-thiabutyl]-

EXAMPLE 18

A solution of 5.09 g of 2-[4-(5-dimethyl-tert.-butylsilyloxy-3-indolyl)-3-thiabutyl]-1,2,3,4-tetrahydrobenzothieno[2,3-c]pyridine [obtainable by etherification of 5-hydroxyindole to give 5-dimethyl-tert.-butylsilyloxyindole (Rf 0.46, dichloromethane), Mannich reaction to give 3-dimethyl-tert.-butylsilyloxygramine (hydrochloride, m.p. 156°-157°) and reaction with 2-(2-mercaptoethyl)-1,2,3,4-tetrahydrobenzothieno[2,3-c]pyridine] and 1.16 g of K₂CO₃ in 200 ml of methanol is allowed to stand at 20° for 16 hours. After the usual working up, 2-[4-(5-hydroxy-3-indolyl)-3-thiabutyl]-1,2,3,4-tetrahydrobenzothieno[2,3-c]pyridine is obtained.

The following 1,2,3,4-tetrahydrobenzothieno[2,3-c]pyridines are obtained analogously from 4-, 6- or 7-hydroxyindole via 4- (Rf 0.52, dichloromethane), 6- (Rf 0.50, dichloromethane) or 7-dimethyl-tert.-butylsilyloxyindole, 4- (hydrochloride, m.p. 168°-170°), 6- (hydrochloride, m.p. 161°-162°), or 7-dimethyl-tert.-butylsilyloxygramine and 2-[4-(4-, 2-[4-(6- or 2-[4-(7-dimethyl-tert.-butylsilyloxy-3-indolyl)-3-thiabutyl]-1,2,3,4-tetrahydrobenzothieno[2,3-c]pyridine: 2-[4-(4-hydroxy-3-indolyl)-3-thiabutyl]-, 2-[4-(6-hydroxy-3-indolyl)-3-thiabutyl]-, 2-[4-(7-hydroxy-3-indolyl)-3-thiabutyl]-.

With the appropriate starting materials of the formula IIIa, the following 1,2,3,4-tetrahydrobenzofuro[2,3-c]pyridines are obtained analogously:

2-[4-(4-hydroxy-3-indolyl)-3-thiabutyl]-, 2-[4-(5-hydroxy-3-indolyl)-3-thiabutyl]-, 2-[4-(6-hydroxy-3-indolyl)-3-thiabutyl]-, 2-[4-(7-hydroxy-3-indolyl)-3-thiabutyl]-; and the following 1,2,3,4,5,6-hexahydrobenzo[f]-isoquinol lines:

2-[4-(4-hydroxy-3-indolyl)-3-thiabutyl]-, 2-[4-(5-hydroxy-3-indolyl)-3-thiabutyl]-, 2-[4-(6-hydroxy-3-indolyl)-3-thiabutyl]-, 2-[4-(7-hydroxy-3-indolyl)-3-thiabutyl]-; and the following 1,2,3,4-tetrahydro-2-azafluorenes: 2-[4-(4-hydroxy-3-indolyl)-3-thiabutyl]-, 2-[4-(5-hydroxy-3-indolyl)-3-thiabutyl]-, 2-[4-(6-hydroxy-3-indolyl)-3-thiabutyl]-, 2-[4-(7-hydroxy-3-indolyl)-3-thiabutyl]-, 2-[4-(4-hydroxy-3-indolyl)-3-thiabutyl]-9-hydroxy-, 2-[4-(5-hydroxy-3-indolyl)-3-thiabutyl]-9-hydroxy-, 2-[4-(6-hydroxy-3-indolyl)-3-thiabutyl]-9-hydroxy-, 2-[4-(7-hydroxy-3-indolyl)-3-thiabutyl]-9-hydroxy-, 2-[4-(4-hydroxy-3-indolyl)-3-thiabutyl]-9-oxo-, 2-[4-(5-hydroxy-3-indolyl)-3-thiabutyl]-9-oxo-, 2-[4-(6-hydroxy-3-indolyl)-3-thiabutyl]-9-oxo-, 2-[4-(7-hydroxy-3-indolyl)-3-thiabutyl]-9-oxo-.

EXAMPLE 19

A mixture of 3.9 g of 2-[4-(5-methoxy-3-indolyl)-butyl]-1,2,3,4-tetrahydrobenzothieno[2,3-c]pyridine and 3.5 g of pyridine hydrochloride is stirred at 160° for 3 hours. After the usual working up, 2-[4-(5-hydroxy-3-indolyl)-butyl]-1,2,3,4-tetrahydrobenzothieno[2,3-c]pyridine is obtained.

EXAMPLE 20

37.4 g of 2-[4-(5-hydroxymethyl-3-indolyl)-butyl]-1,2,3,4-tetrahydrobenzofuro[2,3-c]pyridine are dissolved in 1.6 l of THF, and 300 ml of ether are added. While stirring, 55 g of MnO₂ are added. The mixture is stirred at 20° for 16 hours, a further 100 g of MnO₂ are

added in portions, and the mixture is stirred at 20° for a further 100 hours. After filtration and the usual working up, 2-[4-(5-formyl-3-indolyl)-butyl]-1,2,3,4-tetrahydrobenzofuro[2,3-c]pyridine is obtained.

EXAMPLE 21

3.74 g of 2-[4-(5-hydroxymethyl-3-indolyl)-butyl]-1,2,3,4-tetrahydrobenzofuro[2,3-c]pyridine are dissolved in 50 ml of dichloromethane, 9 g of MnO₂ are added to the solution, the mixture is stirred at 40° for 60 hours, and the insolubles are filtered off. After the usual working up of the filtrate, 2-[4-(5-carboxy-3-indolyl)-butyl]-1,2,3,4-tetrahydrobenzofuro[2,3-c]pyridine is obtained.

EXAMPLE 22

3.72 g of 2-[4-(5-formyl-3-indolyl)-butyl]-1,2,3,4-tetrahydrobenzofuro[2,3-c]pyridine are dissolved in 80 ml of dichloromethane, 9 g of MnO₂ are added, and the suspension is stirred at 40° for 48 hours. After filtration and the usual working up, 2-[4-(5-carboxy-3-indolyl)-butyl]-1,2,3,4-tetrahydrobenzofuro[2,3-c]pyridine is obtained.

EXAMPLE 23

3.88 g of 2-[4-(5-carboxy-3-indolyl)-butyl]-1,2,3,4-tetrahydrobenzofuro[2,3-c]pyridine are suspended in 25 ml of toluene and, under N₂ and while stirring, 3 times the molar amount of a 20% solution of diisobutylaluminum hydride in toluene is added dropwise, and the mixture is boiled for 2 hours, cooled, decomposition is carried out with water, the usual working up is carried out, and 2-[4-(5-formyl-3-indolyl)-butyl]-1,2,3,4-tetrahydrobenzofuro[2,3-c]pyridine is obtained.

EXAMPLE 24

A solution of 3.88 g of 2-[4-(5-carboxy-3-indolyl)-butyl]-1,2,3,4-tetrahydrobenzofuro[2,3-c]pyridine in 40 ml of THF is added dropwise to a stirred suspension of 0.76 g of lithium aluminum hydride in 30 ml of THF under N₂. The mixture is then stirred at 20° for 2 hours, decomposition is carried out with dilute sodium hydroxide solution and then with water, and the mixture is filtered. The usual working up is carried out on the filtrate. 2-[4-(5-Hydroxymethyl-3-indolyl)-butyl]-1,2,3,4-tetrahydrobenzofuro[2,3-c]pyridine is obtained.

EXAMPLE 25

A solution of 4.18 g of 2-[4-(5-methoxycarbonyl-3-indolyl)-butyl]-1,2,3,4-tetrahydrobenzothieno[2,3-c]pyridine in 40 ml of THF is added dropwise to a stirred suspension of 0.57 g of lithium aluminum hydride in 20 ml of THF at 20° under N₂. The mixture is stirred at 20° for 1 hour, and decomposition is carried out with dilute sodium hydroxide solution and then with water, and the mixture is filtered, the usual working up is carried out on the filtrate, and 2-[4-(5-hydroxymethyl-3-indolyl)-butyl]-1,2,3,4-tetrahydrobenzothieno[2,3-c]pyridine is obtained.

The following are obtained analogously by reduction of the corresponding esters:

2-[4-(4-hydroxymethyl-3-indolyl)-butyl]-1,2,3,4-tetrahydrobenzothieno[2,3-c]pyridine
2-[4-(6-hydroxymethyl-3-indolyl)-butyl]-1,2,3,4-tetrahydrobenzothieno[2,3-c]pyridine
2-[4-(7-hydroxymethyl-3-indolyl)-butyl]-1,2,3,4-tetrahydrobenzothieno[2,3-c]pyridine

187
183

2-[4-(4-hydroxymethyl-3-indolyl)butyl]-1,2,3,4-tetrahydrobenzofuro[2,3-c]pyridine
 2-[4-(3-hydroxymethyl-3-indolyl)butyl]-1,2,3,4-tetrahydrobenzofuro[2,3-c]pyridine
 2-[4-(6-hydroxymethyl-3-indolyl)butyl]-1,2,3,4-tetrahydrobenzofuro[2,3-c]pyridine
 2-[4-(7-hydroxymethyl-3-indolyl)butyl]-1,2,3,4-tetrahydrobenzofuro[2,3-c]pyridine
 3-[4-(4-hydroxymethyl-3-indolyl)butyl]-1,2,3,4,5,6-hexahydrobenzo[f]isoquinoline
 3-[4-(5-hydroxymethyl-3-indolyl)butyl]-1,2,3,4,5,6-hexahydrobenzo[f]isoquinoline
 3-[4-(6-hydroxymethyl-3-indolyl)butyl]-1,2,3,4,5,6-hexahydrobenzo[f]isoquinoline
 3-[4-(7-hydroxymethyl-3-indolyl)butyl]-1,2,3,4,5,6-hexahydrobenzo[f]isoquinoline
 2-[4-(4-hydroxymethyl-3-indolyl)butyl]-1,2,3,4-tetrahydro-2-azafluorene
 2-[4-(5-hydroxymethyl-3-indolyl)butyl]-1,2,3,4-tetrahydro-2-azafluorene
 2-[4-(6-hydroxymethyl-3-indolyl)butyl]-1,2,3,4-tetrahydro-2-azafluorene
 2-[4-(7-hydroxymethyl-3-indolyl)butyl]-1,2,3,4-tetrahydro-2-azafluorene
 2-[4-(4-hydroxymethyl-3-indolyl)butyl]-9-hydroxy-1,2,3,4-tetrahydro-2-azafluorene
 2-[4-(5-hydroxymethyl-3-indolyl)butyl]-9-hydroxy-1,2,3,4-tetrahydro-2-azafluorene
 2-[4-(6-hydroxymethyl-3-indolyl)butyl]-9-hydroxy-1,2,3,4-tetrahydro-2-azafluorene
 2-[4-(7-hydroxymethyl-3-indolyl)butyl]-9-hydroxy-1,2,3,4-tetrahydro-2-azafluorene
 2-[4-(4-hydroxymethyl-3-indolyl)-3-thiabutyl]-1,2,3,4-tetrahydrobenzothieno[2,3-c]pyridine
 2-[4-(5-hydroxymethyl-3-indolyl)-3-thiabutyl]-1,2,3,4-tetrahydrobenzothieno[2,3-c]pyridine
 2-[4-(6-hydroxymethyl-3-indolyl)-3-thiabutyl]-1,2,3,4-tetrahydrobenzothieno[2,3-c]pyridine
 2-[4-(7-hydroxymethyl-3-indolyl)-3-thiabutyl]-1,2,3,4-tetrahydrobenzothieno[2,3-c]pyridine
 2-[4-(4-hydroxymethyl-3-indolyl)-3-thiabutyl]-1,2,3,4-tetrahydrobenzofuro[2,3-c]pyridine
 2-[4-(5-hydroxymethyl-3-indolyl)-3-thiabutyl]-1,2,3,4-tetrahydrobenzofuro[2,3-c]pyridine
 2-[4-(6-hydroxymethyl-3-indolyl)-3-thiabutyl]-1,2,3,4-tetrahydrobenzofuro[2,3-c]pyridine
 2-[4-(7-hydroxymethyl-3-indolyl)-3-thiabutyl]-1,2,3,4-tetrahydrobenzofuro[2,3-c]pyridine
 3-[4-(4-hydroxymethyl-3-indolyl)-3-thiabutyl]-1,2,3,4,5,6-hexahydrobenzo[f]isoquinoline
 3-[4-(5-hydroxymethyl-3-indolyl)-3-thiabutyl]-1,2,3,4,5,6-hexahydrobenzo[f]isoquinoline
 3-[4-(6-hydroxymethyl-3-indolyl)-3-thiabutyl]-1,2,3,4,5,6-hexahydrobenzo[f]isoquinoline
 3-[4-(7-hydroxymethyl-3-indolyl)-3-thiabutyl]-1,2,3,4,5,6-hexahydrobenzo[f]isoquinoline
 2-[4-(4-hydroxymethyl-3-indolyl)-3-thiabutyl]-1,2,3,4-tetrahydro-2-azafluorene
 2-[4-(5-hydroxymethyl-3-indolyl)-3-thiabutyl]-1,2,3,4-tetrahydro-2-azafluorene
 2-[4-(6-hydroxymethyl-3-indolyl)-3-thiabutyl]-1,2,3,4-tetrahydro-2-azafluorene
 2-[4-(7-hydroxymethyl-3-indolyl)-3-thiabutyl]-1,2,3,4-tetrahydro-2-azafluorene
 2-[4-(4-hydroxymethyl-3-indolyl)-3-thiabutyl]-hydroxy-1,2,3,4-tetrahydro-2-azafluorene
 2-[4-(5-hydroxymethyl-3-indolyl)-3-thiabutyl]-hydroxy-1,2,3,4-tetrahydro-2-azafluorene

2-[4-(6-hydroxymethyl-3-indolyl)-3-thiabutyl]-9-hydroxy-1,2,3,4-tetrahydro-2-azafluorene
 2-[4-(7-hydroxymethyl-3-indolyl)-3-thiabutyl]-9-hydroxy-1,2,3,4-tetrahydro-2-azafluorene

EXAMPLE 26

A solution of 3.84 g of 3-[4-(6-formyl-3-indolyl)butyl]-1,2,3,4,5,6-hexahydrobenzo[f]isoquinoline in 40 ml of THF is added dropwise to a stirred suspension of 0.57 g of lithium aluminium hydride in 20 ml of THF under N₂. The mixture is then stirred at 20° for 1 hour, and decomposition is carried out with dilute sodium hydroxide solution and then with water, and the mixture is filtered and the usual working up is carried out, and 3-[4-(6-hydroxymethyl-3-indolyl)butyl]-1,2,3,4,5,6-hexahydrobenzo[f]isoquinoline is obtained.

EXAMPLE 27

HCl is passed for 2 hours into a solution of 3.88 g of 2-[4-(5-carboxy-3-indolyl)butyl]-1,2,3,4-tetrahydrobenzofuro[2,3-c]pyridine in 50 ml of absolute ethanol. The mixture is then allowed to stand at 20° for 48 hours, the usual working up is carried out, and 2-[4-(5-ethoxycarbonyl-3-indolyl)butyl]-1,2,3,4-tetrahydrobenzofuro[2,3-c]pyridine is obtained.

EXAMPLE 28

1.8 g of N,N'-carbonyldiimidazole are added to a solution of 4 g of 3-[4-(5-carboxy-3-indolyl)butyl]-1,2,3,4,5,6-hexahydrobenzo[f]isoquinoline in 40 ml of DMF, and the mixture is stirred at 20° for 2 hours, then 0.6 g of NH₄Cl is added, and the mixture is heated at 40° for 3 hours. After the usual working up 3-[4-(5-carbamoyl-3-indolyl)butyl]-1,2,3,4,5,6-hexahydrobenzo[f]isoquinoline is obtained.

EXAMPLE 29

3.88 g of 2-[4-(5-carboxy-3-indolyl)butyl]-1,2,3,4-tetrahydrobenzofuro[2,3-c]pyridine are dissolved in 30 ml of chloroform, the solution is saturated with HCl gas, 1.8 g of thionyl chloride are added dropwise, and the mixture is boiled for 2 hours. Evaporation is carried out, 30 ml of toluene are added, evaporation is repeated, and the resulting crude acid chloride is dissolved in 20 ml of chloroform, and this solution is added dropwise to a stirred saturated solution of ammonia in 50 ml of chloroform, and the mixture is stirred at 20° for 2 hours, filtered and the filtrate is concentrated. After the usual working up 2-[4-(5-carbamoyl-3-indolyl)butyl]-1,2,3,4-tetrahydrobenzofuro[2,3-c]pyridine is obtained.

EXAMPLE 30

0.02 mol of concentrated ammonia (D=0.9) is added dropwise to a solution of 4.02 g of 2-[4-(5-methoxycarbonyl-3-indolyl)butyl]-1,2,3,4-tetrahydrobenzofuro[2,3-c]pyridine in 30 ml of dimethylformamide at 20°. The mixture is stirred at 20° for 1 hour, the usual working up is carried out and 2-[4-(5-carbamoyl-3-indolyl)butyl]-1,2,3,4-tetrahydrobenzofuro[2,3-c]pyridine is obtained.

EXAMPLE 31

A mixture of 38.7 g of 2-[4-(5-carbamoyl-3-indolyl)butyl]-1,2,3,4-tetrahydrobenzofuro[2,3-c]pyridine, 27.1 g of NaOH, 525 ml of water and 450 ml of diethylene glycol monoethyl ether is boiled, with stirring, for 16 hours. The mixture is cooled, the usual working up followed by acidification is carried out, and 2-[4-(5-car-

PATENT SPECIFICATION

(11) 1286554

NO DRAWINGS

- (21) Application No. 62868/69 (22) Filed 24 Dec. 1969
 (31) Convention Application No. 949 (32) Filed 23 Jan. 1969
 (31) Convention Application No. 7655 (32) Filed 20 May 1969
 (31) Convention Application No. 16247 (32) Filed 31 Oct. 1969
 (31) Convention Application No. 16248 (32) Filed 31 Oct. 1969 in
 (33) Switzerland (CH)
 (45) Complete Specification published 23 Aug. 1972
 (51) International Classification C07D 39/00 A61K 27/00
 (52) Index at acceptance

C2C 17X—27X—287 180—270—282 1E5K4 1Q11H 1Q11J
 1Q4 1Q6C 1Q8A 1Q9B 1Q9D1 1Q9F2 200 202
 213 215 220 226 22Y 246 247 250 251 25Y 29X
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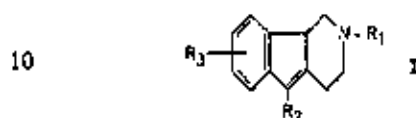
- (72) Inventors JEAN-MICHEL BASTIAN and
 ANTON EBNOTHER



(54) 5-ALKYL INDENOPYRIDINE DERIVATIVES

(71) We, SANDOZ LTD., of 35 Lichstrasse, 4000 Basle, Switzerland, a Swiss Body Corporate, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to new compounds of formula I,

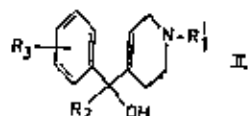


in which

- R_1 signifies hydrogen, alkyl of 1 to 10 carbon atoms, alkenyl of 3 to 6 carbon atoms, or alkynyl of 3 to 6 carbon atoms or the benzyl radical,
 R_2 signifies a primary or secondary alkyl radical of 1 to 5 carbon atoms, and
 R_3 signifies hydrogen, halogen or an alkyl radical of 1 to 4 carbon atoms, with the proviso that R_1 may not signify the methyl radical when R_2 signifies the methyl radical and R_3 signifies hydrogen.

A compound of formula I may be obtained

- 25 a) by cyclizing a compound of formula II,

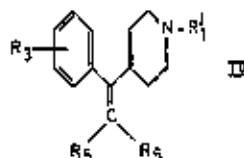


in which

[Price 25p]

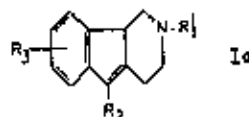
R_1^1 signifies the benzyl radical, alkyl of 1 to 10 carbon atoms, alkenyl of 3 to 6 carbon atoms or alkynyl of 3 to 6 carbon atoms, and

R_2 and R_3 have the above significance, with the proviso that R_1^1 does not signify the methyl radical when R_2 signifies the methyl radical and R_3 signifies hydrogen, or a compound of formula IV,



in which

- R_1^1 and R_3 have the above significance, and each of
 R_2 and R_4 signifies hydrogen or an alkyl radical of 1 to 5 carbon atoms, with the proviso that R_1^1 may not signify the methyl radical when all of R_2 , R_3 and R_4 signify hydrogen, to obtain a compound of formula Ia



in which R_1^1 , R_2 and R_3 have the above significance, or

60° for a further 3 1/2 hours, is subsequently poured into 1000 cc of a 2% potassium carbonate solution and is repeatedly extracted with benzene. The crude base obtained after removing the solvent by evaporation is dissolved in acetone, and the calculated amount of hydrochloric acid in ethanol is added. The resulting hydrochloride is purified by recrystallization from methanol. M.P. 224—226° (decomp.).

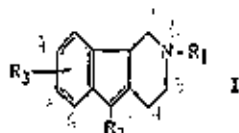
EXAMPLE 20

2 - Allyl - 1,3,4,9b - tetrahydro - 5 - methyl - 2H - indeno[1,2 - c]pyridine.

A solution of 11.8 g of allyl bromide in 50 cc of dimethyl formamide is added dropwise at 50° while stirring during the course of 15 minutes to a suspension of 18.0 g of 1,3,4,9b - tetrahydro - 5 - methyl - 2H - indeno[1,2 - c]pyridine hydrochloride and 28.1 g of potassium carbonate in 200 cc of dimethyl formamide. The reaction mixture is allowed to react at 50° for a further hour and is then poured into benzene. The mixture is extracted thrice with water, the organic phase is dried over magnesium sulphate and the solvent is removed by evaporation. The residue is taken up in acetone and the calculated amount of hydrochloric acid in ethanol is added. The solution is allowed to crystallize, whereby the hydrochloride of the title compound, having a M.P. of 206—208° (decomp.), is obtained.

WHAT WE CLAIM IS:—

1. A process for the production of a compound of formula I,



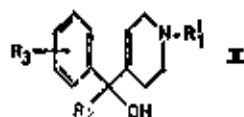
in which

R₁ signifies hydrogen, alkyl of 1 to 10 carbon atoms, alkenyl of 3 to 6 carbon atoms or alkynyl of 3 to 6 carbon atoms or the benzyl radical,

R₂ signifies a primary or secondary alkyl radical of 1 to 5 carbon atoms, and

R₃ signifies hydrogen, halogen or an alkyl radical of 1 to 4 carbon atoms, with the proviso that R₁ may not signify the methyl radical when R₂ signifies the methyl radical and R₃ signifies hydrogen, which comprises

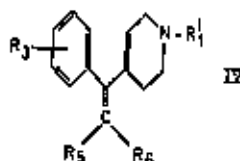
a) cyclizing a compound of formula II,



in which

R₁¹ signifies the benzyl radical, alkyl of 1 to 10 carbon atoms, alkenyl of 3 to 6 carbon atoms or alkynyl of 3 to 6 carbon atoms, and

R₂ and R₃ have the above significance, with the proviso that R₁¹ does not signify the methyl radical when R₂ signifies the methyl radical and R₃ signifies hydrogen, or a compound of formula IV,

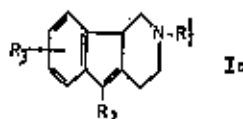


in which

R₁¹ and R₃ have the above significance, and each of

R₅ and R₆ signifies hydrogen or an alkyl radical of 1 to 5 carbon atoms, with the proviso that R₁¹ may not signify the methyl radical when all of R₃, R₅ and R₆ signify hydrogen,

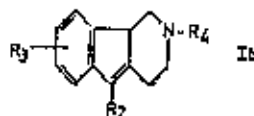
to obtain a compound of formula Ia,



in which

R₁¹, R₂ and R₃ have the above significance, or

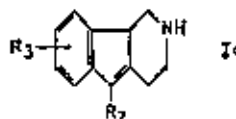
b) converting a compound of formula Ib,



in which

R₄ signifies the methyl or benzyl radical, and

R₂ and R₃ have the above significance, into a compound of formula Ic,



in which

R₂ and R₃ have the above significance, by splitting off the methyl or benzyl radical, or

c) condensing a compound of the above formula Ic with a compound of formula III,



III

in which

- 5 R_1' has the above significance, and
 Y signifies the acid radical of a reactive ester, with the proviso that R_1' in the compounds of formula III may not signify the methyl radical when in the compounds of formula Ic R_2 signifies the methyl radical and R_1 signifies hydrogen, to obtain a compound of the above formula Ia.

2. A process according to Claim 1, where-
 15 in the cyclization is effected with a strong acid at a temperature between 80° and 150°C.

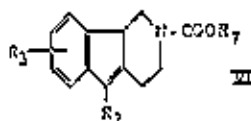
3. A process according to Claim 1, where-
 in the splitting off of the R_1 methyl or benzyl radical in the compound of formula Ib is effected by reacting the compound of formula Ib with a chloroformic acid ester of formula V,



V

in which

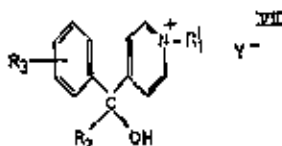
- 25 R_r signifies an alkyl radical of 1 to 5 carbon atoms, the phenyl or benzyl radical,
 to obtain a urethane of formula VI,



- 30 in which

R_1 , R_2 , and R_r have the above significance, and converting the urethane into a compound of formula Ic by acid or alkaline hydrolysis.

4. A process according to Claim 1, where-
 35 in the compound of formula II is produced by reducing a compound of formula VII,



wherein R_1' , R_2 , R_3 and Y have the significance stated in Claim 1, with sodium borohydride in an inert solvent.

- 40 5. A process for the production of a com-

pound of formula I, stated in Claim 1, substantially as herein described, with reference to any one of the Examples.

6. A compound of formula I, stated in Claim 1, whenever produced by the process of any one of the preceding Claims.

7. A compound of formula I, stated in Claim 1.

8. 8 - Chloro - 1,3,4,9b - tetrahydro - 2,5 - dimethyl - 2H - indeno[1,2 - c] - pyridine.

9. 1,3,4,9b - Tetrahydro - 2,5,8 - trimethyl - 2H - indeno[1,2 - c]pyridine.

10. 1,3,4,9b - Tetrahydro - 5 - methyl - 2H - indeno[1,2 - c]pyridine.

11. 1,3,4,9b - Tetrahydro - 5 - methyl - 2 - propargyl - 2H - indeno[1,2 - c]pyridine.

12. 5 - Ethyl - 1,3,4,9b - tetrahydro - 2 - methyl - 2H - indeno[1,2 - c]pyridine.

13. 1,3,4,9b - Tetrahydro - 5 - isopropyl - 2 - methyl - 2H - indeno[1,2 - c]pyridine.

14. 2 - (3 - Butinyl) - 1,3,4,9b - tetrahydro - 5 - methyl - 2H - indeno[1,2 - c] - pyridine.

15. 2 - Ethyl - 1,3,4,9b - tetrahydro - 5 - methyl - 2H - indeno[1,2 - c]pyridine.

16. 1,3,4,9b - Tetrahydro - 2 - isopropyl - 5 - methyl - 2H - indeno[1,2 - c]pyridine.

17. 1,3,4,9b - Tetrahydro - 2 - isobutyl - 5 - methyl - 2H - indeno[1,2 - c]pyridine.

18. 1,3,4,9b - Tetrahydro - 5 - methyl - 2 - pentyl - 2H - indeno[1,2 - c]pyridine.

19. 1,3,4,9b - Tetrahydro - 5 - methyl - 2 - octyl - 2H - indeno[1,2 - c]pyridine.

20. 2 - (2 - Butinyl) - 1,3,4,9b - tetrahydro - 5 - methyl - 2H - indeno[1,2 - c] - pyridine.

21. 1,3,4,9b - Tetrahydro - 2,5,7 - trimethyl - 2H - indeno[1,2 - c]pyridine.

22. 7 - Chloro - 1,3,4,9b - tetrahydro - 2,5 - dimethyl - 2H - indeno[1,2 - c] - pyridine.

23. 7 - Ethyl - 1,3,4,9b - tetrahydro - 2,5 - dimethyl - 2H - indeno[1,2 - c]pyridine.

24. 7 - Fluoro - 1,3,4,9b - tetrahydro - 2,5 - dimethyl - 2H - indeno[1,2 - c] - pyridine.

25. 2 - Benzyl - 1,3,4,9b - tetrahydro - 5 - methyl - 2H - indeno[1,2 - c]pyridine.

26. 2 - Allyl - 1,3,4,9b - tetrahydro - 5 - methyl - 2H - indeno[1,2 - c]pyridine.

27. The compound of any one of Claims 7 to 26, in the form of an acid addition salt.

28. A pharmaceutical composition incorporating as active ingredient the compound of any one of Claims 6 to 26, or a pharmaceutically acceptable acid addition salt thereof, in association with a pharmacologically acceptable carrier or diluent.

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188 192

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

2020/
Bogotá, D.C., 28/04/2010

Doctora
Dilia Rodríguez D'Alemán
Apoderado

Oficio N° 06.178

REFERENCIA	Radicación	06 37930
	Trámite	002
	Evento	001
	Actuación	430
	Folios	002

Como resultado del examen de patentabilidad de la solicitud de patente de invención N° **06 37930**, realizado según el artículo 46 de la decisión 486 de la comisión de la Comunidad Andina, se notifica:

SOLICITUD DE SUMINISTRO DE INFORMACIÓN

El artículo 46 de la Decisión 486 establece que *"La Oficina Nacional competente podrá requerir el informe de expertos o de organismos científicos o tecnológicos que se consideren idóneos para que emitan opinión sobre la patentabilidad de la invención. Asimismo, cuando lo estime conveniente, podrá requerir informes de otras oficinas de propiedad industrial. De ser necesario, a efectos del examen de patentabilidad y a requerimiento de la oficina nacional competente, el solicitante proporcionará, en un plazo que no excederá de 3 meses, uno o más documentos relativos a una o más solicitudes extranjeras referidas total o parcialmente a la misma invención que se examina: ...b) copia de los resultados de exámenes de novedad o de patentabilidad efectuados respecto a esa solicitud extranjera... Si el solicitante no presentara los documentos requeridos dentro del plazo señalado en el presente artículo la oficina nacional competente denegará la patente"*

Como consecuencia de la búsqueda de anterioridades de materia relacionada con la de la presente solicitud, se determinó que existen en el estado de la técnica los siguientes documentos que eventualmente afectarían los requisitos de patentabilidad de la presente solicitud:

- A. Rosowsky. "One step synthesis of novel 2,4-diamino-pyrimidine antifolates". Journal Heterocyclic Chemistry. Vol. 36, 1999, pages 723-728, XP002270518.
- Kandeel e. M. "Synthesis of new 1,2-dihydro-4-amino-2-thioxo-5H-indeno-1,2-D-pyrimidin-5-one derivatives". Pakistan Journal of Scientific and Industrial Research, XX, XX, vol. 29, no. 6, December 1986 (1986-12), pages 424-426, xp009025178. ISSN: 0030-9885.
- Goerlitzer K. et al. "Indenoä 1,2-düpyrimidin-4-yl-amine indenoä 1,2üpyrimidin-4-yl-amines". Pharmazie, Veb Verlag volk und gesundheit. Berlin, DD, vol. 52, no.9, 1997, pages 670-672, XP001179310. ISSN: 0031-7144.

Siendo que la publicación referenciada hace parte del resultado del examen de búsqueda realizado para la solicitud WO 2005/042500, equivalente a la solicitud colombiana aquí estudiada, y no siendo viable la consecución de dichos artículos por este despacho, se requiere que el solicitante, en virtud de lo establecido en el artículo 46 de la Decisión 486 de la Comisión de la Comunidad Andina, proporcione las publicaciones completas, con lo que podrá realizarse un análisis absoluto de la patentabilidad de la invención correspondiente a la presente solicitud.

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

ÁLIX CARMENZA CÉSPEDES DE VERGEL
Directora de Nuevas Creaciones (c)

El anterior requerimiento fue notificado por fijación en lista, de fecha 07 MAYO 2010

CONCEPTO TÉCNICO No. 1632	EXAMINADOR TÉCNICO Código No. 202044
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INDENOPYRIDINE AND INDENOPYRIMIDINE COMPOUND AND METHOD FOR PRODUCING THE SAME

190,94
D1

Publication number: JP2001139556 (A)

Publication date: 2001-05-22

Inventor(s): ITO KUNIHITO; UMEDA NOBUHIRO; UCHIDA SEIICHI; SHIIKI KOSUKE; HORIKOSHI HIROMI; MOCHIZUKI NOBUO +

Applicant(s): NIPPON SODA CO +

Classification:

- International: A61K31/4427; A61K31/444; A61K31/497; A61K31/517; A61P11/00; A61P11/16; A61P13/12; A61P15/10; A61P25/28; A61P27/06; A61P37/02; A61P43/00; A61P9/04; A61P9/10; A61P9/12; C07D221/06; C07D239/70; C07D401/04; C07D401/14; C07D403/04; A61K31/4427; A61K31/4965; A61K31/517; A61P11/00; A61P13/00; A61P15/00; A61P25/00; A61P27/00; A61P37/00; A61P43/00; A61P9/00; C07D221/00; C07D239/00; C07D401/00; C07D403/00; (IPC1-7): A61K31/444; A61P11/00; A61P13/12; A61P15/10; A61P25/28; A61P27/06; A61P37/02; A61P43/00; A61P9/04; C07D221/06; C07D239/70; C07D401/04; C07D403/04

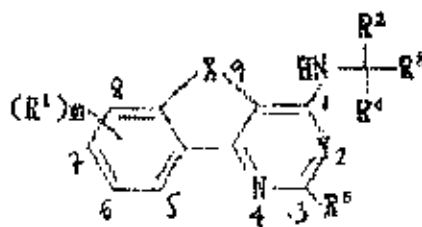
European:

Application number: JP20000072712 20000315

Priority number(s): JP20000072712 20000315; JP19990073646 19990318; JP19990247435 19990801

Abstract of JP 2001139556 (A)

PROBLEM TO BE SOLVED: To produce an indenopyridine and an indenopyrimidine compounds useful as a medicine and to provide an advantageous method for producing the compounds. **SOLUTION:** The indenopyridine and indenopyrimidine compounds are represented by the general formula (1) [wherein R1 denotes hydrogen atom, a 1-6C alkyl or the like; m denotes 0 or an integer of 1-4; X denotes CH2 or C(=O); Y denotes N or CH; R2 and R3 denote each hydrogen atom, a 1-6C alkyl group or the like, R4 denotes phenyl group, a heterocyclic group or the like which may be substituted; R5 denotes carboxy group, a 1-6C alkylcarbonyl group, a carbamoyl group, a heterocyclic group or the like which may be substituted]. The method for producing the same is provided.



(1)

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NOTICES

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1. This document has been translated by computer. So the translation may not reflect the original precisely.
2. **** shows the word which can not be translated.
3. In the drawings, any words are not translated.

DETAILED DESCRIPTION

[Detailed Description of the Invention]

[0001]

[Field of the Invention] This invention relates to indeno pyridine and an indeno pyrimidine compound. this invention compound is useful as cGMP specific phosphodiesterase (PDE) inhibitor.

[0002]

[Description of the Prior Art] cGMP is a substance which bears the role important as a second messenger in information transmission paths in the living body.

cGMP specific phosphodiesterase (PDE) inhibitor which is the dialytic ferment. Intracellular cGMP concentration is raised, for example, it is useful for prevention and/or the therapy of hypertension, cardiac insufficiency, myocardial infarction, angina pectoris, arteriosclerosis, the after [PTCA] restenosis, the cardiac edema, the pulmonary hypertension, renal failure, a kidney edema, a liver edema, asthma, bronchitis, dementia, immune disorder, glaucoma, or an impotence.

On the other hand, although it is indicated to WO 93/No. 08167 that 5H-indeno [1,2-b] pyridine and a 5H-indeno [1 and 2-d] pyrimidine derivative are useful as germicides for agriculture and horticulture, cGMP specific PDE inhibitory action is not indicated. Conventionally, the PDE inhibitor known has a problem in respect of side effects etc. in order to check not only cGMP specific PDE but cAMP PDE etc., and in inhibition intensity etc., it cannot be satisfied, and a compound with high selectivity whose activity is stronger is desired.

[0003]

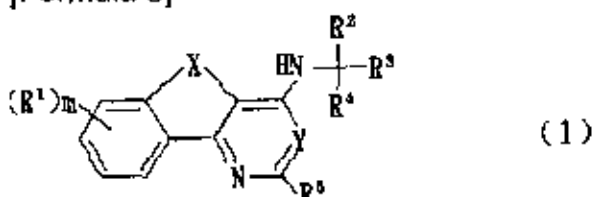
[Problem(s) to be Solved by the Invention] This invention is providing indeno pyridine and an indeno pyrimidine compound useful as medicine.

[0004]

[Means for Solving the Problem] This invention is a general formula (1).

[0005]

[Formula 5]



492/196

[0006] R^1 among [type, A nitro group, a halogen atom, a C_{1-6} alkyl group, a C_{1-6} alkoxy group, a C_{1-6} halo alkyl group, a C_{1-6} haloalkoxy group, a C_{1-6} alkylthio group, a C_{1-6} alkoxy carbonyl group, Or mono- ***** expresses with a C_{1-6} alkyl group the carbamoyl group by which J1 substitution may be carried out. X expresses CH_2 or $C(=O)$. Y expresses N or CH. m expresses the integer of 0 or 1-4. R^2 and R^3 , or it is different from each other and a hydrogen atom, a hydroxy group, a halogen atom, a C_{1-6} alkyl group, a C_{1-6} alkoxy group, a C_{1-6} halo alkyl group, or the phenyl group that may be replaced is expressed. R^4 are a hydrogen atom, a C_{1-6} alkyl group, a C_{3-8} cycloalkyl group, the phenyl group that may be replaced, a naphthyl group which may be replaced, the benzyl which may be replaced, $C(=O)Or^1$, and $C(=O)r^2$ (here, r^1 and r^2). The heterocycle group of saturation or an unsaturation containing a hydrogen atom, a C_{1-6} alkyl group, a C_{2-6} alkenyl group, the phenyl group that may be replaced, the benzyl which may be replaced or N which may be replaced, O, or 1-4 S atoms is expressed. Or even if replaced. The heterocycle group of saturation or an unsaturation containing good N, O, or 1-4 S atoms is expressed. R^5 , the C_{1-6} alkyl group which may be replaced by the hydrogen atom, the cyano group, the phenylthio group, the C_{1-6} halo alkyl group, the C_{1-6} alkylthio group, the C_{3-8} cycloalkyl group, the carboxy group, or a C_{1-6} alkoxy carbonyl group, even if replaced. A good phenyl group, the benzyl which may be replaced, Or^3 , Nr^4r^5 , $C(=O)Or^6$, $C(=O)Nr^7r^8$ (here) r^3 , r^4 , r^5 , r^6 , r^7 , and r^8 , the C_{1-6} alkyl group which may be replaced by the hydrogen atom, the C_{3-8} cycloalkyl group, the carboxy group, or a C_{1-6} alkoxy carbonyl group, the phenyl group which may be replaced, and the benzyl which may be replaced -- or, even if replaced. The heterocycle group of saturation or an unsaturation containing good N, O, or 1-4 S atoms is expressed. Or the heterocycle group of saturation or an unsaturation containing N, O, or 1-4 S atoms which may be replaced is expressed. (However, the compound which are $m=0$, $X=C(=O)$, $Y=CH$, $R^2=R^3=H$, $R^4=4$ -t-butylphenyl, and $R^5=4$ -pyridyl is excluded.) They are indeno pyridine expressed with], an indeno pyrimidine compound, and its manufacturing method.

[0007] R^1 in this invention Halogen atoms, such as a nitro group, fluoride, chlorine, and bromine, C_{1-6} alkyl groups, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, s-butyl, and t-butyl, C_{1-6} alkoxy groups, such as methoxy and ethoxy, propoxy, isopropoxy, butoxy, and t-butoxy, C_{1-6} halo alkyl groups, such as chloromethyl, dichloromethyl, trichloromethyl, fluoromethyl, difluoromethyl, trifluoromethyl, 1-fluoroethyl, 1,1-difluoroethyl, and pentafluoroethyl, C_{1-6} haloalkoxy groups, such as fluoromethoxy, difluoromethoxy, trifluoromethoxy, and chloromethoxy, C_{1-6} alkylthio groups, such as a methylthio, ethylthio, propylthio, isopropylthio, butylthio, and t-butylthio, C_{1-6} alkoxy carbonyl groups, such as carbomethoxy, ethoxycarbonyl, carbopropoxy, isopropoxycarbonyl, butoxycarbonyl, and t-butoxycarbonyl, Or even if J1 substitution of the

mono-***** is carried out by C_{1-6} alkyl groups, such as carbamoyl, methylcarbamoyl, dimethylcarbamoyl, ethylcarbamoyl, diethylcarbamoyl, propylcarbamoyl, isopropylcarbamoyl, and butylcarbamoyl. A good carbamoyl group is expressed.

[0008] R^2 and R^3 -- same or being different from each other -- a hydrogen atom and a hydroxy group. C_{1-6} alkyl groups, such as halogen atoms, such as fluoride, chlorine, and bromine, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, s-butyl, and t-butyl, C_{1-6} alkoxy groups, such as methoxy and ethoxy, propoxy, isopropoxy, butoxy, and t-butoxy, C_{1-6} halo alkyl groups, such as chloromethyl, dichloromethyl, trichloromethyl, fluoromethyl, difluoromethyl, trifluoromethyl, 1-fluoroethyl, 1,1-difluoroethyl, and pentafluoroethyl, -- or (in arbitrary positions.) Even if replaced by C_{1-6} alkyl groups, such as halogen atoms, such as fluoride, chlorine, and bromine, methyl, and ethyl, or methoxy, and which ethoxy C_{1-6} alkoxy group, a good phenyl group is expressed.

[0009] R^4 C_{1-6} alkyl groups, such as a hydrogen atom, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, s-butyl, and t-butyl, C_{3-8} cycloalkyl groups, such as cyclopropyl, cyclopentyl, cyclohexyl, and cycloheptyl one, arbitrary positions -- C_{1-6} alkyl groups, such as halogen atoms, such as fluoride, chlorine, and bromine, methyl, and ethyl, Methoxy, which ethoxy C_{1-6} alkoxy group, or methylenedioxy, C_{1-3} , such as ethylene dioxy, -- it may be replaced by alkylene dioxy group -- a phenyl group. (It may be replaced by arbitrary positions by C_{1-6} alkyl groups, such as halogen atoms, such as fluoride, chlorine, and bromine, methyl, and ethyl, or methoxy, and any ethoxy C_{1-6} alkoxy group) A naphthyl group, (It may be replaced by arbitrary positions by C_{1-6} alkyl groups, such as halogen atoms, such as fluoride, chlorine, and bromine, methyl, and ethyl, or methoxy, and any ethoxy C_{1-6} alkoxy group) Benzyl, $C(=O)Or^1$ and $C(=O)r^2$ -- here -- r^1 and r^2 -- a hydrogen atom. C_{1-6} alkyl groups, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, s-butyl, and t-butyl, C_{2-6} alkenyl groups, such as ethenyl, 1-propenyl, and 2-propenyl, (It may be replaced by arbitrary positions by C_{1-6} alkyl groups, such as halogen atoms, such as fluoride, chlorine, and bromine, methyl, and ethyl, or methoxy, and any ethoxy C_{1-6} alkoxy group) A phenyl group, (It may be replaced by arbitrary positions by C_{1-6} alkyl groups, such as halogen atoms, such as fluoride, chlorine, and bromine, methyl, and ethyl, or methoxy, and any ethoxy C_{1-6} alkoxy group) benzyl -- or (in arbitrary positions.) it may be replaced by C_{1-6} alkyl groups, such as halogen atoms, such as fluoride, chlorine, and bromine, or methyl, and ethyl, -- a heterocycle group (it is only hereafter written as a heterocycle group.) of saturation or an unsaturation containing N, such as pyridyl, quinolyl, and isoquinolyl, O, or 1-4 S atoms is expressed. Heterocycle groups, such as] or (replaced by arbitrary positions by C_{1-6} alkyl groups, such as halogen atoms, such as fluoride, chlorine, and bromine, or methyl, and ethyl) pyridyl, quinolyl, and isoquinolyl, are expressed.

[0010] R^5 A hydrogen atom, a cyano group, a phenoxy group, a phenylthio group, C_{1-6} halo alkyl groups,

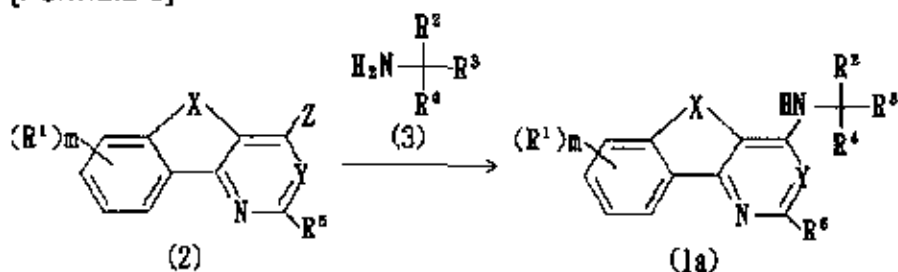
such as chloromethyl, dichloromethyl, trichloromethyl, fluoromethyl, difluoromethyl, trifluoromethyl, 1-fluoroethyl, 1,1-difluoroethyl, and pentafluoroethyl, C_{1-6} alkoxy groups, such as methoxy and ethoxy, propoxy, isopropoxy, butoxy, and t-butoxy, C_{1-6} alkylthio groups, such as a methylthio, ethylthio, propylthio, isopropylthio, butylthio, and t-butylthio, C_{3-8} cycloalkyl groups, such as cyclopropyl, cyclopentyl, cyclohexyl, and cycloheptyl one, (In arbitrary positions.) it may be replaced by C_{1-6} alkoxy carbonyl groups, such as a carboxy group or carbomethoxy, and ethoxycarbonyl, -- C_{1-6} alkyl groups, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, s-butyl, and t-butyl, arbitrary positions -- halogen atoms, such as fluoride, chlorine, and bromine, Even if replaced by C_{1-6} alkyl groups, such as methyl and ethyl, or methoxy, and which ethoxy C_{1-6} alkoxy group, a good phenyl group, (It may be replaced by arbitrary positions by C_{1-6} alkyl groups, such as halogen atoms, such as fluoride, chlorine, and bromine, methyl, and ethyl, or methoxy, and any ethoxy C_{1-6} alkoxy group) Benzyl, Or^3 , Nr^4r^5 , $C(=O)Or^6$, $C(=O)Nr^7r^8$ (here, r^3 , r^4 , r^5 , r^6 , r^7 , and r^8) C_{3-8} cycloalkyl groups, such as a hydrogen atom, cyclopropyl, cyclopentyl, cyclohexyl, and cycloheptyl one, (In arbitrary positions.) it may be replaced by C_{1-6} alkoxy carbonyl groups, such as a carboxy group or carbomethoxy, and ethoxycarbonyl, -- C_{1-6} alkyl groups, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, s-butyl, and t-butyl, (It may be replaced by arbitrary positions by C_{1-6} alkyl groups, such as halogen atoms, such as fluoride, chlorine, and bromine, methyl, and ethyl, or methoxy, and any ethoxy C_{1-6} alkoxy group) A phenyl group, (It may be replaced by arbitrary positions by C_{1-6} alkyl groups, such as halogen atoms, such as fluoride, chlorine, and bromine, methyl, and ethyl, or methoxy, and any ethoxy C_{1-6} alkoxy group) benzyl -- or (in arbitrary positions.) Even if replaced by C_{1-6} alkyl groups, such as halogen atoms, such as fluoride, chlorine, and bromine, methyl, and ethyl, heterocycle groups, such as good imidazolyl, thiazolyl, oxazolyl, pyrazolyl, and pyridyl, are expressed. Heterocycle groups, such as] or (replaced by arbitrary positions by C_{1-6} alkyl groups, such as halogen atoms, such as fluoride, chlorine, and bromine, methyl, and ethyl) imidazolyl, thiazolyl, oxazolyl, pyrazolyl, and pyridyl, are expressed.

[0011]

[A mode of implementation of an invention] A manufacturing method of this invention compound is explained below.

[0012]Manufacturing method 1 [0013]

[Formula 6]



[0014](R¹, m, R², R³, R⁴, R⁵, X, and Y express the same meaning as the above among a formula, and Z expresses a methylthio group, a methylsulfonyl group, or a halogen atom.)

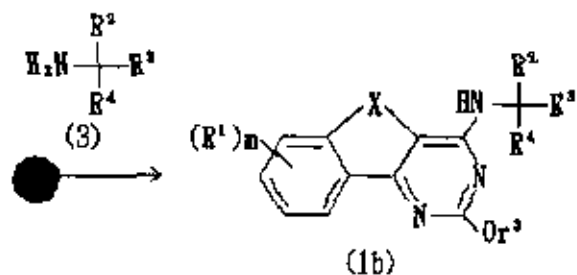
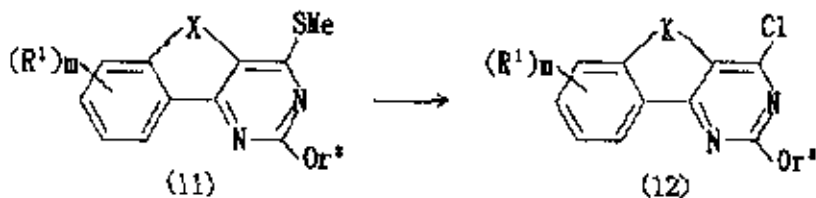
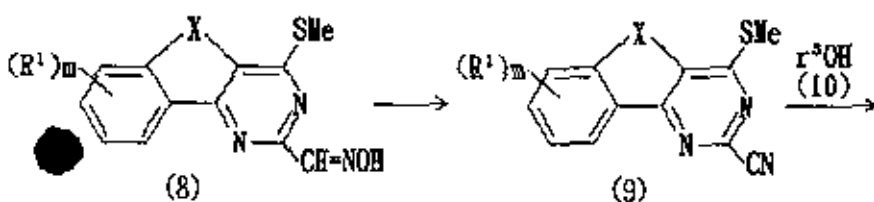
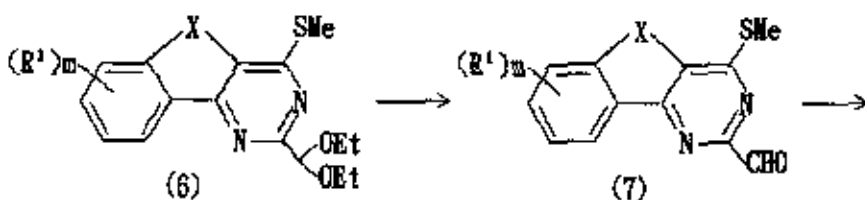
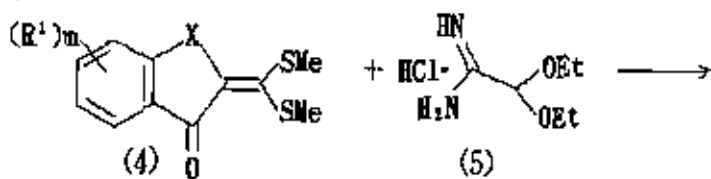
[0015]An object compound (1a) is obtained in a solvent by making a compound (2) and a compound (3) react with the reaction temperature of 10-150 **. As a solvent, aromatic hydrocarbon, such as ether, such as alcohols, such as methanol, ethanol, and n-butanol, and dioxane, benzene, and toluene, pyridine, dimethylformamide (DMF), dimethylsulfoxide (DMSO), etc. are mentioned.

[0016]A raw material compound (2) can be manufactured with a publicly known method (WO93/08167) or a conventional method.

[0017]Manufacturing-method 2: R⁵ can also manufacture a compound which is Or³ or Nr⁴r⁵ by a following method.

[0018]

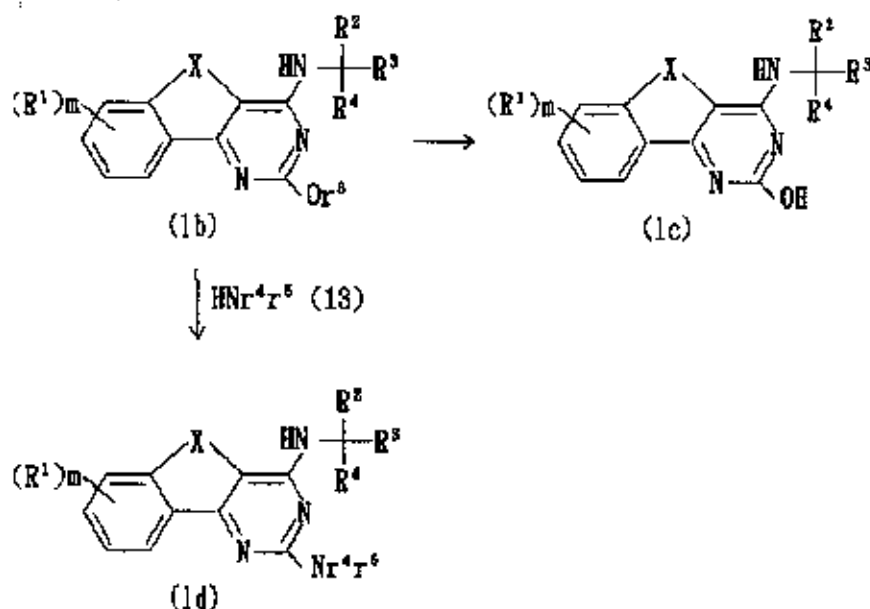
[Formula 7]



[0019]

[Formula 8]

201



[0020] (R¹, m, R², R³, R⁴, r³, r⁴, and r⁵ express the same meaning as the above among a formula.)

[0021] A compound (6) is obtained by making a compound (4) and a compound (5) react with reaction temperature of 10-100 °C under existence of a base among a solvent. As a solvent, aromatic hydrocarbon, such as ether, such as alcohols, such as water, ethanol, and n-butanol, and dioxane, benzene, and toluene, pyridine, DMF, DMSO, etc. are mentioned. As a base, alkaline metal alkoxides, such as sodium methoxide and potassium t-butoxide, inorganic bases, such as metal hydrides, such as organic bases, such as triethylamine, N,N-dimethylaniline, pyridine, and the 1,8-diazabicyclo [5.4.0] undecene 7 (DBU), and sodium hydride, potassium carbonate, and sodium hydroxide, are mentioned.

[0022] A compound (7) is obtained among solvents, such as trifluoroacetic acid, by making a compound (6) react with reaction temperature of 10-100 °C.

[0023] A compound (8) is obtained among solvents, such as methanol and ethanol, by making hydroxylamine hydrochloride react to a compound (7) with reaction temperature of 10-100 °C.

[0024] A compound (9) is obtained by making a compound (8) react with reaction temperature of 10-100 °C in solvents, such as an acetic anhydride.

[0025] A compound (11) a compound (9) and a compound (10) Ether, such as dioxane, It is obtained under existence of inorganic bases, such as sodium hydroxide, among solvents, such as aromatic hydrocarbon, such as benzene and toluene, pyridine, DMF, and DMSO, by making it react with reaction temperature of 10-100 °C.

[0026] A compound (12) is obtained among a solvent in a compound (11) by adding sodium hypochlorite at -5-40 °C under existence of acid. Halogenated hydrocarbon, such as water and chloroform, is mentioned as a solvent. Inorganic acid, such as chloride and sulfuric acid, etc. are mentioned as acid.

[0027] An object compound (1b) is obtained by making a compound (12) and a compound (3) react with reaction temperature of 10-150 °C among a solvent. As a solvent, aromatic hydrocarbon, such as ether, such as alcohols, such as methanol, ethanol, and n-butanol, and dioxane, benzene, and toluene, pyridine, DMF, DMSO, etc. are mentioned.

[0028] A compound (1c) is obtained by making a compound (1b) react with reaction temperature of 10-100 °C

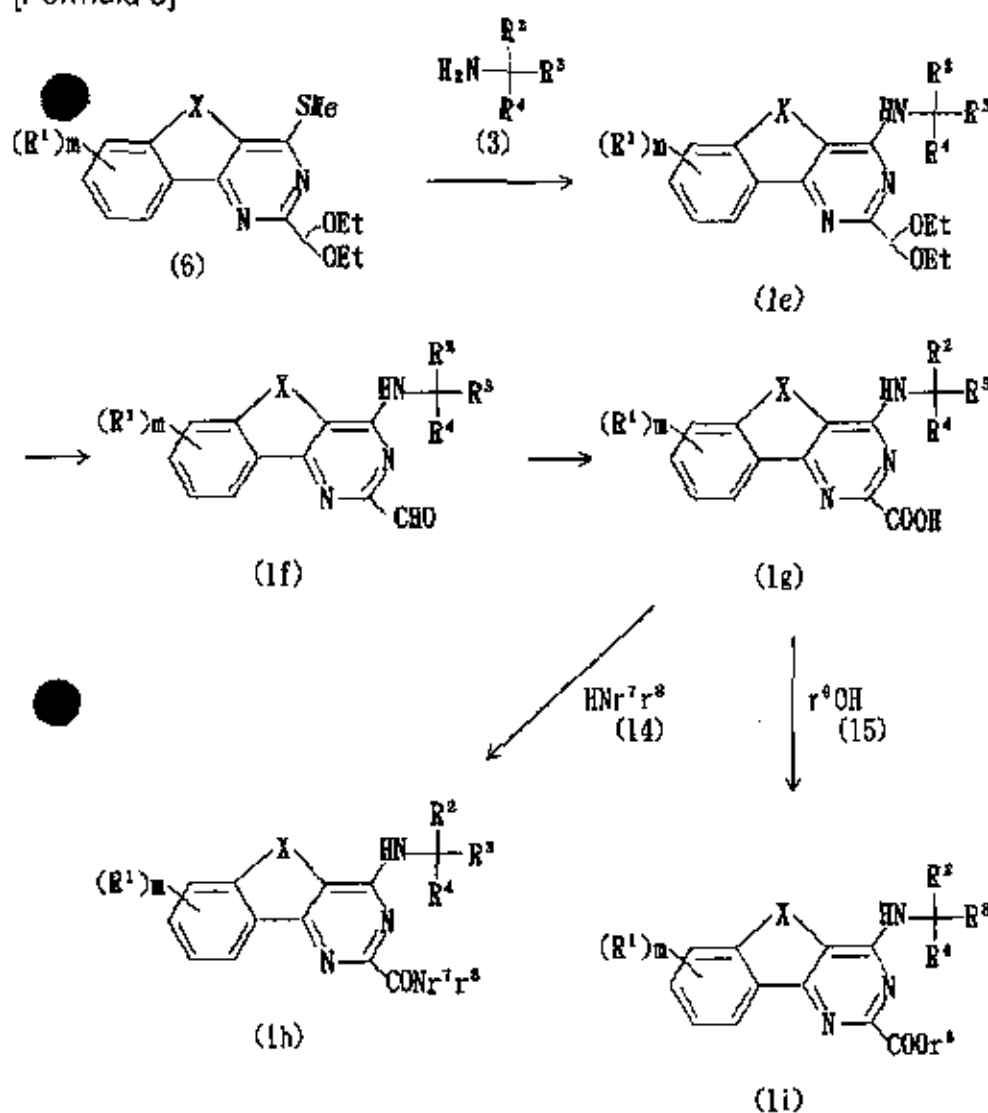
under existence of inorganic bases, such as sodium hydroxide, among solvents, such as water, methanol, and ethanol.

[0029]An object compound (1d) is inside of a solvent, or a non-solvent, and is obtained by making a compound (1b) and a compound (13) react with reaction temperature of 10-150 **. As a solvent, alcohols, such as methanol, ethanol, and n-butanol, Halogenated hydrocarbon, such as aromatic hydrocarbon, such as ether, such as dioxane, benzene, and toluene, dichloromethane, chloroform, and 1,2-dichloroethane, DMF, DMSO, etc. are mentioned. If Lewis acid, such as titanium tetrachloride, is used as a catalyst, a reaction may advance promptly.

[0030]Manufacturing-method 3: R⁵ can also manufacture a compound which is C(=O) Or⁶ or C(=O) Nr⁷r⁸ by a following method.

[0031]

[Formula 9]



[0032]A compound (1e) is obtained by making a compound (6) and a compound (3) react with the reaction temperature of 10-150 ** among a solvent. As a solvent, aromatic hydrocarbon, such as ether, such as alcohols, such as methanol, ethanol, and n-butanol, and dioxane, benzene, and toluene, pyridine, DMF, DMSO, etc. are mentioned.

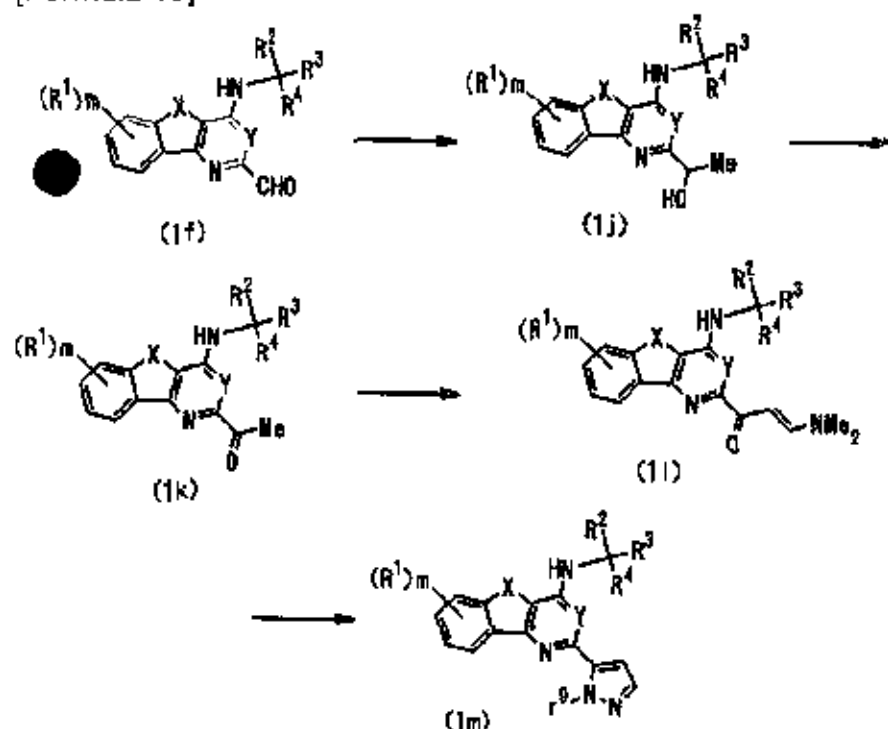
[0033] A compound (1f) is obtained by making compounds in a solvent (1e), such as trifluoroacetic acid, react with reaction temperature of 10-100 **. A compound (1g) is obtained by making a compound (1f) react to a 2in solvent-methyl-2-butene, a chlorous acid, and sodium-dihydrogenphosphate dihydrate with reaction temperature of 10-100 **.

[0034] An object compound (1h) can also be obtained among a solvent by carrying out dehydration condensation of a compound (1g) and the compound (14) with a conventional method. This dehydrating condensation reaction can be performed under existence of a suitable condensing agent. In this case, as a condensing agent, 1,3-dicyclohexylcarbodiimide, a 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, 2-ethoxy-1-carboethoxy-1,2-dihydroquinoline, etc. can be mentioned, for example. In this reaction, a reaction can be more promptly advanced by making N-imide hydroxysuccinate, 1-hydroxybenzotriazol, and 3,4-dihydro-3-hydroxy-4-oxo 1,2,3-benzotriazine live together in the system of reaction. If it is a solvent [inertness / reaction] as a reactional solvent, there will be no restriction in particular, but. For example, ether, such as diethylether, a tetrahydrofuran (THF), and 1,4-dioxane, Halogenated hydrocarbon, such as aromatic hydrocarbon, such as benzene, toluene, and xylene, dichloromethane, chloroform, and 1,2-dichloroethane, acetonitrile, dimethylformamide (DMF), dimethyl sulfoxide (DMSO), pyridine, etc. can be mentioned. a reaction -15 ** - a boiling point grade of a solvent -- it is preferably carried out at 0-80 **. A compound (1i) is obtained by making a compound (1g) react with reaction temperature of 10-150 ** under existence of acid, using a compound (15) as a solvent. Inorganic acid, such as chloride and sulfuric acid, is used as acid.

[0035] Manufacturing-method 4: A compound which is a pyrazole by which R^5 may be replaced can also be manufactured by a following method.

[0036]

[Formula 10]



[0037] A compound (1j) is obtained by making a methylmagnesium star's picture react at reaction temperature-100-50 ** among a solvent in a compound (1f) under inactive air currents, such as argon and nitrogen. Ether, such as ether, THF, and dioxane, is mentioned as a solvent. A compound (1k) can be obtained by oxidizing a compound (1j) with a conventional method among a solvent. As an oxidation method, the organic oxidant represented by metal salt, such as chromium, manganese, and silver, a metallic oxide, or dimethyl sulfoxide (DMSO) can perform easily. If it is a solvent [inertness / reaction] as a reactional solvent, there will be no restriction in particular, but halogenated hydrocarbon, such as dichloromethane, chloroform, and 1,2-dichloroethane, can be mentioned, for example. A compound (1l) can be obtained by making a compound (1k) react with the reaction temperature of 10-150 ** among solvents, such as a N,N-dimethyl HORUMUAMIDOJI methyl acetal.

[0038] An object compound (1 m) can be obtained under existence of a base among a solvent by making a compound (1l) react to type hydrogen with reaction temperature of 10-100 **. Alcohols, such as methanol, ethanol, and n-butanol, are mentioned as a solvent. As a base, inorganic bases, such as organic bases, such as triethylamine and pyridine, sodium hydroxide, and potassium carbonate, are mentioned. Hydrazine and monohydrate, methylhydrazine, etc. are mentioned as type hydrogen.

[0039] In this invention, after ending reaction can obtain an object by performing the usual post-processing. Structure of this invention compound was determined from IR, NMR, MS, etc.

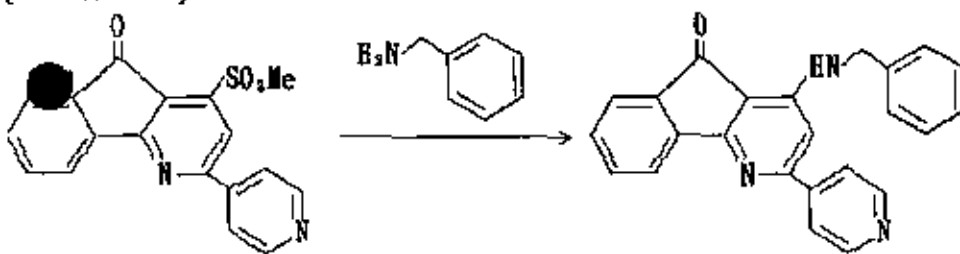
[0040] Those isomers are contained in the range of this invention although an optical isomer may exist in this invention compound (1) and its synthetic intermediate.

[0041]

[Example] Next, working example and a reference example are given and this invention is explained still more concretely.

[0042] Manufacture of working example 12-(4-pyridyl)-4-benzylamino 5H-indeno [1,2-] [b] pyridin-5-one (compound number I-1) [0043]

[Formula 11]

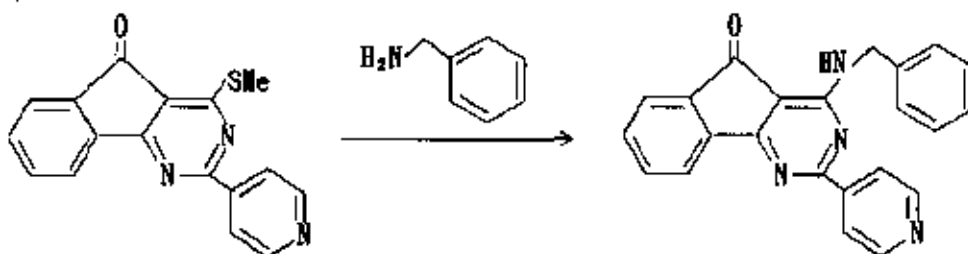


[0044] 0.2 g of 2-(4-pyridyl)-4-methylsulfonyl 5H-indeno [1,2-] [b] pyridin-5-one, 0.1 g of benzylamine, and DMF 10ml were stirred at 100 ** for 1 hour. Reaction mixture was poured out into ice water, ethyl acetate extracted, and it dried with anhydrous magnesium sulfate after washing with the saturation salt solution. Silica gel column chromatography (chloroform: methanol = 100:1) refined the rough product produced by carrying out decompression distilling off of the solvent, and 0.11 g of objects were obtained. m. p. 205 to 207 **

[0045] Manufacture of working example 22-(4-pyridyl)-4-benzylamino 5H-indeno [1,2-] [d] pyrimidine 5-one (compound number II-1) [0046]

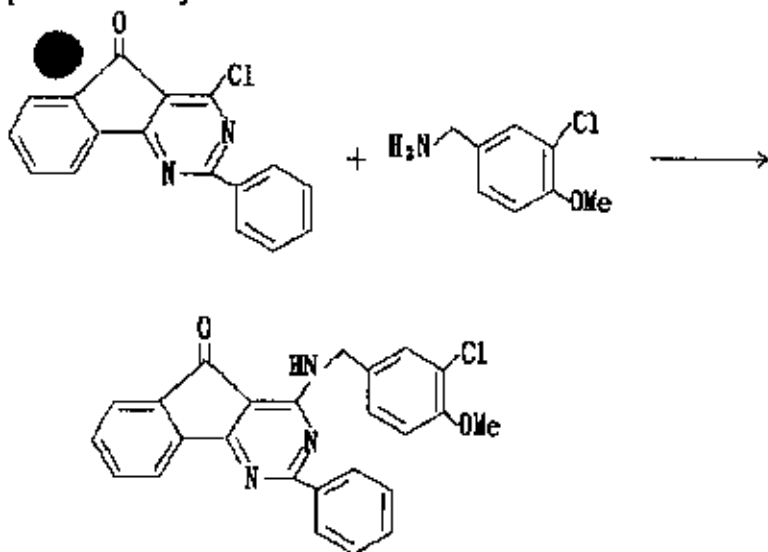
[Formula 12]

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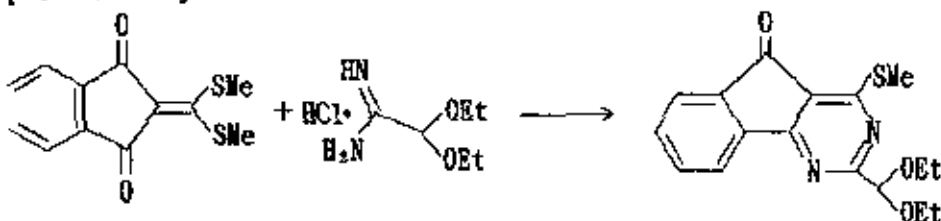
[0047] 1 g of 2-(4-pyridyl)-4-methylthio 5H-indeno [1,2-] [d] pyrimidine 5-one, 0.96 g of benzylamine, and DMF 15 ml were stirred at 100 °C for 1 hour. Reaction mixture was poured out into ice water and the precipitated crystal was dried. Silica gel column chromatography (chloroform) refined the obtained rough product, and 0.06 g of objects were obtained. m. p. 200 to 202 °C [0048] Manufacture of working example 32-phenyl-4-(3-chloro-4-methoxy benzylamino)-5H-indeno [1,2-] [d] pyrimidine 5-one (compound number II-16) [0049]

[Formula 13]



[0050] 0.19 g of 2-phenyl-4-chloro-5H-indeno [1,2-] [d] pyrimidine 5-one, 0.17 g of 3-chloro-4-methoxy benzylamine, and DMF 10 ml were stirred at 100 °C for 1 hour. Reaction mixture was poured out into ice water, ethyl acetate extracted, and it dried with anhydrous magnesium sulfate after washing with the saturation salt solution. Silica gel column chromatography (chloroform) refined the rough product obtained by carrying out decompression distilling off of the solvent, and 0.1 g of objects were obtained. m. p. 184 °C [0051] Manufacture of reference example 12-diethoxymethyl-4-methylthio 5H-indeno [1,2-] [d] pyrimidine 5-one [0052]

[Formula 14]

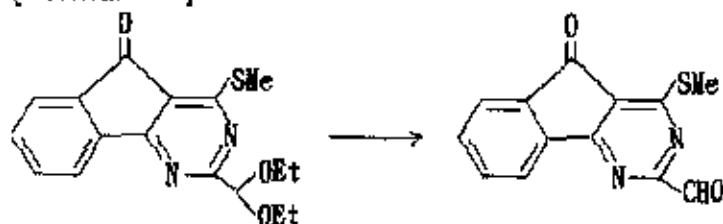


[0053] 9.35 g of 2-bis(methylthio)methylene-Indang 1,3-dione, 6.83 g of JIE 0 KISHIME chill carboxamidine

hydrochlorides, the potassium carbonate 5.16g, and DMF 950ml were stirred at 70 °C for 2 hours. Reaction mixture was poured out into ice water and the precipitated crystal was separated. water – subsequently it was washed by hexane, and it dried and 9.41 g of objects were obtained.

[0054] Manufacture of reference example 22-formyl-4-methylthio 5H-indeno [1,2-] [d] pyrimidine 5-one [0055]

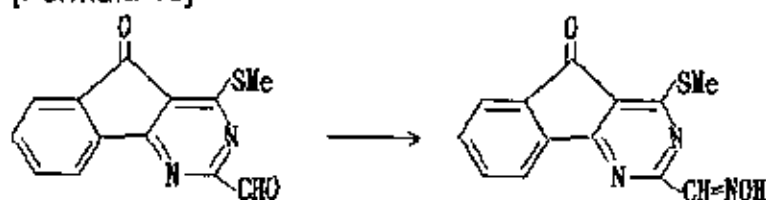
[Formula 15]



[0056] 4.0 g of 2-diethoxymethyl-4-methylthio 5H-indeno [1,2-] [d] pyrimidine 5-one and 40 ml of trifluoroacetic acid were flowed back for 4 hours. Decompression distilling off of the trifluoroacetic acid was carried out, and 20 ml of benzene was added. Decompression distilling off of the benzene was carried out, and 3.02 g of objects were obtained.

[0057] Reference example 32 - Manufacture of hydroxy imino methyl-4-methylthio 5H-indeno [1,2-] [d] pyrimidine 5-one [0058]

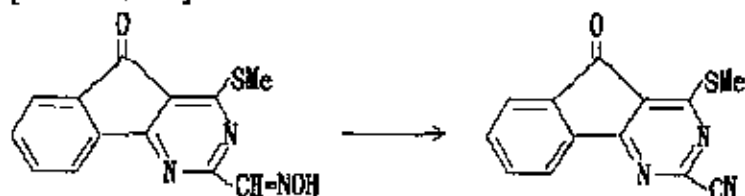
[Formula 16]



[0059] 3.02 g of 2-formyl-4-methylthio 5H-indeno [1,2-] [d] pyrimidine 5-one, the hydroxylamine hydrochloride 0.92g, and 40 ml of ethanol were flowed back for 1 hour. Reaction mixture was poured out into ice water, the precipitated crystal was separated, it was washed and dried by water and hexane, and 3.09 g of objects were obtained.

[0060] Manufacture of reference example 42-cyano 4-methylthio 5H-indeno [1,2-] [d] pyrimidine 5-one [0061]

[Formula 17]



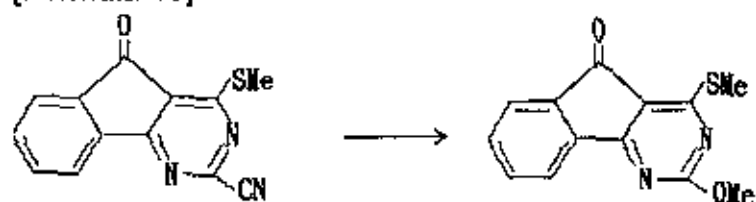
[0062] 2 - 3.09 g of hydroxy imino methyl-4-methylthio 5H-indeno [1,2-] [d] pyrimidine 5-one and 10 ml of acetic anhydride were flowed back for 1 hour. Silica gel column chromatography (chloro FURUMU: methanol = 1000:3) refined the rough product obtained by carrying out decompression distilling off of the acetic anhydride, and 1.46 g of objects were obtained.

[0063] Manufacture of reference example 52-methoxy-4-methylthio 5H-indeno [1,2-] [d] pyrimidine 5-one

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[0064]

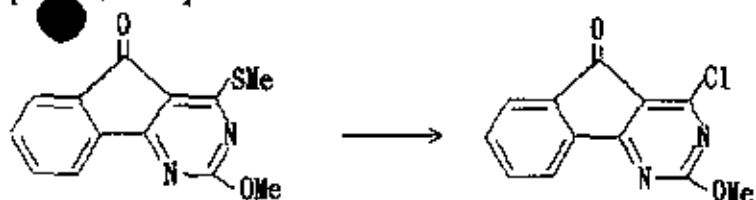
[Formula 18]



[0065] After it dissolved in 10 ml of methanol and 1.0 g of 2-cyano 4-methylthio 5H-indeno [1,2-] [d] pyrimidine 5-one was 0 **, 0.2 g of 1N-sodium hydroxide was added, and it stirred at 70 ** for 2 hours. After reaction mixture was 0 **, 1.2 ml of concentrated hydrochloric acid was added, and it stirred at the room temperature for 30 minutes. Silica gel column chromatography (chloroform) refined the rough product produced by carrying out decompression distilling off of the methanol, and 1.08 g of objects were obtained.

[0066] Manufacture of reference example 62-methoxy-4-chloro-5H-indeno [1,2-] [d] pyrimidine 5-one [0067]

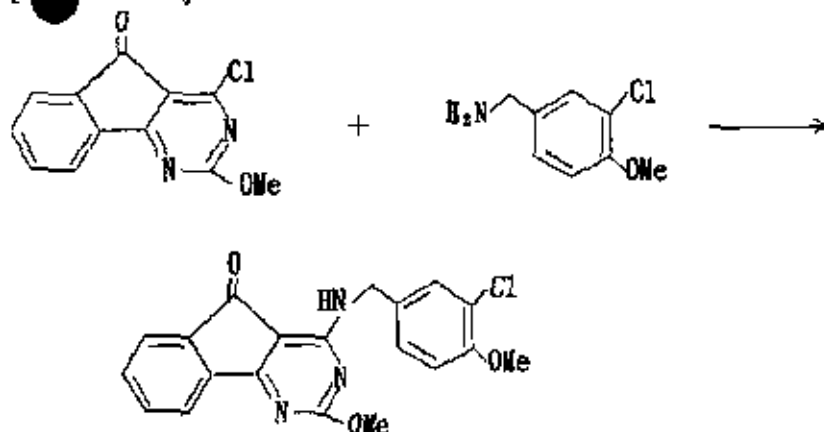
[Formula 19]



[0068] 0.36 g of 2-methoxy-4-methylthio 5H-indeno [1,2-] [d] pyrimidine 5-one, 5 ml of chloroform, 5 ml of water, and 0.76 ml of concentrated hydrochloric acid were stirred at 0 **. The sodium hypochlorite solution 4.73g was added to reaction mixture, and it stirred at 0 ** for 2 hours. 10 ml of chloroform extracted and it dried with anhydrous magnesium sulfate after washing with the saturation salt solution. Decompression distilling off of the solvent was carried out, and 0.34 g of objects were obtained.

[0069] Manufacture of working example 42-methoxy-4-(3-chloro-4-methoxy benzylamino)-5H-indeno [1,2-] [d] pyrimidine 5-one (compound number II-47) [0070]

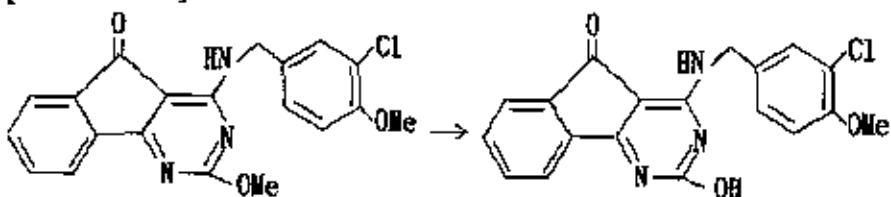
[Formula 20]



[0071] 0.34 g of 2-methoxy-4-chloro-5H-indeno [1,2-] [d] pyrimidine 5-one, 0.32 g of 3-chloro-4-methoxy benzylamine, and DMF 10ml were stirred at 100 ** for 2 hours. Reaction mixture was poured out into ice water, ethyl acetate extracted, and it dried with anhydrous magnesium sulfate after washing with the

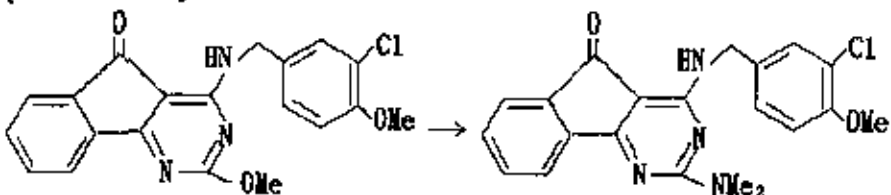
saturation salt solution. Silica gel column chromatography (chloroform) refined the rough product produced by carrying out decompression distilling off of the solvent, and 0.07 g of objects were obtained. m. p.198 ** [0072]Manufacture of working example 52-hydroxy-4-(3-chloro-4-methoxy benzylamino)-5H-indeno [1,2-] [d] pyrimidine 5-one (compound number II-48) [0073]

[Formula 21]



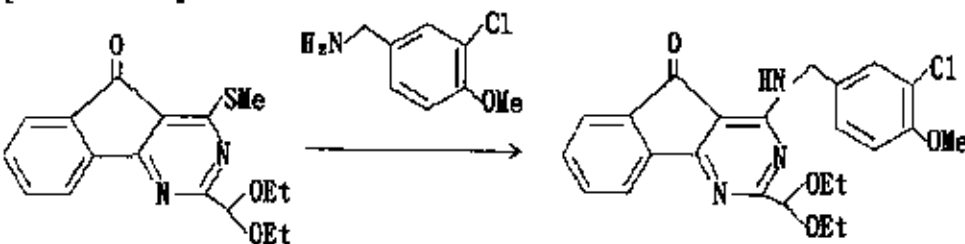
[0074]0.05 g of 2-methoxy-4-(3-chloro-4-methoxy benzylamino)-5H-indeno [1,2-] [d] pyrimidine 5-one, 1 ml of 1N-sodium hydroxide, and 20 ml of methanol were flowed back for 3 hours. Decompression distilling off of the methanol was carried out, 5 ml of water was added, and pH was set to 6-7 with 1N-hydrochloric acid. The precipitated crystal was separated and it washed with water, and it dried and 0.04 g of objects were obtained. m. p.300 or more ** [0075]Manufacture of working example 62-(N,N-dimethylamino)-4-(3-chloro-4-methoxy benzylamino)-5H-indeno [1,2-] [d] pyrimidine 5-one (compound number II-49) [0076]

[Formula 22]



[0077]0.05 g of 2-methoxy-4-(3-chloro-4-methoxy benzylamino)-5H-indeno [1,2-] [d] pyrimidine 5-one, 1 ml of 40% dimethylamine, and 3 ml of methanol were flowed back for 4 hours. Silica gel column chromatography (chloroform) refined the rough product obtained by distilling off a solvent, and 0.01 g of objects were obtained. m. p.300 or more ** [0078]Manufacture of working example 72-diethoxymethyl-4-(3-chloro-4-methoxy benzylamino)-5H-indeno [1,2-] [d] pyrimidine 5-one (compound number II-51) [0079]

[Formula 23]



[0080]8.0 g of 2-diethoxymethyl-4-methylthio 5H-indeno [1,2-d] pyrimidine, 6.24 g of 3-chloro-4-methoxy benzylamine, and DMSO80ml were stirred at 100 ** for 8 hours. Ice water was filled with reaction mixture and ethyl acetate extracted, and it dried with water and dried with anhydrous magnesium sulfate after 1-time washing with the saturation salt solution 3 times. Silica gel column chromatography (benzene/ethyl acetate =5/1) refined the rough product produced by carrying out decompression distilling off of the solvent, and 3.9 g of objects were obtained. m. p.162 to 164 ** [0081]Manufacture of reference example 72-formyl-4-(3-

206

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES

2020
Bogotá, D.C., 25/04/2010

Abogado
Dilia Rodríguez D'Alemán
(Apoderado)

ASUNTO	Radicación	06 37930
	Trámite	002
	Evento	001
	Actuación	430
	Oficio	06 1771
	Folios	009

Patente de Invención ☒ Patente de Modelo de Utilidad ☐

Vía Nacional ☐

Vía PCT (fase nacional) ☒ Cap. I ☒ Cap. II ☐

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

1. Documentos estudiados

- 1.1. Descripción: Folios: 6 a 61
- 1.2. Reivindicaciones: Folios: 62 a 68
Folios: 177 a 180 Memorial de 18/11/2009
- 1.3. Datos PCT:
- | | |
|------------------------------------|-----------------|
| <i>Solicitud Internacional:</i> | PCT/US03/031471 |
| <i>Capítulo II</i> | |
| <i>Fecha Sol. Internacional:</i> | 03/10/2003 |
| <i>Publicación. Internacional:</i> | WO05/042500 |
| <i>Fecha Pub. Internacional:</i> | 12/05/2005 |
| <i>Fecha Inicio Fase Nacional:</i> | 03/05/2006 |
| <i>Fecha Sol. Nacional:</i> | 21/04/2006 |
- 1.4. Respuesta del solicitante: Folios: 173 a 180 Memorial de 18/11/2009

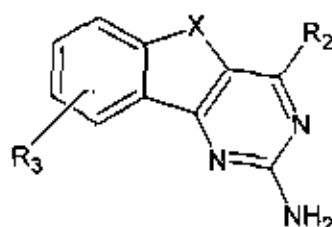
2. Objeto de la invención

Título de la solicitud

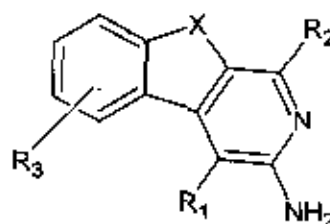
Arilidenopiridinas y arilidenopirimidinas y su uso como antagonista del receptor adenosina A2a

Reivindicaciones

Reivindicaciones 1 a 16: Se reivindican compuestos que tienen la estructura (I) y (II):



Fórmula (I)



Fórmula (II)

En especial, se reivindica la especie química:

- 2-amino-4-furan-2-il-indeno[1,2-d]pirimidin-5-ona
- 2-amino-4-fenil-indeno[1,2-d]pirimidin-5-ona
- 2-amino-4-tiofen-2-il-indeno[1,2-d]pirimidin-5-ona
- 2-amino-4-(5-metil-furan-2-il)-indeno[1,2-d]pirimidin-5-ona

Reivindicaciones 17: Se reivindica una composición farmacéutica que comprende el compuesto de la reivindicación (1) y un vehículo.

Sustento Descriptivo

La invención se refiere a arilindenopiridinas y arilindenopirimidinas capaces de tratar enfermedades neurodegenerativas y de movimiento mediante el antagonismo de los receptores de adenosina A2a.

- Una vez catalogada la invención ésta se clasificó en la sección: **A 61 K³¹/505//³¹/5355** de la **Clasificación Internacional de Patentes**.

3. De la solicitud de Patente

3.1 Reivindicaciones (artículo 30 D. 486)

Teniendo en cuenta el contenido y alcance de la materia reclamada en los folios 177 a 180 esta Dependencia se permite señalar lo siguiente:

- Los radicales **R₁**, **R₂**, **R₃** y **X** se definen en términos de categorías funcionales por lo que es necesario que el señor solicitante determine cuáles son las especies químicas que se encuentran debidamente sustentadas en el aparte descriptivo de la solicitud, toda vez que los compuestos que se encuentran ejemplificados no presentan en estricto sentido la gran variedad de estructuras cíclica que se pueden catalogar dentro de los géneros funcionales *arilo*, *heteroarilo*, *heterociclilo* y *cicloalquilo C₃₋₇*.

Las normas IUPAC para la denominación de compuestos orgánicos¹ de la referencia permiten concluir que los términos empleados para la definición de los compuestos

¹ ARYL GROUPS:

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

208
212

de fórmulas (I) y (II) no son precisos y que con su incorporación se da cabida a estructuras funcionalmente más complejas que las consideradas bajo los conceptos inventivos de las citadas fórmulas, por lo que nuevamente se requiere al señor solicitante en los términos del presente examen técnico para que incorpore en la definición Markush sólo aquellos radicales cíclicos que se encuentran debidamente sustentados en la memoria descriptiva y que además los designe por su denominación IUPAC.

4. 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: 03/10/2003, se procedió a efectuar la búsqueda de documentos relacionados en el estado de la técnica con fecha de publicación anterior a ésta.

Nº	Documento	Título	Fecha de Publicación
D1	JP2001139556	"Indenopyridine and indenopyrimidine compound and method for producing the same"	22/05/2001
D2	WO9308167	"Novel heterocyclic derivative and agrohorticultural bactericide containing same"	29/04/1993
D3	US4740602	"Indole derivatives"	26/04/1988
D4	GB1286554	"5-alkyl indenopyridine derivatives"	23/08/1972

Anterioridades D1 y D2 en los folios 106 a 115 y 190 a 205 (traducción al inglés de D1), anterioridades D3 y D4 en los folios 181 a 187.

ARENES:

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

AROMATIC COMPOUNDS:

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

HETEROARENES:

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

HETEROARYL GROUPS:

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

HETEROCYCLYL GROUPS:

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

CYCLOALKYL GROUPS:

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

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

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

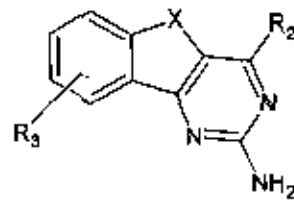
5. Análisis de patentabilidad (artículo 14 D. 486)

5.1 Novedad (artículo 16 D. 486)

El estudio de novedad del objeto reivindicado se realizó mediante comparación técnica y análisis de identidad técnica entre los elementos característicos de los compuestos reivindicados y las enseñanzas de la publicación D2.

• **Se reivindican:**

Compuestos que tienen la estructura de fórmula (I):



Fórmula (I)

En particular, las especies químicas:

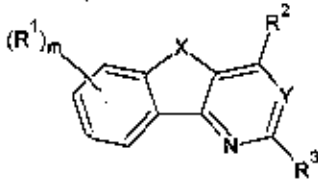
- 2-amino-4-furan-2-il-indeno[1,2-d]pirimidin-5-ona
- 2-amino-4-fenil-indeno[1,2-d]pirimidin-5-ona
- 2-amino-4-tiofen-2-il-indeno[1,2-d]pirimidin-5-ona
- 2-amino-4-(5-metil-furan-2-il)-indeno[1,2-d]pirimidin-5-ona

Y las composiciones farmacéuticas que comprenden un compuesto conforme a la reivindicación (1) y un vehículo.

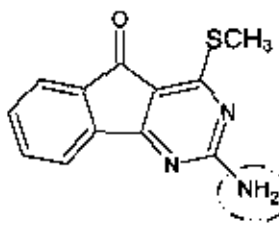
• **El estado del arte más cercano a la invención revela el siguiente documento:**

Anterioridad D2:

La publicación D2 revela compuestos de fórmula general:



Materia Reivindicada	Antecedente D2 {WO9308167}
Fórmula (I) 3-amino-Indeno-pirimidina	
X es CH2, CHOH, C=O R2 es alquilo, ariilo, heteroarilo, heterocíclico,	X es C=Z donde Z=O, CH(OH) Y es N

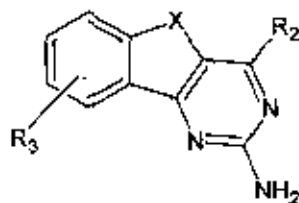
Materia Reivindicada	Antecedente D2 (WO9308167)
cicloalquilo C₃₋₇, alcoxi C₁₋₈, arioxi, alquilsulfonilo C₁₋₈, arilsulfonilo, ariilo o NR₂₄R₂₅ donde R₂₄ y R₂₅ tomados juntos con el nitrógeno forman un grupo heteroarilo o heterociclilo o cada uno de manera independiente son -H, alquilo C₁₋₈, arilo, heteroarilo, heterociclilo R₃ es -H, halógeno, OH, alquilo C₁₋₈, aril-alquilo, cicloalquilo C₃₋₇	R₁ es -H, alquilo inferior, alcoxi inferior R₂ es -H, S(O)_nr⁵ donde r⁵ representa alquilo inferior y n es un número entre 0, 1 ó 2 o un grupo alcoxi inferior. R₃ es -H, NH₂, alcoxi inferior, alquilo inferior, fenilo o un grupo heterocíclico de 5 ó 6 miembros. Fórmula II-19 (folio 110) 

5.2 Nivel Inventivo (artículo 18 D. 486)

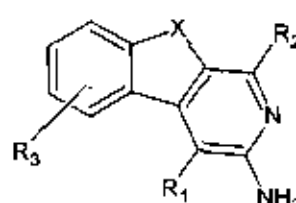
El nivel inventivo del objeto reivindicado se evaluó mediante comparación y análisis de identidad técnica entre los elementos químicos y funcionales que definen la fórmula (I) y los compuestos revelados por el estado del arte.

- **Se reivindican:**

Compuestos que tienen la estructura (I) y (II):



Fórmula (I)



Fórmula (II)

En particular, las especies químicas:

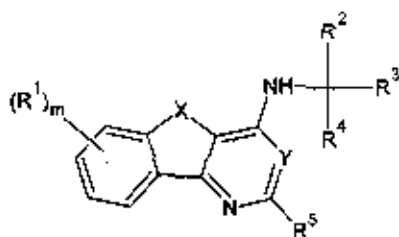
2-amino-4-furan-2-il-indeno[1,2-d]pirimidin-5-ona
 2-amino-4-fenil-indeno[1,2-d]pirimidin-5-ona
 2-amino-4-tiofen-2-il-indeno[1,2-d]pirimidin-5-ona
 2-amino-4-(5-metil-furan-2-il)-indeno[1,2-d]pirimidin-5-ona

Y las composiciones farmacéuticas que comprenden un compuesto conforme a la reivindicación (1) y un vehículo.

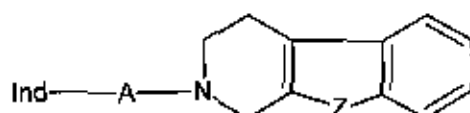
- **El estado del arte más cercano a la invención revela los siguientes documentos:**

Anterioridad D1:

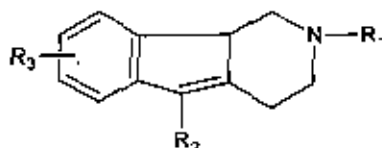
El documento D1 revela compuestos de fórmula general:

**Anterioridad D3:**

El documento D3 hace referencia a derivados de indol que presentan actividad sobre el sistema nervioso central, en especial porque son estimulantes del sistema dopaminérgico presináptico y postsináptico, por ello se utilizan como neurolépticos y antiparkinsonianos.

**Anterioridad D4:**

La publicación D4 hace mención a derivados de 5-alkil-indeno-pirimidina de fórmula general:

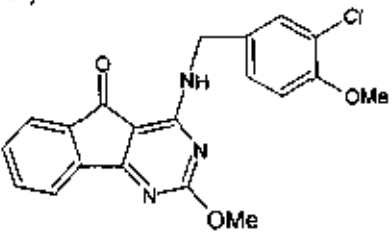
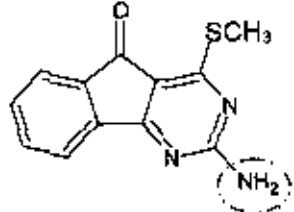
**Análisis de diferencias técnicas (Fórmula (I)):**

De esta manera, al considerar los elementos característicos de los compuestos de fórmula (I) reivindicados, esta Superintendencia encuentra las siguientes diferencias técnicas con respecto al estado del arte más cercano.

Con respecto al documento D1 la diferencia técnica estriban en que los derivados de 9-oxo-indeno-pirimidina allí divulgados no presentan un grupo amino como sustituyente de la posición 3 en la estructura fusionada. Sin embargo, la estructura Markush allí enseñada permite que en la posición 1 del anillo se encuentre un grupo amino sustituido por fenilo (ver folio 107).

Tabla 1. Comparación Estructural Fórmula (I) reivindicada

Materia Reivindicada	Antecedente D1 (JP2001139556)	Antecedente D2 (WO9308167)
Fórmula (I) 3-amino-Indeno-pirimidina		
X es CH₂, CHOH, C=O R₂ es alquilo, arilo, heteroarilo, heterociclilo, cicloalquilo C₃-7, alcoxi C₁-8, ariloxi, alquilsulfonilo C₁	X es CH₂, C(=O) Y es N o CH R¹ es -H, alquilo C₁-8,	X es C=Z donde Z=O, CH(OH) Y es N R₁ es -H, alquilo inferior, alcoxi inferior

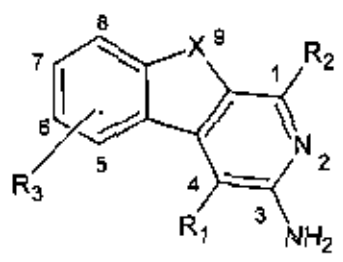
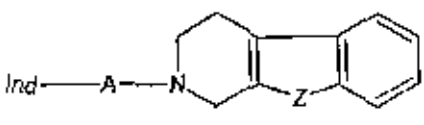
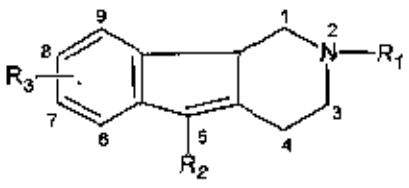
Materia Reivindicada	Antecedente D1 (JP2001139556)	Antecedente D2 (WO9308167)
R_1, arilsulfonilo, ariltio o $NR_{24}R_{25}$ donde R_{24} y R_{25} tomados juntos con el nitrógeno forman un grupo heteroarilo o heterociclilo o cada uno de manera independiente son -H, alquilo C_{1-4}, arilo, heteroarilo, heterociclilo R_2 es -H, halógeno, OH, alquilo C_{1-8}, aril-alquilo, cicloalquilo C_{3-7}	m es 0 ó 1 a 4 R_2 y R_3 es -H, alquilo C_{1-8} R_4 es fenilo o un grupo heterociclilo que puede estar sustituido R_5 es un grupo carboxi, un grupo alquil C_{1-8} carbonil, un grupo carbamilo, un grupo heterociclilo que puede estar sustituido. (folio 107) 	R_2 es -H, $S(O)_n r^5$ donde r^5 representa alquilo inferior y n es un número entre 0, 1 ó 2 o un grupo alcoxi inferior. R_3 es -H, NH_2, alcoxi inferior, alquilo inferior, fenilo o un grupo heterociclilo de 5 ó 6 miembros. Fórmula II-19 (folio 110) 

Análisis de diferencias técnicas (Fórmula (II)):

Con respecto a D3 las diferencias estriban en que el anillo de piridina no incorpora un grupo amino como sustituyente de la posición 3 ni sustituyentes sobre las posiciones 1 y 4, tal y como en el caso de la materia reivindicada. Además, la estructura Markush allí divulgada incluye sustituyentes de tipo indol-A- sobre el heteroátomo.

Con respecto a D4 las diferencias estriban en que sobre el anillo carbocíclico de cinco miembros se encuentra un sustituyente tipo R_2 que corresponde a un grupo alquilo. Y por otra parte, en dicha fórmula no se incorpora un sustituyente amino sobre el anillo heterocíclico.

Tabla 2. Comparación Estructural Fórmula (II) reivindicada

Materia Reivindicada	Antecedente D3 (US4740602)	Antecedente D4 (GB1286554)
 Fórmula (II) 3-amino-Indeno-piridina		
X es CH_2, $CHOH$, $C=O$ R_1 es $-COR_5$, donde R_5 es -H, alquilo C_{1-8}, arilo, aril-alquilo. O puede ser: $COOR_5$, $CONR_9R_{10}$, alquilo C_{1-8}. R_2 es alquilo, arilo, heteroarilo, heterociclilo, cicloalquilo C_{3-7}, alcoxi C_{1-8}, ariloxi, alkilsulfonilo C_{1-8}, arilsulfonilo, ariltio o $NR_{24}R_{25}$ donde R_{24} y R_{25} tomados juntos con	Z es $C(=O)$, $CHOH$, S, SO, SO_2, O A es $(CH_2)_n$, $CH_2-S-CH_2CH_2-$, $CH_2-SO_2-CH_2CH_2-$ Ind es 3-indolil	R_1 es -H, alquilo C_{1-10}, alquenilo C_{3-6}, alquinilo C_{3-6}, bencilo R_2 es alquilo primario o secundario C_{1-5} R_3 es -H, halógeno, alquilo C_{1-4}

el nitrógeno forman un grupo heteroarilo o heterociclito o cada uno de manera independiente son -H, alquilo C ₁₋₆ , arilo, heteroarilo, heterociclito R ₃ es -H halógeno, OH, alquilo C ₁₋₆ , aril- alquilo, cicloalquilo C ₃₋₇		
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Del Problema técnico objetivo y del efecto inesperado:

De acuerdo con la memoria descriptiva de la solicitud la invención corresponde a una alternativa terapéutica para el tratamiento de la enfermedad de Parkinson, como quiera que las estructuras de fórmula general (I) y (II) son capaces de antagonizar la actividad de la adenosina A2a.

Al respecto es preciso señalar que aún cuando sólo con el documento D3 se concluye de manera objetiva y razonable que los derivados de indeno-piridina presentan actividad como antiparkinsonianos, ello no es obstáculo para poder señalar que en virtud de las enseñanzas del estado del arte una persona versada en ciencias farmacéuticas podría derivar los elementos característicos de los compuestos reivindicados, a partir de las enseñanzas que en conjunto revelan las publicaciones D3 y D4 e inferir sobre su actividad farmacológica.

Ahora bien, en lo que respecto al núcleo de las indeno-pirimidinas es posible concluir que al combinar las enseñanzas de la publicación D2 con las reveladas por el documento D1 es posible derivar el conjunto de elementos técnicos que definen los compuestos reivindicados. Y en lo que concierne a la actividad farmacológica de los derivados, claramente en la publicación D1 se establece su aplicación en el tratamiento de la demencia.

Así las cosas, tanto los elementos técnicos como la actividad farmacológica de los núcleos reivindicados fue anticipada por el estado del arte, por lo que esta Superintendencia infiere de manera razonable que carece de altura inventiva y no comporta un verdadero salto cualitativo en la regla técnica.

En razón a esta situación, la materia reivindicada no cumple las disposiciones normativas del artículo 18 del ordenamiento comunitario (D. 486).

6. Conclusión:

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

Nº	Documento Nº	Reivindicaciones Afectadas	Requisito que Afecta
D1	JP2001139556	1 a 17	Nivel Inventivo
D2	WO9308167	1 a 17	Novedad y Nivel Inventivo
D3	US4740602	1 a 17	Nivel Inventivo
D4	GB1286554	1 a 17	Nivel Inventivo

7. Respuesta a los argumentos del señor solicitante:

Mediante memorial de fecha 18/11/2009 el señor solicitante argumenta lo siguiente:

- "el solicitante quisiera anotar que el objeto de las reivindicaciones independientes es el de establecer la materia de la invención de la manera más completa y abierta posible, en tanto que el objeto de las reivindicaciones dependientes es el de estrechar el alcance de la reivindicación de la cual dependen hasta su forma más particular".

"(...) el examinador notará que las reivindicaciones cumplen a cabalidad con su objetivo por lo que el solicitante no considera necesario delimitar las definiciones dadas a los sustituyentes en las reivindicaciones 1 a 6".

Al respecto es preciso señalar que los elementos técnicos esenciales y característicos de los compuestos reivindicados se encuentran definidos en la cláusula independiente y a partir de ellos se encuentran compuestos que han sido anticipados por el estado del arte. Así, aún cuando las reivindicaciones dependientes pretendan enseñar sobre modalidades particulares de la invención y en palabras del señor solicitante intenten estrechar el alcance de la reivindicación, es claro que existen compuestos dentro de la definición genérica de la estructura Markush que se encuentran comprendidos en el estado de la técnica que divulga la publicación D2, por lo que la conclusión razonable se relacionan con falta de novedad de la materia reivindicada.

- "(...) para que las razones que aduce ese despacho para desvirtuar la novedad fuesen ciertas, sería forzoso que se demostrara que la invención de mi mandante esté comprendida en el estado de la técnica de forma total, lo cual no sucede como se demuestra".

Como se mencionó en apartes anteriores, algunos de los compuestos que se obtienen a partir de la definición genérica de la fórmula Markush, incorporada en la cláusula 1, se encuentran en el estado de la técnica, por lo que no es cierto que este despacho deba demostrar que la totalidad del género funcional reivindicado en la cláusula 1 se encuentra divulgado expresamente en el antecedente para poder afectar la novedad de la materia reivindicada, basta con demostrar que algunas de las especies químicas que se obtienen de la generalización estructural se hallan en el estado del arte para poder afirmar de manera razonable y objetiva que la materia no cumple con el requisito de novedad.

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

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

ALIX CARMENZA CÉSPEDES DE VERGEL
Directora de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha
07 MAYO 2010

CONCEPTO TÉCNICO No. 1626

EXAMINADOR TÉCNICO
Código No. 202044