

U.F.



Industria y Comercio
SUPERINTENDENCIA

Delegatura de Propiedad Industrial
División de Nuevas Creaciones

SOLICITUD
PATENTE DE INVENCION

21. EXPEDIENTE No. **04-200062**

54. TITULO **TIENO/2,3-D/PIRIMIDINAS CON ACTIVIDAD AGONISTA COMBINADA**
DE LH Y FSH

51. CLASIFICACION INTERNACIONAL

71. SOLICITANTE **AKZO NOBEL N.V.**

DOMICILIO **Arnhem, Holanda.**

74. APODERADO **EMILIO FERRERO**
Código No. 1092

22. BOGOTA, D.C.,

S.S



Industria y Comercio
SUPERINTENDENCIA

PETITORIO



14 020062 00

Radicación : 04123062 00000000

Fecha (MM): 2004-03-04 17:03:55

Trámite : 011 PCT-PATENT 379 FASE NAC1 411 PRESENTAL

Dependencia: 2829 DIVISION DE NUEVAS CREACIONES

Folio: 95

FORMULARIO UNICO DE SOLICITUD DE PATENTE PCT ENTRADA EN FASE NACIONAL

SOLICITUD DE:

1

☒ Patente de Invención.
☐ Capítulo I.

☐ Patente de Modelo de Utilidad.
☒ Capítulo II.

2

**SOLICITANTE
(71)**

Nombre: **AKZO NOBEL N.V.**
sociedad constituida y existente bajo las
leyes de Holanda.
Dirección: **Velperweg 76,**
6824 BM Amhem,
Holanda
Domicilio: **Amhem,**
Holanda

IDENTIFICACIÓN

C.C. ☐ NIT ☐
C.E. ☐ Otro ☐
Cual _____
Número _____

3

**REPRESENTANTE
O APODERADO**

Nombre: **EMILIO FERRERO**
Dirección: **Carrera 4ª. No. 72-35**
Teléfono: **347 36 11**
Fax: **217 92 11**
E-mail: **clientes@camyo.com.**
Domicilio: **Bogotá, Colombia.**

IDENTIFICACIÓN

C.C. ☒ NIT ☐
C.E. ☐ Otro ☐
Cual _____
Número **438.019** T.P **31.929**

4

**INVENTOR (ES)
(72)**

1. **Robert, Gerard, Jules, Marie, HANSSEN**
N.V. Organon, P.O. Box 20,
5340 BH Oss,
Holanda

2. **Cornells, Marius, TIMMERS**
N.V. Organon, P.O.Box 20,
5340 BH Oss,
Holanda

5

PCT (86)

Solicitud Internacional No. **PCT/EP02/09647**

Fecha: **29 de Agosto de 2002**

Publicación Internacional No. **WO 03/020726 A1**

Fecha : **13 de Marzo de 2003**

6

Título (54)

TIENO [2,3-D]PIRIMIDINAS CON ACTIVIDAD AGONISTA COMBINADA DE LH Y FSH

7

Clasificación Internacional (51)

C07D 495/04, A61K 31/505, A61P 15/08

8

Prioridad

SI ☒ NO ☐

(33) País de Origen

EP

(32) Fecha

4 de Septiembre de 2001

(31) Número de Solicitud

01203327.0

9

Comprobante de pago No.: 04 - 16.320

Fecha: 1 de Marzo de 2004

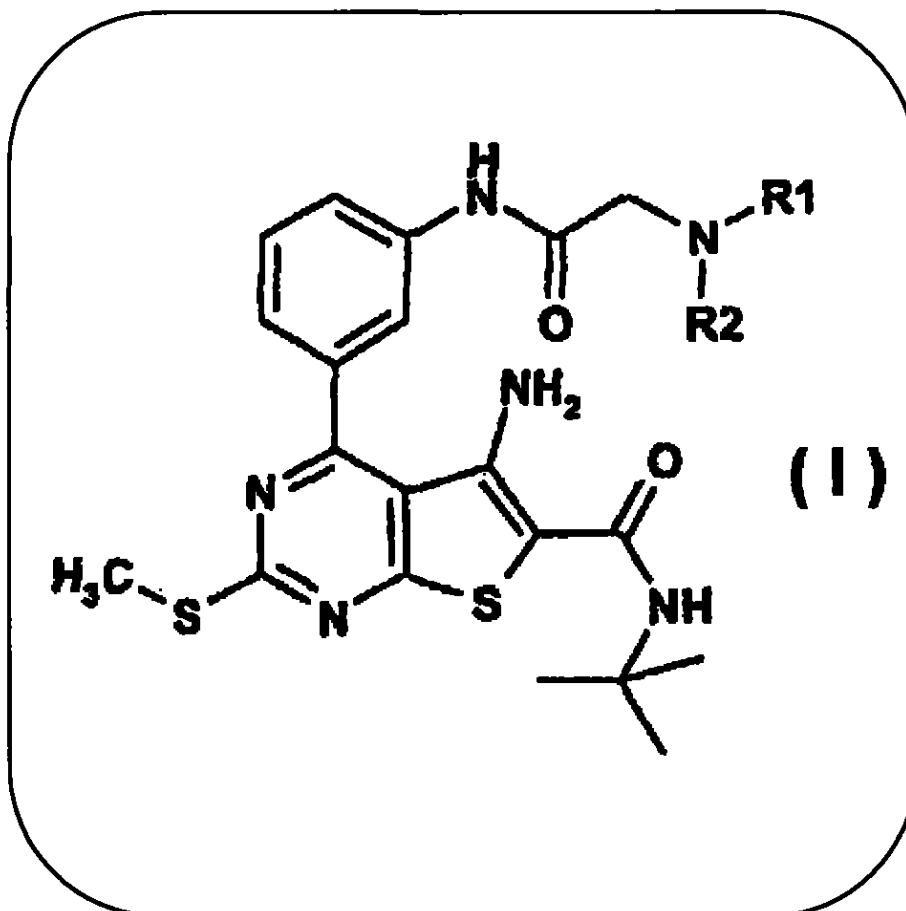
10

Anexos:

- ☒ Comprobante de pago de la tasa de presentación de la solicitud por \$ 422.000.00.
☐ Comprobante de pago por reivindicación de prioridad.
☒ Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
☒ Poderes, si fuere el caso.
☒ Documento de cesión del inventor al solicitante o a su causante.
☐ Declaraciones.
☒ Copia de la solicitud Internacional. (Resumen, descripción, reivindicaciones, dibujos)
☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
☒ Copia del examen preliminar efectuado por la IPEA.
☒ Traducción del examen preliminar efectuado por la IPEA.
☐ De ser el caso, copia del contrato de acceso.
☐ De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
☐ De ser el caso, certificado de depósito del material biológico.
☒ Arte final 12x12
☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
☐ Otros

11

FIGURA CARACTERÍSTICA



12

Solicito la concesión de la patente,

NOMBRE:

EMILIO FERRERO

FIRMA:

C.C. 438.019 de Usaquén T.P. 31.929

PRP

For patents, utility models, industrial designs, trademarks, commercial names, trade emblems, slogans.

Para patentes, modelos de utilidad, diseños industriales, marcas de fábrica, nombres comerciales, enseñas, lemas comerciales.

REPRESENTACION Y PODER

REPRESENTATION AND POWER OF ATTORNEY

I (we), the undersigned/Yo (nosotros), abajo firmado (s)

AKZO NOBEL N.V.

of/domiciliado (s) en Velperweg 76, 6824

BM Arnhem, THE NETHERLANDS

por el presente nombramos a EMILIO FERRERO, tpa. 31929; GONZALO PERDOMO, tpa. 831; LUZ CLEMENCIA DE PAEZ, tpa. 23555 y GERMAN CAVELIER, tpa. 832, domiciliados en la Carrera 4ª N° 72-93, Bogotá, Colombia, en obediencia a lo dispuesto en el parágrafo 1º del Artículo 543 del Código de Comercio, el primero como principal y los demás como suplentes, en su orden, como mis (nuestros) representantes en todos los asuntos de propiedad industrial con facultad para recibir notificaciones y nombrar apoderados judiciales o extrajudiciales. El primer representante suplente reemplazará al principal en caso de ausencia o impedimento temporal o definitivo de aquél. La misma regla se aplicará cuando el segundo representante suplente haya de reemplazar al primero, o el tercero al segundo. En tales casos, el representante principal, o el primero, o segundo suplente, en su caso, o ambos, declararán su intención de no ejercer la representación mediante declaración autenticada por Notario Público en Colombia, o por Notario u otro Funcionario Público, o Cónsul de Colombia, en el extranjero; y si se tratare de impedimento, con el certificado respectivo. Si alguno de los nombrados faltare definitivamente, el siguiente tomará su lugar. Cuando cesare la ausencia o impedimento del representante principal, o de su primer o segundo suplente, en su caso, podrán ejercer la representación, en su orden, uno u otros según el caso, asumiéndola por el solo hecho de ejercerla, cesando en ese momento el ejercicio de la representación por el primero, segundo o tercer suplente en su caso.

Además, confiero (conferimos) poder a los abogados arriba nombrados, para obtener la protección de mi (nuestra) propiedad industrial y contra la competencia desleal, a cuyo efecto autorizo (amos) a los dichos apoderados para que me (nos) representen ante cualesquiera entidades o personas, ejerzan o no jurisdicción, especialmente ante las del orden administrativo, contencioso-administrativo y judicial, así como los tribunales de arbitramento, en todo lo concerniente a los siguientes asuntos: a) Obtención de patentes de invención, modelos de utilidad, y diseños industriales; el registro de marcas de fábrica, colectivas, defensivas, de servicio, lemas comerciales, nombres comerciales, enseñas, variedades vegetales y denominaciones de origen; su renovación, traspaso, cambio de nombre o domicilio, cancelación voluntaria; y el registro de licencias de uso de esos derechos; b) Las acciones de competencia desleal, protección del consumidor, oposiciones u observaciones, cancelación administrativa y judicial, nulidad, medidas cautelares, concesión de licencias, la tutela, la protección de secretos industriales, y en general los juicios civiles, penales, administrativos o contencioso-administrativos relacionados con estos derechos; acciones y procesos que promovamos o se nos promuevan. Y para que en todos los asuntos arriba determinados, puedan sustituir este mandato, transigir, conciliar, admitir los hechos del proceso, asistir, cancelar, recibir, renunciar, y ratificar los actos de agentes oficiosos.

In due compliance with the terms of paragraph 1st. of article 543 of the Commercial Code, do hereby appoint EMILIO FERRERO, tpa. 31929; GONZALO PERDOMO, tpa. 831; LUZ CLEMENCIA DE PAEZ, tpa. 23555 and GERMAN CAVELIER, tpa. 832, domiciled at Carrera 4ª N° 72-93, Bogotá, Colombia, the first as principal and the others as alternates, in the order of their appointment, as our representatives for all industrial property matters with faculty to receive notifications and to appoint attorneys in and out of Court. The first alternate shall replace the principal in case of his absence or of temporal or definitive impediment. The same rule will apply when the second alternate representative is to replace the first one, or when the third is to replace the first or second alternates in their turn, or both of them, second. In such cases, the principal representative, or the first or second alternates in their turn, or both of them, shall state their intention not to act as representatives through a declaration given before a Notary Public in Colombia, or before a Notary or another Public Official or a Colombian Consul abroad; and in case of impediment, the appropriate certificate shall suffice. If any of the appointees were to be definitely absent, the following alternate shall take his place. When the absence or impediment of the principal representative, or of the first or second alternate in their turn ceases, the representation can be taken again in their sequence, by the principal, the first or second alternate depending on case, and the mere fact or its exercise will suffice. The exercise of the representation by the first, second or third alternates in their turn shall end at such time.

In addition, we grant a Power of Attorney in favor of the above-named attorneys-at-law so that they may obtain the protection of my (our) industrial property and against the unfair competition, ~~provided that the said attorneys to represent me (us) before the said entities or persons, with or without jurisdiction, especially before administrative, administrative contencioso-administrativo, as well as before Arbitration Court, in all matters concerning the following:~~ a) Obtainment of patents, utility models and industrial designs; the registration of trademarks, collective, defensive and service marks, slogans, commercial names, trade emblems, vegetal varieties and denominations of origin; its renewal, assignment, change of name or domicile, voluntary cancellation; and the registration of licenses of use of the above rights; b) Actions of unfair competition, protection to the consumer, oppositions or observations, administrative or Court cancellation, nullity, infringement, granting of licenses, the action for writ mandamus, the protection of trade secrets, and in general the civil, penal, and administrative suits relating to those rights; actions and suits instituted by me (us) or against me (us). And that in all the above matters they may substitute this Power of Attorney, compromise, conciliate, admit the facts of the case, desist, cancel, receive, resign, and ratify acts done by representatives without a power of attorney.

Given and signed this Dutch Summit day 6 AUG 1998

F.G.M. Hermans

In/en

Director Patents Pharma

Signature

AKZO NOBEL N.V.

E.H. Reerink

Deputy Director
Legal Affairs

CAVELIER ABOGADOS
WFODERE-179 (MINUTA N° 12.1.12.5)

TRADUCCION No. 18.11/98
MARIA ELVIRA MARELO
Traductora e Intérprete Oficial
Inglés - Español - Inglés
Bos. N.º 2470 Min. Justicia

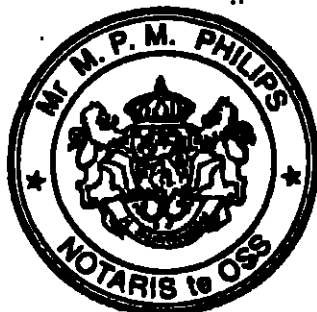
LEGALIZACION

El Señor Cónsul de Colombia debe expedir un certificado consular sobre (1) la existencia legal de la compañía que otorga el poder, (2) que ésta ejerce su objeto social, y (3) que las personas que otorgan el poder están autorizadas para darlo. A este efecto les solicitamos que muestren al Señor Cónsul las pruebas que acreditan esos hechos (1), (2) y (3).

LEGALIZATION

The Colombia Consul must issue a certificate, on (1) the legal existence of the company, (2) that it is in accordance with the Power-of-Authority, (2) that it is in accordance with the company purposes, and (3) that the persons who execute the Power of Attorney is authorized to do so. To this effect, these show the Consul the evidence to prove the above facts (1), (2) and (3).

Seen for legalization of the signatures of Mr. F.G.M. Hermans and Mr. E.H. Reerink by me, Mr. Martinus Petrus Maria Philips, notary public at Oss, the Netherlands, on this 26th day of August 1998.



[Signature]

TRADUCCION No. 18.11/98
MARIA ELVIRA MARTELO
Traductora e Interprete Oficial
Inglés - Español - Inglés
Res. No. 2879 Min. Justicia

15499



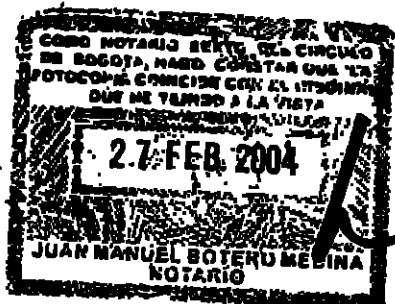
CHAMBER OF COMMERCE AND INDUSTRY
FOR OOST-BRABANT (NEDERLAND)

EXCLUSIVE POWER FOR LEGALIZATION OF
THE ABOVE/AFGEZ. VERMINDERED SIGNATURE(S)

27 AUG 1998

KAMER VAN KOOPHANDEL
OOST-BRABANT
's-HERTOGENBOSCH

J. Schellekens



Gezien voor legalisatie van de handtekening
van dhr/mw Schellekens

's-Gravenhage, 09 SEP 1998



De Minister van
Buitenlandse Zaken
voordreef,

Leges f 20,- H.H. van POORTEN

NOTA PARA EL SEÑOR CONSUL DE COLOMBIA: Según los artículos 65 del C. de P.C. y 480 del C. de Co., si el poderdante es una sociedad, el Señor Cónsul debe certificar que tuvo a la vista las pruebas de su existencia, que ejerce su objeto social y que quien confiere el poder es su representante.



CONSULADO DE COLOMBIA

El suscrito. Cónsul de Colombia en La Haya, Holanda,
vistos los documentos presentados por los interesados,

CERTIFICA:

Que el Señor Martinus Petrus Maria PHILIPS, quien como Notario Público de Oss, Países Bajos, autenticó las firmas de los signatarios del poder precedente, ejercía en la fecha las funciones indicadas, y su firma corresponde a la registrada en este Consulado.

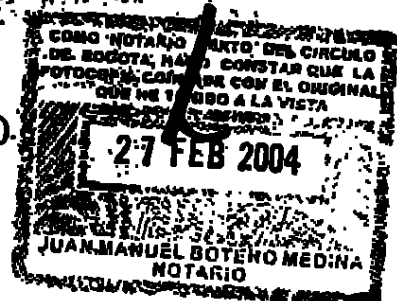
Que la Compañía AKZO NOBEL N.V. es una Sociedad constituida de acuerdo con las leyes de los Países Bajos, cumple su objeto conforme a las mismas y se halla registrada en la Cámara de Comercio y Fábricas de Centraal Gelderland, Arnhem, bajo el número 09007809;

Que los Señores Franciscus Guilielmus Maria HERMANS y Engbert Harmen REERINK, signatarios del presente documento, quienes en su carácter de Apoderados de la Empresa AKZO NOBEL N.V., conjuntamente tienen facultad para ello, y cuyas firmas fueron autenticadas ante el Notario Público de Oss, Señor Martinus Petrus Maria PHILIPS, son los representantes legales de la citada Empresa en este País.

El Cónsul de Colombia en La Haya, Países Bajos, no asume responsabilidad alguna por el contenido del documento.

Esta certificación se expide en La Haya, Países Bajos, a los seis (06) días del mes de Noviembre de mil novecientos noventa y ocho (1998).

Impuesto de Timbre	US\$	6.00.
Derechos Consulares	US\$.	100.00
Costo Total Pagado	US\$.	106.00



Certificación No. 206

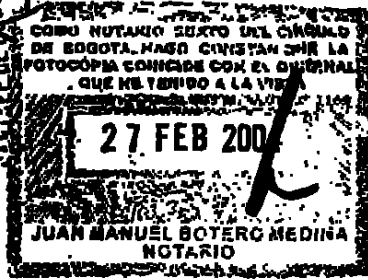
JOSE IGNACIO VILLEGAS CORTES
CONSUL DE COLOMBIA
LA HAYA

TRADUCCION No. 18.11/98
MARIA ELVIRA MARTELO
Traductora e Interprete Oficial
Inglés - Español - Inglés
Res. No. 2879 Min. Justicia

NO SE ASUME
RESPONSABILIDAD DEL TEXTO

90 NOV 1971 AM 11:56

JEFE DE LEGALIZACIONES
SANTAE DE BOGOTA D.C.



MINISTERIO DE RELACIONES
EXTERIORES

300803

ESTA FIRMA APARECE EN EL
DOCUMENTO DESEMPEÑA
LAS FUNCIONES INDICADAS

5

TRADUCCIÓN OFICIAL No. 18.11/98 preparada por María Elvira Martelo, Traductora Oficial debidamente aprobada por el Ministerio de Justicia de Colombia por Resolución 2879 de 1995 y reconocida por el Ministerio de Relaciones Exteriores.

(A continuación se traducen los sellos y legalizaciones de un documento escrito en inglés y español, por el cual AKZO NOBEL N.V. otorga poder a EMILIO FERRERO, GONZALO PERDOMO, LUZ CLEMENCIA DE PAEZ Y GERMAN CAVELIER).. Dado y firmado el 6 de agosto de 1998. (Firma ilegible) F.G.M. Hermans, Director de Patentes Farmacéuticas. (Firma ilegible) E.H. Reerink, Subdirector de Asuntos Jurídicos. (Sello Corporativo) AKZO NOBEL N.V.

(Al dorso) Visto por mí, Sr. Martinus Petrus Maria Philips, notario público en Oss, Países Bajos, hoy 26 de agosto de 1998, para legalización de las firmas de F.G.M. Hermans y E.H. Reerink. (Firma ilegible).

(Legalización) CAMARA DE INDUSTRIA Y COMERCIO PARA OOST-BRABANT (PAÍSES BAJOS). Visto exclusivamente para la legalización de la(s) firma(s) que antecede(n). Agosto 27 de 1998. (Firma ilegible) J. Schellenkens. (Sello en holandés).

(En español) Certificación de las firmas que anteceden y de la existencia legal de AKZO NOBEL N.V. expedida por el Consulado de Colombia en La Haya el día 6 de noviembre de 1998, bajo el N .

206. Firmado JOSE IGNACIO VILLEGAS CORTES, Cónsul de Colombia, La Haya. Pagado impuesto de timbre.

(Al dorso) Legalización de la firma que antecede expedida por el MINISTERIO DE RELACIONES EXTERIORES bajo el No. 300803 del 19 de NOVIEMBRE de 1998, firmado por el Jefe de Legalizaciones.

Es traducción fiel y completa de la cual se deja copia en esta oficina para su confrontación.

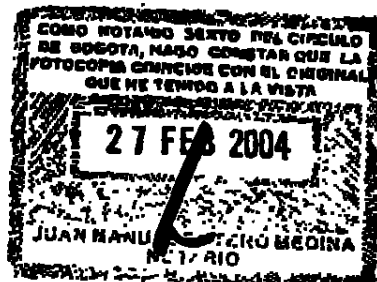
COLO 11214-801-001-3

Id. 6

Nov. 20/98

Maria E. Martelo
TRADUCCION No. 11198
MARIA ELVIRA MARTELO
Traductora e interprete Oficial
Inglés - Español - Inglés
Res. No. 2879 Min. Justicia

COMO NOTARIO SEXTO DEL CIRCULO DE SANTA FE DE BOGOTA, HAGO CONSTAR QUE LA(S) ANTERIOR(ES) FIRMA(S) PUESTA(S) POR *[Firma]* IDENTIFICADOS CON C.C. No.(s) *[Firma]* ES/SON AUTENTICA(S)
SANTA FE DE BOGOTA, 23 NOV. 1998



MINISTERIO DE RELACIONES EXTERIORES
198457
[Firma]
CUNA FIRMA APARECE EN EL DOCUMENTO DESDEPENSA LAS FUNCIONES INDICADAS

NO SE ASUME RESPONSABILIDAD DEL TEXTO
98 NOV 24 PM 12:06
JEFE DE LEGALIZACIONES
SANTA FE DE BOGOTA D.C.

ABOGADOS

EDIFICIO SISKI
CARRERA 4ª N° 72-35
BOGOTÁ, 8- COLOMBIA

CESION

ASSIGNMENT

Yo, (nosotros), abajo firmado(s)

I (we), the undersigned

HANSSEN,
Robert, Gerard, Jules, Marie
N.V. Organon
P.O. Box 20
5340 BH Oss - The Netherlands

TIMMERS,
Cornelia, Marius
N.V. Organon
P.O. Box 20
5340 BH Oss - The Netherlands

domiciliado (s) en

of

declaro(amos) bajo juramento ser único(s) y verdadero(s)
inventor(es) de la invención:

state(s) under oath to be sole and true inventor(s) of the
invention:

"THIENO[2,3-D]PYRIMIDINES WITH COMBINED LH AND FSH AGONISTIC ACTIVITY"

declaro(amos) así mismo que cedo(amos) y transfiero
(erimos), sin limitación, a favor de la sociedad

state as well, that assign, without reservations or
limitations in favour of

Akzo Nobel N.V.

Akzo Nobel N.V.

constituida y existente de conformidad con las leyes de

a corporation constituted and existing in conformity
with the laws of

Holanda

The Netherlands

domiciliada en

domiciled in

Velperweg 76
6824 BM Arnhem, Holanda

Velperweg 76
6824 BM ARNHEM - The Netherlands

todos los derechos inherentes a dicha invención y
que los citada Compañía queda facultada para
solicitar en su nombre la patente correspondiente
en la República de Colombia.

all rights inherent to said invention and that the above
mentioned company hereby is enabled to apply, in its
name, for the corresponding patent in the
Republic of Colombia

Dado y firmado hoy/Given and signed this

19th day of January

en/in

HANSSEN,
Robert, Gerard, Jules, Marie

TIMMERS,
Cornelia, Marius

Firma

Signature

CAVELIER ABOGADOS
WPPODERE-343

(Legalization required)

(Legalización necesaria)

AUTENTICACION NOTARIAL (INDIVIDUE)

NOTARIAL AUTHENTICATION (INDIVIDUAL)

8

A los días del mes de _____ de _____
ante mí, Notario Público de _____
compareció(eron) personalmente _____

On this _____ day of _____
before me, a Notary Public of _____
personally appeared _____

a quien(es) doy fe de conocer y me consta que es(son)
persona(s) firmante(s) del documento que precede, y
quien(es) tiene(n) capacidad legal para otorgarlo.

to me known, and known to me to be the person(s) who
executed that foregoing document, and who has(have)
legal capacity to execute it.

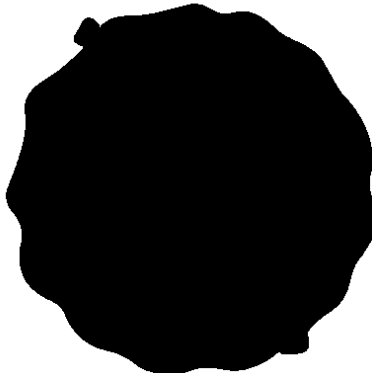
Notario Público Notary Public

APOSTILLE (Convention de La Haye de 5 octobre 1961)	
1.	Country:
This public document	
2.	has been signed by
3.	acting in the capacity of
4.	bears the seal/stamp of
Certified	
5.	at
6.	the
7.	by
8.	No.
9.	Seal/stamp
10.	Signature
..... 	

Seen by me, mr. Robbert Alexander Gallas, civil-law notary practising in The Hague, for the authentication of the signatures on the attached document of:

- Mr Robert Gerard Jules Marie Hanssen, born on the thirtieth of April nineteenhundred sixty in Maastricht, The Netherlands, residing at Bernheze, The Netherlands, holder of a Dutch passport, number NB9304370; and
- Mr Cornelis Marius Timmers, born on the nineteenth of May nineteenhundred seventy in Katwijk, The Netherlands, residing at Oss, The Netherlands, holder of a Dutch drivers licence, number 3168595091,

The Hague, the twenty-sixth day of January twothousandfour.



All instructions are carried out on the basis of an agreement as meant in Section 400 of Book 7 of the Dutch Civil Code by Pels Rijcken & Droogleevers Fortuijn, a partnership consisting of private companies with limited liability. The agreement is subject to terms of business registered with the District Court at The Hague. A limitation of liability is included in these terms of business. The terms of business will be provided on request. These can also be accessed at www.pdf.nl.

A P O S T I L L E

(Convention de La Haye du 5 octobre 1961)

1. Pais: NEDERLAND
El presente documento público
2. ha sido firmado por mr R.A. Gallas
3. quien actúa en calidad de notario, en 's-Gravenhage
4. y está revestido del sello/timbre de el susodicho notario

Certificado

5. en 's-GRAVENHAGE 6. el día 27 januari 2004
7. por de Griffier van de Arrondissementsrechtbank
8. bajo el número: 2004-286
9. Sello/timbre: 10. Firma:

J.A. van der Heljden



TRADUCCIÓN OFICIAL 023/2004 DE UN DOCUMENTO ESCRITO EN INGLÉS Y EN ESPAÑOL, REALIZADA POR EDUARDO CALADO NOGUERA, TRADUCTOR OFICIAL APROBADO POR RESOLUCIÓN 541 DEL 27 DE FEBRERO DE 1976 POR EL MINISTERIO DE JUSTICIA Y DEBIDAMENTE REGISTRADO ANTE EL MINISTERIO DE RELACIONES EXTERIORES DE LA REPÚBLICA DE COLOMBIA Y MEDIANTE EL CUAL HANSSSEN, Robert, Gerard, Jules, Marie, N.V Organon, P.O. Box 20, 5340 BH Oss, The Netherlands (Holanda) y Cornelis, Marius TIMMERS, N.V. Organon, P.O. Box 20, 5340 BH es, The Netherlands (Holanda) declaramos ser los inventores únicos y verdaderos de la invención: (Tieno[2,3]pirimidinas con actividades combinadas de agonistas LH y FSH) , DECLARA POR EL PRESENTE QUE CEDE DICHA INVENCION A AKZO NOBEL N.V EMPRESA CONSTITUIDA Y EXISTENTE BAJO LAS LEYES DE HOLANDA, DOMICILIADA EN VELPERWEG 76, 6824 BM ARNHEM, HOLANDA, JUNTO CON TODOS LOS DERECHOS INHERENTES Y QUE DICHA COMPAÑÍA QUEDA FACULTADA PARA SOLICITAR EN SU NOMBRE LA PATENTE CORRESPONDIENTE EN LA REPÚBLICA DE COLOMBIA.

FIRMADO: ROBERT, GERARD, JULES, MARIE HANSSSEN Y CORNELIS MARIUS TIMMERS.

Visto por mi, ROBBERT ALEXANDER GALLAS, notario de ley civil practicante en La Haya, para la autenticación de las firmas que aparecen en el documento adjunto de Robert Gerard Jules Marie Hanssen, nacido el 30 de abril de 1960 en Maastricht, Holanda, residente en Bernheze, Holanda, portador de un pasaporte holandés número NB9304370 y Cornelis Marius Timmers, nacido el 19 de mayo de mil novecientos setenta en Katwijk, Holanda, residente en Oss,

Holanda, portador de la licencia de conducción holandesa número 3168595091.

La Haya, 26 de enero de 2004.

APOSTILLA:

(Convención de La Haya del 5 de octubre de 1961)

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6. el 27 de enero de 2004

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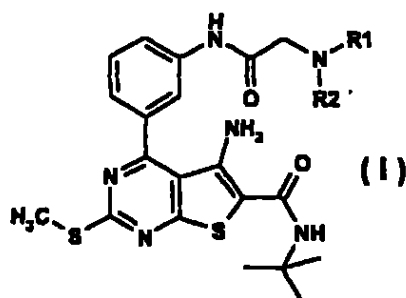
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(54) Title: THIENO[2,3-D]PYRIMIDINES WITH COMBINED LH AND FSH AGONISTIC ACTIVITY



(57) Abstract: The invention relates to thieno[2,3-d]pyrimidine derivatives accord-
ing to general formula (I), or a pharmaceutically acceptable salt thereof, wherein
N(R1)R2 are joined in a (2-6C)heterocycloalkyl ring. The compounds of the inven-
tion have LH as well as FSH receptor activating activity and can be used in fertility
regulating therapies.

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Thieno[2,3-*d*]pyrimidines with combined LH and FSH agonistic activity

The invention relates to compounds having glycoprotein hormone agonistic activity, in particular to compounds having both Luteinizing Hormone (LH) and Follicle Stimulating Hormone (FSH) agonistic activity. The invention furthermore relates to pharmaceutical compositions containing the same as well as to the use of these compounds in medical therapy, particularly for use as a control of fertility.

Gonadotropins serve important functions in a variety of bodily functions including metabolism, temperature regulation and the reproductive process. The hypophyseal gonadotropins FSH and LH for example play a pivotal role in the stimulation of follicle development and maturation whereas LH is involved in induction of the ovulatory process (Sharp, R.M. Clin. Endocrinol 33, 787-807, 1990; Dorrington and Annstrong, Recent Prog. Horm. Res 35, 301-342, 1979; Levy et al, Human Reproduction 15, 2258-2265, 2000).

Currently, LH is applied clinically, in combination with FSH, for ovarian stimulation i.e. ovarian hyperstimulation for *in vitro* fertilisation (IVF) and induction of ovulation in infertile anovulatory women (Insler, V., Int. J. Fertility 33, 85-97, 1988, Navot and Rosenwaks, J. Vitro Fert. Embryo Transfer 5, 3-13, 1988), as well as for male hypogonadism and male infertility.

Gonadotropins act on specific gonadal cell types to initiate ovarian and testicular differentiation and steroidogenesis. The actions of these pituitary and placental hormones are mediated by specific plasma membrane receptors that are members of the large family of G-protein coupled receptors. They consist of a single polypeptide with seven transmembrane domains and are able to interact with the Gs protein, leading to the activation of adenylyl cyclase.

Gonadotropins destined for therapeutic purposes can be isolated from human urine sources and are of low purity (Morse et al, Amer. J. Reproduct. Immunol. and Microbiology 17, 143, 1988). Alternatively, they can be prepared as recombinant gonadotropins. In addition to these proteins, gonadotropin receptors can be activated or deactivated by synthetic low molecular weight compounds. Bicyclic heteroaromatic

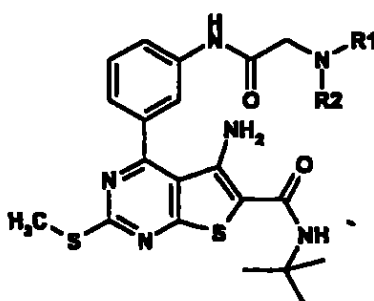
compounds have been described in WO 00/61586. By *in vitro* and *in vivo* experiments they are shown to be useful as LH agonists.

In normal females the release of pituitary LH and FSH is characterized by a mid-cycle surge which precedes the ovulation. Ovulation is characterized by three distinct physiological phenomena *i.e.* oocyte maturation, follicular rupture and luteinization. While the role of the LH-surge in the *in vivo* induction of these phenomena is undisputed, the role of the FSH-surge is less clear. However, it has been shown recently that FSH induces oocyte maturation *in vitro* by inducing cumulus cells to produce a factor that positively overcomes hypoxanthine induced meiotic arrest (Lu et al, Mol. Cell. Endocrinol. 164, 191-196, 2000). This factor is thought to be a meiosis activating sterol (MAS).

In ovulation induction, it is desirable to provide the effects of LH as the major component. According to the present invention compounds have been found with particular advantageous properties when used in protocols for enhanced fertility. In these compounds LH activity is accompanied by a FSH activity.

Thus the present invention provides low molecular weight compounds that in addition to LH activity unexpectedly also have FSH activity. In general these compounds are thieno[2,3-d]pyrimidines which at the 4-position of the pyrimidine ring are substituted by a phenyl group which in turn is substituted at the meta position.

The present invention resides in thieno[2,3-d]pyrimidine derivatives according to general formula I,



(Formula I)

or a pharmaceutically acceptable salt thereof, wherein N(R1)R2 are joined in a (2-6C)heterocycloalkyl ring.

The most preferred compounds are tert-butyl 5-amino-2-methylthio-4-(3-(2-(azetidin-1-yl)-acetamido)-phenyl)-thieno[2,3-d]pyrimidine-6-carboxamide; tert-butyl 5-amino-2-methylthio-4-(3-(2-(morpholin-4-yl)-acetamido)-phenyl)-thieno[2,3-d]pyrimidine-6-carboxamide; tert-butyl 5-amino-2-methylthio-4-(3-(2-(thiomorpholin-4-yl)-acetamido)-phenyl)-thieno[2,3-d]pyrimidine-6-carboxamide; tert-butyl 5-amino-2-methylthio-4-(3-(2-(piperidin-1-yl)-acetamido)-phenyl)-thieno[2,3-d]pyrimidine-6-carboxamide; tert-butyl 5-amino-2-methylthio-4-(3-(2-(pyrrolidin-1-yl)-acetamido)-phenyl)-thieno[2,3-d]pyrimidine-6-carboxamide and tert-butyl 5-amino-2-methylthio-4-(3-(2-(piperazin-1-yl)-acetamido)-phenyl)-thieno[2,3-d]pyrimidine-6-carboxamide.

10

The term joined in a (2-6C)heterocycloalkyl ring in the definition of Formula I, means that R1 and R2 together with the nitrogen atom to which they are bonded form a ring having 2-6 carbon atoms, optionally containing one or more heteroatoms selected from N, O and/or S. Examples of such rings are azetidine, pyrrolidine, piperidine, piperazine, morpholine and thiomorpholine.

15

It has been shown that compounds of the above mentioned formula I show agonistic LH and FSH activity. In an *in vitro* bioassay using CHO cells stably transfected with the human LH or FSH receptor, respectively, the EC_{50} with regard to the LH receptor was found to be less than $5 \cdot 10^{-8}$ M whereas with regard to the FSH receptor the EC_{50} was less than 10^{-9} M. Typically the FSH activity ranges from an activity of about 1% of the LH agonist stimulation to about 10% of the LH agonist stimulation.

20

The invention further resides in a pharmaceutical composition comprising a thieno[2,3-d]pyrimidine derivative compound or salts thereof having the general formula I.

25

Thus, the compounds according to the invention can be used in therapy. A further aspect of the invention resides in the use of a thieno[2,3-d]pyrimidine compound having the general formula I for the manufacture of a medicament for the control of fertility, more preferably induction of ovulation. The present compounds are used to activate both the LH and FSH receptors. The compound of the present invention can be used therefore in a method to treat females with fertility problems.

30

For therapeutic use, salts of the compounds of formula I are those wherein the counterion is pharmaceutically acceptable. However, acid addition salts of bases according to formula I, may also find use, for example, in the preparation or purification of a pharmaceutically acceptable compound. All salts, whether pharmaceutically acceptable or not, are included within the ambit of the present invention.

Examples of acid addition salts include those derived from mineral acids such as hydrochloric acid, phosphoric acid, sulphuric acid, preferably hydrochloric acid, and organic acids like citric acid, tartaric acid, acetic acid, lactic acid, maleic acid, malonic acid, fumaric acid, glycolic acid, succinic acid, and the like.

10

Suitable administration routes for the compounds of formula I or pharmaceutically acceptable salts thereof, also referred to herein as the active ingredient are intramuscular injections, subcutaneous injections, intravenous injections or intraperitoneal injections, oral and intranasal administration. Preferably, the compounds may be administered orally. The exact dose and regimen of administration of the active ingredient, or a pharmaceutical composition thereof, will necessarily be dependent upon the therapeutic effect to be achieved (treatment of infertility; contraception), and may vary with the particular compound, the route of administration, and the age and condition of the individual subject to whom the medicament is to be administered.

20 In general, parenteral administration requires lower dosages than other methods of administration which are more dependent upon adsorption. However, a dosage for humans preferably contains 0.0001-25 mg per kg body weight. The desired dose may be presented as one dose or as multiple subdoses administered at appropriate intervals throughout the day. In case of female recipients, doses may be administered at appropriate daily intervals throughout the menstrual cycle for follicular support or as a single dose for ovulation induction. The dosage as well as the regimen of administration may differ between a female and a male recipient.

25 In case of *in vitro* or *ex vivo* applications, like in IVF applications, the compounds of the inventions are to be used in the incubation media in a concentration of approximately 0.01-5 µg/ml.

30

The present invention thus also relates to pharmaceutical compositions comprising a thieno[2,3-d]pyrimidine compound according to formula I in admixture with

pharmaceutically acceptable auxiliaries, and optionally other therapeutic agents. The auxiliaries must be "acceptable" in the sense of being compatible with the other ingredients of the composition and not deleterious to the recipients thereof.

Pharmaceutical compositions include those suitable for oral, rectal nasal, topical
5 (including transdermal, buccal and sublingual), vaginal or parenteral (including subcutaneous, intramuscular, intravenous and intradermal) administration. The compositions may be prepared by any method well known in the art of pharmacy, for example, using methods such as those described in Gennaro *et al.*, Remington's Pharmaceutical Sciences (18th ed., Mack Publishing company, 1990, see especially Part
10 8: *Pharmaceutical Preparations and Their Manufacture*).

Such methods include the step of bringing in association the active ingredient with any auxiliary agent. The auxiliary agent(s), also named accessory ingredients, include those conventional in the art (Gennaro, *supra*), such as, fillers, binders, diluents, disintegrants, lubricants, colorants, flavoring agents and wetting agents.

15 Pharmaceutical compositions suitable for oral administration may be presented as discrete dosage units such as pills, tablets or capsules, or as a powder or granules, or as a solution or suspension. The active ingredient may also be presented as a bolus or paste. The compositions can further be processed into a suppository or enema for rectal administration.

20 For parenteral administration, suitable compositions include aqueous and non-aqueous sterile injection. The compositions may be presented in unit-dose or multi-dose containers, for example sealed vials and ampoules, and may be stored in a freeze-dried (lyophilised) condition requiring only the addition of sterile liquid carrier, for example, water prior to use.

25 Compositions, or formulations, suitable for administration by nasal inhalation include fine dusts or mists which may be generated by means of metered dose pressurized aerosols, nebulisers or insufflators.

The thieno[2,3-d]pyrimidine compounds of the invention can also be administered
30 in the form of implantable pharmaceutical devices, consisting of a core of active material, encased by a release rate-regulating membrane. Such implants are to be applied subcutaneously or locally, and will release the active ingredient at an approximately constant rate over relatively large periods of time, for instance from

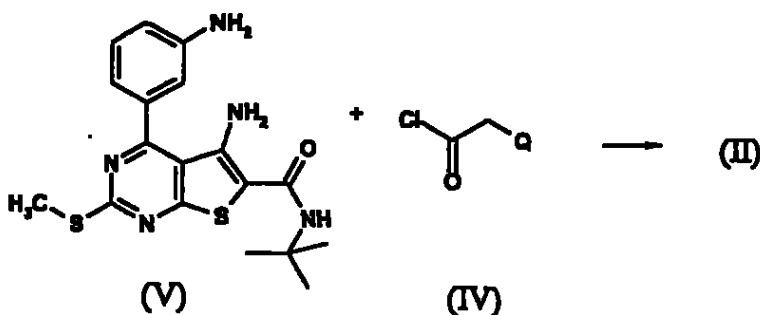
weeks to years. Methods for the preparation of implantable pharmaceutical devices as such are known in the art, for example as described in European Patent 0,303,306 (AKZO N.V.).

Thus, the compounds according to the present invention can be used for the same clinical purposes as the native LH, with the advantage that they possess FSH activity, display altered stability properties and can be administered differently.

The compounds of the present invention, represented by formula (I) can generally be prepared by nucleophilic substitution of halides (II) wherein Q = Cl or Br with (cyclic) secondary amines of formula (III) in an appropriate solvent such as N,N-dimethylformamide or THF at room temperature in the presence of a tertiary base such as N,N-diisopropylethylamine (DIPEA).

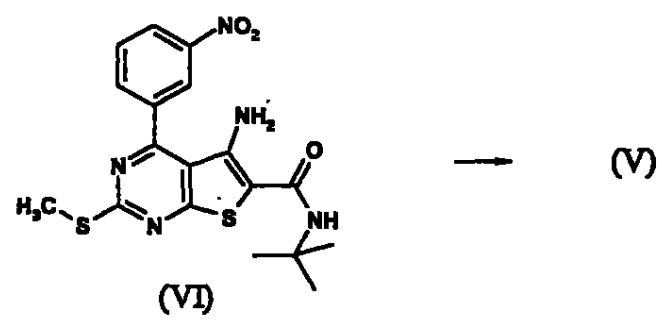


Derivatives of formula (II) wherein Q = Cl or Br can be prepared by regioselective acylation of meta aniline derivative (V) with acyl chlorides of type (IV), wherein Q = Cl or Br in the presence of a tertiary base such as N,N-diisopropylethylamine in a suitable solvent such as dichloromethane or THF.



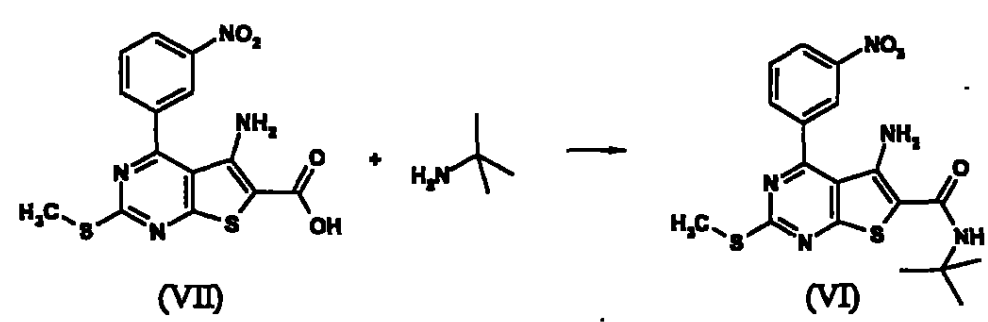
Compound (V) is accessible by art-known reduction of the nitro function in derivative (VI) using an appropriate reducing agent such as tin(II) chloride in a protic solvent such as ethanol in the presence of hydrochloric acid at elevated temperature (J. Heilbron, J. Chem. Soc, 1279 (1940)).

5



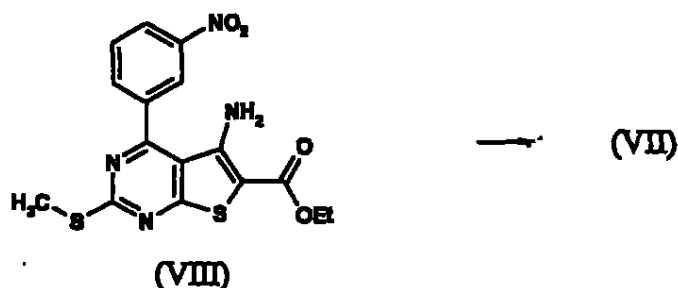
Thienopyrimidine (VI) can be prepared by condensation of carboxylic acid (VII) with tert-butyl amine under the influence of a coupling agent such as *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (TBTU) or bromotripyrrolidinophosphonium hexafluorophosphate (PyBrOP) and a tertiary base, e.g. *N,N*-diisopropylethylamine.

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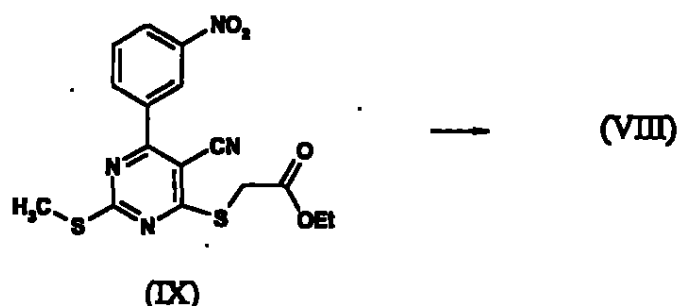


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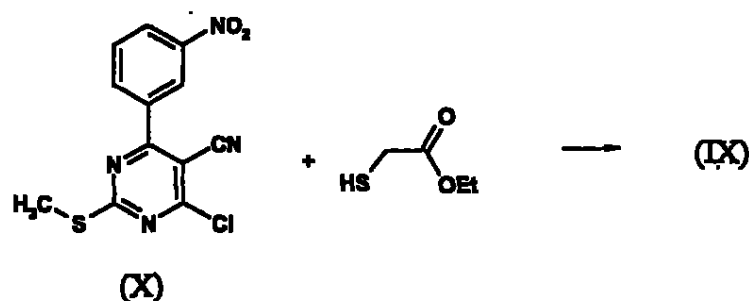
Saponification of ethyl ester (VIII) to the corresponding carboxylic acid (VII) takes place in the presence of a base such as lithium hydroxide, potassium hydroxide or sodium hydroxide in aqueous dioxane at elevated temperature (80 °C to reflux).



Bicycle (VIII) is formed by substitution of chloride (X) with ethyl mercaptoacetate under the agency of *N,N*-diisopropylethylamine, followed by base-catalyzed ring-closure of the intermediate thioether (IX). This type of thieno[2,3-*d*]pyrimidine ring formations has been described in: S.A. Abdel-Hady, M.A. Badawy, Y.A. Ibrahim, Sulfur Lett. 9, 101 (1989) and S. Tumkevicius, Liebigs Ann., 1703 (1995).

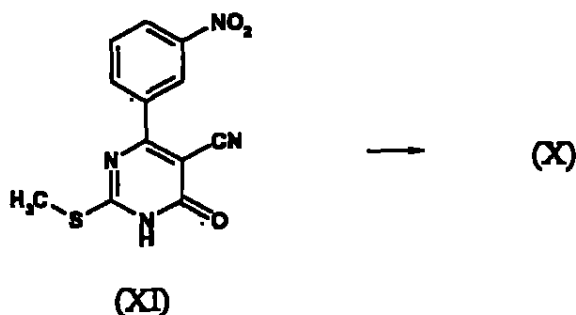


Suitable conditions for the cyclization reaction are sodium ethoxide in ethanol or *N,N*-diisopropylethylamine in toluene/ethanol (1/1, v/v) at reflux temperature.

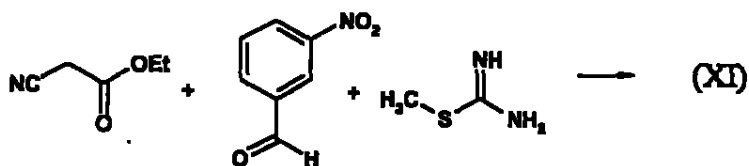


The requisite chloroimine (X) can be synthesized following literature procedures as described for example by A.A. Santilli, D.H. Kim and S.V. Wanser, J. Heterocycl. Chem. 8, 445, 1971. According to this procedure, lactam (XI) is treated with POCl₃ at elevated temperature (80 °C to reflux) to give chloride (X). The addition of an

appropriate solvent, e.g. dioxane, and/or the addition of either PCl_5 or *N,N*-dimethylaniline to the reaction mixture may result in shorter reaction times and higher yields of chloride (X).



An appropriate route towards lactam (XI) comprises the multicomponent condensation of ethyl cyanoacetate with 3-nitro-benzaldehyde and S-methyl isothiurea in ethanol under the agency of a base such as potassium carbonate at elevated temperature (60 °C).



Related procedures have been disclosed in: S. Kambe, K. Saito and H. Kishi, *Synthesis*, 287 (1979); A.M. Abd-Elfattah, S.M. Hussain and A.M. El-Reedy, *Tetrahedron* **39**, 3197 (1983); S.M. Hussain, A.A. El-Barbary and S.A. Mansour, *J. Heterocycl. Chem.* **22**, 169 (1985).

Methods to determine receptor binding as well as *in vitro* and *in vivo* assays to determine biological activity of gonadotropins are well known. In general, expressed receptor is contacted with the compound to be tested and binding or stimulation or inhibition of a functional response is measured.

To measure a functional response isolated DNA encoding the LH or the FSH receptor gene, preferably the human receptor, is expressed in suitable host cells. Such a cell might be the Chinese Hamster Ovary cell, but other cells are also suitable.

Preferably the cells are of mammalian origin (Jia et al, Mol.Endocrin., 5, 759-776, 1991).

Methods to construct recombinant LH or FSH expressing cell lines are well known in the art (Sambrook et al., Molecular Cloning: a Laboratory Manual, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, latest edition). Expression of receptor is attained by expression of the DNA encoding the desired protein. Techniques for site directed mutagenesis, ligation of additional sequences, PCR, and construction of suitable expression systems are all, by now, well known in the art. Portions or all of the DNA encoding the desired protein can be constructed synthetically using standard solid phase techniques, preferably to include restriction sites for ease of ligation. Suitable control elements for transcription and translation of the included coding sequence can be provided to the DNA coding sequences. As is well known, expression systems are now available which are compatible with a wide variety of hosts, including prokaryotic hosts such as bacteria and eukaryotic hosts such as yeast, plant cells, insect cells, mammalian cells, avian cells and the like.

Cells expressing the receptor are then contacted with the test compound to observe binding, or stimulation or inhibition of a functional response.

Alternatively isolated cell membranes containing the expressed receptor may be used to measure binding of compound.

For measurement of binding radioactively or fluorescently labeled compounds may be used. As reference compound human recombinant LH or FSH can be used. In the alternative also competition binding assays can be performed.

Another assay involves screening for LH or FSH receptor agonist compounds by determining stimulation of receptor mediated cAMP accumulation. Thus, such a method involves expression of the receptor on the cell surface of a host cell and exposing the cell to the test compound. The amount of cAMP is then measured. The level of cAMP will be reduced or increased, depending on the inhibitory or stimulating effect of the test compound upon binding to the receptor.

In addition to direct measurement of e.g. cAMP levels in the exposed cell, cells can be used which in addition to transfection with receptor encoding DNA are also transfected with a second DNA encoding a reporter gene the expression of which responds to the level of cAMP. Such reporter genes might be cAMP inducible or might be constructed in such a way that they are connected to novel cAMP responsive elements. In general, reporter gene expression might be controlled by any response

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- 11 -

element reacting to changing levels of cAMP. Suitable reporter genes are e.g. LacZ, alkaline phosphatase, firefly luciferase and green fluorescence protein. The principles of such transactivation assays are well known in the art and are described e.g. in Stratowa, Ch, Himmler, A and Czernilofsky, A.P., Curr.Opin.Biotechnol.6, 574 (1995).

5 For selecting active compounds on the LH or FSH receptor, testing at 10^{-5} M must result in an activity of more than 20% of the maximal activity when LH or FSH is used as a reference. Another criterion might be the EC_{50} value, which must be $< 10^{-5}$ M, preferably $< 10^{-7}$ M.

10 The skilled artisan will recognize that desirable EC_{50} values are dependent on the compound tested. For example, a compound with an EC_{50} which is less than 10^{-5} M is generally, considered a candidate for drug selection. Preferably this value is lower than 10^{-7} M. However, a compound which has a higher EC_{50} , but is selective for the particular receptor, may be even a better candidate.

15 Screening for LH receptor agonistic compounds can also be performed by using a mouse Leydig cell bioassay (Van Damme, M., Robersen, D. and Diczfalusy, E., Acta Endocrinol. 77: 655-671 (1974), Mannaerts, B., Kloosterboer, H. and Schuurs, A., Neuroendocrinology of reproduction. R. Rolland et al. Eds., Elsevier Science Publishers B.V., 49-58 (1987)). In this assay, stimulation of LH receptor mediated testosterone production can be measured in Leydig cells isolated from male mice.

20 FSH agonistic activity of compounds can also be determined in an *ex vivo* model using cultured mouse follicles according to Nayudu, P. and Osborn, S. (J. Reproduction and Fertility 95, 349-362 (1992)). Therefore, mouse ovarian follicles are isolated and cultured in the presence of FSH agonistic compounds to induce follicular growth. Measurements of follicular diameter and estradiol in the culture medium are indicative
25 for follicular growth.

To measure LH *in vivo* activity of compounds, ovulation induction in immature mice can be studied. In this assay immature female mice are primed with urinary FSH and approximately 48 hours later treated with a LH agonistic compound. The animals are killed after LH agonist treatment and the number of ova in the oviduct is
30 microscopically assessed.

To measure FSH *in vivo* activity of compounds immature female rats are treated at 0, 8, 24 and 32 hours with a FSH agonistic compound to induce follicular growth. At 52 hours after the start of the experiment the animals are injected with hCG to induce ovulation. The animals are killed 72 hours after the start of the experiment and the

number of ova in the oviduct is microscopically assessed. In addition ovarian weight is determined.

The compounds of the present invention can be applied clinically in those regimens where now LH or hCG is used. These include LH substitution among subjects with hypogonadal hypogonadism either male or female, midcycle administration to induce ovulation (ovulation induction (OI) or controlled hyperstimulation (COH) or stimulation of the corpus luteum.

The following examples are illustrative for the invention and should in no way be interpreted as limiting the scope of the invention.

Examples

Example 1

tert-Butyl 5-amino-2-methylthio-4-(3-(2-(azetidin-1-yl)-acetamido)-phenyl)-thieno[2,3-d]pyrimidine-6-carboxamide

(a). 5-Cyano-4-(3-nitrophenyl)-2-methylthio-6-oxopyrimidine

A mixture of S-methylisothiourrea sulfate (69.0 g), 3-nitrobenzaldehyde (75.0 g), ethyl cyanoacetate (56.0 ml) and potassium carbonate (72.5 g) in abs. EtOH (1500 ml) was stirred at 60°C for 16 h. The reaction mixture was cooled to 0°C in an ice bath. The resulting precipitate was filtered off, washed with abs. EtOH and dissolved in hot water (100°C). The solution was cooled to room temperature, acidified with 2N HCl to pH 2 and cooled to 0°C in an ice bath. The resulting precipitate was filtered off and washed with ice water. Residual water in the precipitate was removed by coevaporation with 1,4-dioxane.

Yield: 54.0 mg.

MS-ESI: $[M+H]^+ = 289.0$

TLC: $R_f = 0.3$, silica gel, DCM/MeOH = 9/1 (v/v).

(b). 6-Chloro-5-cyano-4-(3-nitrophenyl)-2-methylthio-pyrimidine

$POCl_3$ (100 ml) was added to a stirred solution of 5-cyano-4-(3-nitrophenyl)-2-methylthio-6-oxopyrimidine (example 1(a), 25.0 g) in dry 1,4-dioxane (300 ml). After 3

h at 90°C, the mixture was cooled to room temperature and concentrated under reduced pressure. The residue was dissolved in 1,4-dioxane (100 ml) and the resulting solution was cooled to 0°C. Ice water was cautiously added. The resulting precipitate was filtered off and washed with water. Residual water in the precipitate was removed by coevaporation with 1,4-dioxane.

Yield: 26.0 g.

MS-ESI: $[M+H]^+ = 307.0$

TLC: $R_f = 0.5$, silica gel, heptane/EtOAc = 3/2 (v/v).

10 (c). Ethyl 5-cyano-4-(3-nitrophenyl)-2-methylthio-6-(ethoxycarbonylmethylthio)-pyrimidine

DIPEA (15.7 ml) was added to a stirred solution of ethyl 2-mercaptoacetate (9.3 ml) and 6-chloro-5-cyano-4-(3-nitrophenyl)-2-methylthio-pyrimidine (example 1(b), 26.0 g) in a mixture of EtOH (250 ml) and DCM (250 ml). After 1 h at room temperature, 0.1N aq. HCl (500 ml) was added to the mixture which was then extracted with DCM (3*500 ml), dried (MgSO₄) and concentrated under reduced pressure.

Yield: 28.0 g

MS-ESI: $[M+H]^+ = 390.4$

TLC: $R_f = 0.5$, silica gel, heptane/EtOAc = 3/2 (v/v).

20

(d). Ethyl 5-amino-4-(3-nitrophenyl)-2-methylthio-thieno[2,3-d]pyrimidine-6-carboxylate

A mixture of ethyl 5-cyano-4-(3-nitrophenyl)-2-methylthio-6-(ethoxycarbonylmethylthio)-pyrimidine (example 1(c), 28.0 g) and DIPEA (30 ml) in a mixture of toluene (150 ml) and EtOH (150 ml) was stirred at reflux temperature (100°C) for 16 h. The mixture was then cooled to room temperature and concentrated under reduced pressure. Residual DIPEA was removed by coevaporation with toluene.

Yield: 28.0 g

MS-ESI: $[M+H]^+ = 391.2$

30 TLC: $R_f = 0.6$, silica gel, heptane/EtOAc = 3/2 (v/v).

(e). Ethyl 5-amino-4-(3-aminophenyl)-2-methylthio-thieno[2,3-d]pyrimidine-6-carboxylate

EtOH (400 ml) was added to a mixture of ethyl 5-amino-4-(3-nitrophenyl)-2-methylthio-thieno[2,3-d]pyrimidine-6-carboxylate (example 1(d), 28.0 g), concentrated

35

aq. HCl (15 ml) and tin (II) chloride (41.0 g) in 1,4-dioxane (400 ml). The mixture was stirred at 90°C for 16 h. The mixture was then cooled to room temperature and concentrated under reduced pressure. The residue was suspended in EtOAc (1000 ml). 4N aq. NaOH was added to obtain a pH of 10-11. The mixture was vigorously stirred and the organic layer was separated, dried (MgSO₄) and concentrated under reduced pressure.

Yield: 21.0 g

MS-ESI: [M+H]⁺ = 361.0

TLC: R_f = 0.6, silica gel, heptane/EtOAc = 3/2 (v/v).

10

(f). 5-Amino-4-(3-aminophenyl)-2-methylthio-thieno[2,3-d]pyrimidine-6-carboxylic acid

Potassium hydroxide (32.4 g) was added to a solution of ethyl 5-amino-4-(3-aminophenyl)-2-methylthio-thieno[2,3-d]pyrimidine-6-carboxylate (example 1(e), 21.0 g) in a mixture of 1,4-dioxane (300 ml) and water (100 ml). After 16 h at 90°C, the mixture was cooled to 10°C and 2N aq. citric acid (300 ml) was added under vigorous stirring. The resulting precipitate was filtered off, washed with water (180 ml) and dried in vacuo.

Yield: 14.0 g

20 MS-ESI: [M+H]⁺ = 333.0

TLC: R_f = 0.5, silica gel, DCM/MeOH = 9/1 (v/v).

(g). tert-Butyl 5-amino-4-(3-aminophenyl)-2-methylthio-thieno[2,3-d]pyrimidine-6-carboxamide

25 TBTU (16.1 g) was added to a solution of 5-amino-4-(3-aminophenyl)-2-methylthio-thieno[2,3-d]pyrimidine-6-carboxylic acid (example 1(f), 14.0 g), DIPEA (17.4 ml) and tert-butylamine (7.3 g) in DCM/DMF (1/1, v/v, 250 ml). After 3 h at room temperature, the mixture was washed with sat. aq. NaHCO₃ (3*100 ml), 0.1 N aq. HCl (100 ml) and water (100 ml). The organic layer was concentrated under reduced pressure. The crude product was purified by crystallisation from warm abs. EtOH (300 ml).

Yield: 10.5 g

MS-ESI: [M+H]⁺ = 388.2

HPLC: R_t = 30.72 min, Luna C-18(2), 5 µm, 250*2.0 mm, detection UV = 210 nm, oven temperature = 40°C, flow = 0.25 ml/min, eluent water/ACN/MeOH = 90/9.5/0.5 to 0/95/5, run time = 50 min.

35

(h). tert-Butyl 5-amino-2-methylthio-4-(3-(2-bromoacetamido)-phenyl)-thieno[2,3-d]pyrimidine-6-carboxamide

Bromoacetylchloride (615 mg) was added to a solution of *tert*-butyl 5-amino-2-methylthio-4-(3-aminophenyl)-thieno[2,3-*d*]-pyrimidine-6-carboxamide (example 1(g), 1.08 g) and DIPEA (2.43 ml) in dry DCM (20 ml). After 3 h at room temperature, the mixture was diluted with DCM, washed with sat. aq. NaHCO₃, dried (MgSO₄) and concentrated under reduced pressure. The crude product was purified by chromatography on silica gel using heptane/EtOAc = 3/2 (v/v) as eluent.

10 Yield: 910 mg

MS-ESI: [M+H]⁺ = 510.2

TLC: R_f = 0.3, silica gel, heptane/EtOAc = 3/2 (v/v).

(i). tert-Butyl 5-amino-2-methylthio-4-(3-(2-(azetidin-1-yl)-acetamido)-phenyl)-thieno[2,3-d]pyrimidine-6-carboxamide

tert-Butyl 5-amino-4-(3-(2-bromoacetamido)-phenyl)-2-methylthio-thieno[2,3-*d*]pyrimidine-6-carboxamide (example 1(h), 91 mg) was added to a solution of azetidine hydrochloride (120 mg) and N,N-diisopropylethylamine (0.25 ml) in DCM (5 ml). After 16 h at room temperature, the mixture was washed with sat. aq. NaHCO₃, dried (MgSO₄) and concentrated under reduced pressure. The crude product was purified by HPLC using a Luna C-18 column with the following gradient: 0.1% aq.TFA + 10% aq. ACN/ACN = 90/10 to 10/90 in 30 min. The title compound was then lyophilized from water with 0.1% TFA.

Yield: 56 mg (TFA-salt)

25 MS-ESI: [M+H]⁺ = 485.2

HPLC: R_t = 13.45 min, column Luna C-18(2), 3 μm, 100*2.0 mm, detection UV = 210 nm, oven temperature = 40°C, flow = 0.25 ml/min, eluent phosphate buffer 50 mM pH 2.1/water/ACN = 10/70/20 to 10/10/80 (v/v), run time = 20 min.

30 **Example 2**

tert-Butyl 5-amino-2-methylthio-4-(3-(2-(morpholin-4-yl)-acetamido)-phenyl)-thieno[2,3-d]pyrimidine-6-carboxamide

Morpholine (5.0 ml) was added to a solution of *tert*-butyl 5-amino-4-(3-(2-bromoacetamido)-phenyl)-2-methylthio-thieno[2,3-*d*]pyrimidine-6-carboxamide (example 1(h), 1.0 g) in THF (50 ml). After 16 h at room temperature, the mixture was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using DCM/MeOH = 9/1 as eluent. The crude product was further purified by HPLC using a Luna C-18 column with the following gradient: 0.1% aq. TFA/water/ACN = 3/97/0 to 3/7/90 in 30 min. The pure title compound was lyophilized from a mixture of 0.1% aq. TFA and water.

Yield: 215 mg (TFA-salt)

MS-ESI: $[M+H]^+ = 515.2$

HPLC: $R_t = 20.62$ min, Luna C-18 (2), 5 μ m, 150*2 mm, detection UV = 210 nm, oven temperature = 40°C, flow = 0.25 ml/min, eluent phosphate buffer 50 mM pH 2.1/water/ACN/MeOH = 10/72/17/1 to 10/18/68/4 (v/v), run time = 40 min.

Example 3

tert-Butyl 5-amino-2-methylthio-4-(3-(2-(thiomorpholin-4-yl)-acetamido)-phenyl)-thieno[2,3-*d*]pyrimidine-6-carboxamide

Thiomorpholine (2.16 ml) was added to a solution of *tert*-butyl 5-amino-2-methylthio-4-(3-(2-bromoacetamido)-phenyl)-thieno[2,3-*d*]pyrimidine-6-carboxamide (example 1(h), 1.09 g) in DCM (50 ml). After 16 h at room temperature, the mixture was diluted with DCM, washed with sat. aq. NaHCO₃, dried (MgSO₄) and concentrated under reduced pressure. The crude product was purified by HPLC using a Luna C-18 column with the following gradient: 0.1% aq. TFA + 10% aq. ACN/ACN = 100/0 to 10/90 in 30 min. The pure title compound was lyophilized from water acidified with aq. 1N HCl.

Yield: 816 mg

MS-ESI: $[M+H]^+ = 531.2$

HPLC: $R_t = 14.72$ min, column Luna C-18(2), 3 μ m, 100*2 mm, detection UV = 210 nm + 254 nm, oven temperature = 40°C, flow = 0.25 ml/min, eluent phosphate buffer 50 mM pH 2.1/water/ACN/MeOH = 10/72/17/1 to 10/18/68/4(v/v), run time = 20 min.

Example 4

tert-Butyl 5-amino-2-methylthio-4-(3-(2-(piperidin-1-yl)-acetamido)-phenyl)-thieno[2,3-*d*]pyrimidine-6-carboxamide

Piperidine (3.0 ml) was added to a solution of *tert*-butyl 5-amino-4-(3-(2-bromoacetamido)-phenyl)-2-methylthio-thieno[2,3-*d*]pyrimidine-6-carboxamide (example 1(h), 1.0 g) in CH₂Cl₂ (50 ml). After 16 h at room temperature, the mixture was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using DCM/MeOH = 9/1 as eluent. The crude product was further purified by HPLC using a Luna C-18 column with the following gradient: 0.1% aq. TFA/ACN = 100/0 to 10/90 in 30 min. The pure title compound was lyophilized from a mixture of 0.1% aq. TFA and water.

Yield: 851 mg (TFA-salt)

MS-ESI: [M+H]⁺ = 513.2

HPLC: Rt = 37.3 min, Luna C-18 (2), 5 μm, 150*2 mm, detection UV = 210 nm, oven temperature = 40°C, flow = 0.25 ml/min, eluent phosphate buffer 50 mM pH 2.1/water/ACN = 20/60/20 to 20/0/80 (v/v), run time = 40 min.

Example 5

tert-Butyl 5-amino-2-methylthio-4-(3-(2-(pyrrolidin-1-yl)-acetamido)-phenyl)-thieno[2,3-*d*]pyrimidine-6-carboxamide

Pyrrolidine (3.0 ml) was added to a solution of *tert*-butyl 5-amino-4-(3-(2-bromoacetamido)-phenyl)-2-methylthio-thieno[2,3-*d*]pyrimidine-6-carboxamide (example 1(h), 1.0 g) in CH₂Cl₂ (50 ml). After 16 h at room temperature, the mixture was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using DCM/MeOH = 9/1 as eluent. The crude product was further purified by HPLC using a Luna C-18 column with the following gradient: 0.1% aq. TFA/ACN = 100/0 to 10/90 in 30 min. The pure title compound was lyophilized from a mixture of 0.1% aq. TFA and water.

Yield: 616 mg (TFA-salt)

MS-ESI: [M+H]⁺ = 499.2

HPLC: Rt = 37.5 min, Luna C-18 (2), 5 μ m, 150*2 mm, detection UV = 210 nm, oven temperature = 40°C, flow = 0.25 ml/min, eluent phosphate buffer 50 mM pH 2.1/water/ACN = 20/60/20 to 20/0/80 (v/v), run time = 40 min.

5 **Example 6**

tert-Butyl 5-amino-2-methylthio-4-(3-(2-(piperidin-1-yl)-acetamido)-phenyl)-thieno[2,3-*d*]pyrimidine-6-carboxamide

Piperazine (2.5 g) was added to a solution of *tert*-butyl 5-amino-4-(3-(2-bromoacetamido)-phenyl)-2-methylthio-thieno[2,3-*d*]pyrimidine-6-carboxamide
10 (example 1(h), 1.0 g) in CH₂Cl₂ (50 ml). After 16 h at room temperature, the mixture was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using DCM/MeOH = 7/1 as eluent. The crude product was further purified by HPLC using a Luna C-18 column with the following gradient: 0.1% aq. TFA/ACN = 100/0 to 10/90 in 30 min. The pure title compound was lyophilized
15 from a mixture of 0.1% aq. TFA and water.

Yield: 766 mg (bis TFA-salt)

MS-ESI: [M+H]⁺ = 514.4

HPLC: Rt = 33.7 min, Luna C-18 (2), 5 μ m, 150*2 mm, detection UV = 210 nm, oven temperature = 40°C, flow = 0.25 ml/min, eluent phosphate buffer 50 mM pH
20 2.1/water/ACN = 20/60/20 to 20/0/80 (v/v), run time = 40 min.

Example 7

CHO-LH and CHO-FSH *in vitro* bioactivity

25 LH agonistic activity of compounds were tested in Chinese Hamster Ovary (CHO) cells stably transfected with the human receptor and cotransfected with a cAMP responsive element (CRE) / promotor directing the expression of a firefly luciferase reporter gene. Binding of ligand to the Gs-coupled LH receptor will result in an increase of cAMP, which in turn will induce an increased transactivation of the luciferase reporter
30 construct. The luciferase signal was quantified using a luminescence counter. For test compounds, EC₅₀ values (concentration of test compound causing half-maximal (50 %)

stimulation) were calculated. For that purpose the software program GraphPad PRISM, version 3.0 (GraphPad software Inc., San Diego) was used.

In a similar way FSH agonistic activity of compounds was tested in CHO cells transfected with the luciferase reporter gene and the human FSH receptor. Results are shown in Table 1.

In vivo bioactivity

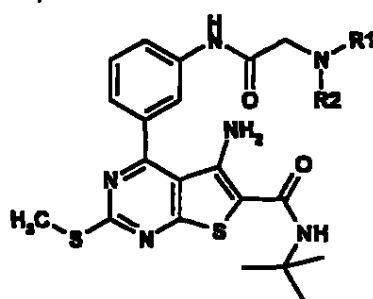
To measure *in vivo* activity of LH/FSH receptor agonistic compounds ovulation induction in immature mice was studied. In this assay immature female mice were primed with urinary FSH (Humegon 12.5 IU/animal). Approximately 48 hours later the animals were treated with a LH /FSH agonistic compound at a dose-level of 50 mg/kg. The animals were killed 24 hours after LH/FSH agonist treatment and the number of ova in the oviduct was microscopically assessed. Results are shown in Table 1.

Table 1

Example no.	Name	EC50 CHO LHR (M)	EC50 CHO FSHR (M)	no. animals tested	mean no. of ova (50 mg/kg p.o.)
1	tert-Butyl 5-amino-2-methylthio-4-(3-(2-(acetidin-1-yl)-acetamido)-phenyl)-thieno[2,3-d]pyrimidine-6-carboxamide	3.86E-09	4.62E-07	15	1.6
2	tert-Butyl 5-amino-2-methylthio-4-(3-(2-(morpholin-4-yl)-acetamido)-phenyl)-thieno[2,3-d]pyrimidine-6-carboxamide	2.24E-08	4.20E-08	10	9.3
3	tert-Butyl 5-amino-2-methylthio-4-(3-(2-(thiomorpholin-4-yl)-acetamido)-phenyl)-thieno[2,3-d]pyrimidine-6-carboxamide	8.03E-09	1.04E-06	10	19.8
4	tert-Butyl 5-amino-2-methylthio-4-(3-(2-(piperidin-1-yl)-acetamido)-phenyl)-thieno[2,3-d]pyrimidine-6-carboxamide	6.63E-09	2.01E-07		
5	tert-Butyl 5-amino-2-methylthio-4-(3-(2-(pyrrolidin-1-yl)-acetamido)-phenyl)-thieno[2,3-d]pyrimidine-6-carboxamide	6.68E-09	4.80E-07		
6	tert-Butyl 5-amino-2-methylthio-4-(3-(2-(piperazin-1-yl)-acetamido)-phenyl)-thieno[2,3-d]pyrimidine-6-carboxamide	3.17E-09	1.50E-07		

Claims

1. A thieno[2,3-d]pyrimidine derivative according to general formula I,



(Formula I)

5

or a pharmaceutically acceptable salt thereof, wherein R1 and R2 together with the nitrogen atom to which they are bonded form a ring having 2-6 carbon atoms, optionally containing one or more heteroatoms selected from N, O and/or S.

2. A compound selected from the group of tert-butyl 5-amino-2-methylthio-4-(3-(2-(azetidin-1-yl)-acetamido)-phenyl)-thieno[2,3-d]pyrimidine-6-carboxamide; tert-butyl 5-amino-2-methylthio-4-(3-(2-(morpholin-4-yl)-acetamido)-phenyl)-thieno[2,3-d]pyrimidine-6-carboxamide; tert-butyl 5-amino-2-methylthio-4-(3-(2-(thiomorpholin-4-yl)-acetamido)-phenyl)-thieno[2,3-d]pyrimidine-6-carboxamide; tert-butyl 5-amino-2-methylthio-4-(3-(2-(piperidin-1-yl)-acetamido)-phenyl)-thieno[2,3-d]pyrimidine-6-carboxamide; tert-butyl 5-amino-2-methylthio-4-(3-(2-(pyrrolidin-1-yl)-acetamido)-phenyl)-thieno[2,3-d]pyrimidine-6-carboxamide or tert-butyl 5-amino-2-methylthio-4-(3-(2-(piperazin-1-yl)-acetamido)-phenyl)-thieno[2,3-d]pyrimidine-6-carboxamide.
3. A compound according to claims 1-2 for use in therapy.
4. A pharmaceutical composition comprising a thieno[2,3-d]pyrimidine compound according to claims 1-2 or a pharmaceutically acceptable salt or solvate thereof, in admixture with a pharmaceutically acceptable auxiliary.

20

5. Use of thieno[2,3-d]pyrimidine compounds according to claims 1-2 or a pharmaceutically acceptable salt or solvate thereof for the manufacture of a medicament for the control of fertility.
6. A method to treat fertility disorders in patients in need thereof by administration of an effective amount of a compound according to claims 1-2.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 02/09647

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D495/04 A61K31/505 A61P15/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, MPI Data, BIOSIS, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 00 61586 A (AKZO NOBEL NV ;ADANG ANTON EGBERT PETER (NL); GERRITSMA GERRILDINA) 19 October 2000 (2000-10-19) cited in the application page 3, line 9-16; claims 1,8,11,15; examples 111,116; table 1	1-6

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

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P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

A document member of the same patent family

Date of the actual completion of the international search

2 December 2002

Date of mailing of the international search report

10/12/2002

Name and mailing address of the ISA

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Authorized officer

Guspanova, J

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

30

25

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference

(if desired) (12 characters maximum)

2001.647 WO

Box No. I TITLE OF INVENTION

"Thieno[2,3-d] pyrimidines with combined LH and FSH agonistic activity"

Box No. II APPLICANT

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this box is the applicant's State (i.e. country) of residence if no State of residence is indicated below)

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☐

the United States of America only

☐

the States indicated in the Supplemental Box

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Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this box is the applicant's State (i.e. country) of residence if no State of residence is indicated below)

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This person is:

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☐

all designated States

☐

all designated States except the United States of America

☒

the United States of America only

☐

the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:

☒

agent

☐

common representative

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

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☐ Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Continuation of Box No. III FURTHER APPLICANTS AND/OR (FURTHER) INVENTORS

If none of the following sub-boxes is used, this sheet is not to be included in the request.

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this box is the applicant's State (i.e. country) of residence (if no State of residence is indicated below))

TIMMERS, C.M.
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This person is:

- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only (If this check-box is marked, do not fill in below.)

State (i.e. country) of nationality: NL

State (i.e. country) of residence: NL

This person is applicant for the purposes of

- ☐ all designated States
- ☐ all designated States except the United States of America
- ☒ the United States of America only
- ☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this box is the applicant's State (i.e. country) of residence (if no State of residence is indicated below))

This person is:

- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only (If this check-box is marked, do not fill in below.)

State (i.e. country) of nationality:

State (i.e. country) of residence:

This person is applicant for the purposes of

- ☐ all designated States
- ☐ all designated States except the United States of America
- ☐ the United States of America only
- ☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this box is the applicant's State (i.e. country) of residence (if no State of residence is indicated below))

This person is:

- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only (If this check-box is marked, do not fill in below.)

State (i.e. country) of nationality:

State (i.e. country) of residence:

This person is applicant for the purposes of

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- ☐ all designated States except the United States of America
- ☐ the United States of America only
- ☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this box is the applicant's State (i.e. country) of residence (if no State of residence is indicated below))

This person is:

- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only (If this check-box is marked, do not fill in below.)

State (i.e. country) of nationality:

State (i.e. country) of residence:

This person is applicant for the purposes of

- ☐ all designated States
- ☐ all designated States except the United States of America
- ☐ the United States of America only
- ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.

Box No. V DESIGNATION OF STATES

Mark the applicable check-boxes below; at least one must be marked.

The following designations are hereby made under Rule 4.9(a):

Regional Patent

- ☒ **AP** ARIPO Patent: GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, MZ Mozambique, SD Sudan, SL Sierra Leone, SZ Swaziland, TZ United Republic of Tanzania, UG Uganda, ZM Zambia, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT (if other kind of protection or treatment desired, specify on dotted line)
- ☒ **EA** Eurasian Patent: AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- ☒ **EP** European Patent: AT Austria, BE Belgium, CH & LI Switzerland and Liechtenstein, CY Cyprus, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, TR Turkey, and any other State which is a Contracting State of the European Patent Convention and of the PCT BG Bulgaria, CZ Czech Republic, EE Estonia, SK Slovakia
- ☒ **OA** OAPI Patent: BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GQ Equatorial Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT (if other kind of protection or treatment desired, specify on dotted line)

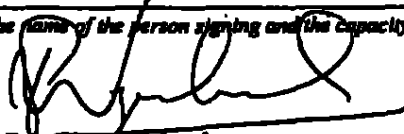
National Patent (if other kind of protection or treatment desired, specify on dotted line):

- | | | |
|--|--|---|
| ☒ AE United Arab Emirates | ☐ GM Gambia | ☒ NZ New Zealand |
| ☒ AG Antigua and Barbuda | ☒ HR Croatia | ☐ OM Oman |
| ☒ AL Albania | ☒ HU Hungary | ☒ PH Philippines |
| ☐ AM Armenia | ☒ ID Indonesia | ☒ PL Poland |
| ☐ AT Austria | ☒ IL Israel | ☐ PT Portugal |
| ☒ AU Australia | ☒ IN India | ☒ RO Romania |
| ☐ AZ Azerbaijan | ☒ IS Iceland | ☒ RU Russian Federation |
| ☒ BA Bosnia and Herzegovina | ☒ JP Japan | |
| ☒ BB Barbados | ☒ KE Kenya | ☐ SD Sudan |
| ☐ BG Bulgaria | ☐ KG Kyrgyzstan | ☐ SE Sweden |
| ☒ BR Brazil | ☒ KP Democratic People's Republic of Korea | ☒ SG Singapore |
| ☐ BY Belarus | ☒ KR Republic of Korea | ☒ SI Slovenia |
| ☒ BZ Belize | ☐ KZ Kazakhstan | ☐ SK Slovakia |
| ☒ CA Canada | ☒ LC Saint Lucia | ☐ SL Sierra Leone |
| ☐ CH & LI Switzerland and Liechtenstein | ☒ LK Sri Lanka | ☐ TJ Tajikistan |
| ☒ CN China | ☒ LR Liberia | ☐ TM Turkmenistan |
| ☒ CO Colombia | ☐ LS Lesotho | ☐ TN Tunisia |
| ☒ CR Costa Rica | ☒ LT Lithuania | ☐ TR Turkey |
| ☐ CU Cuba | ☐ LU Luxembourg | ☒ TT Trinidad and Tobago |
| ☒ CZ Czech Republic | ☒ LV Latvia | |
| ☐ DE Germany | ☒ MA Morocco | ☐ TZ United Republic of Tanzania |
| ☐ DK Denmark | ☐ MD Republic of Moldova | ☒ UA Ukraine |
| ☒ DM Dominica | ☒ MG Madagascar | ☐ UC Uganda |
| ☒ DZ Algeria | ☒ MK The former Yugoslav Republic of Macedonia | ☒ US United States of America |
| ☒ EC Ecuador | ☒ MN Mongolia | |
| ☒ EE Estonia | ☐ MW Malawi | ☒ UZ Uzbekistan |
| ☐ ES Spain | ☒ MX Mexico | ☒ VN Viet Nam |
| ☐ FI Finland | ☒ MZ Mozambique | ☒ YU Yugoslavia |
| ☐ GB United Kingdom | ☒ NO Norway | ☒ ZA South Africa |
| ☒ GD Grenada | | ☐ ZM Zambia |
| ☒ GE Georgia | | ☐ ZW Zimbabwe |
| ☐ GH Ghana | | |

Check-boxes below reserved for designating States which have become party to the PCT after issuance of this sheet

- | | | |
|--------------------------------|--------------------------------|--------------------------------|
| ☐ | ☐ | ☐ |
| ☐ | ☐ | ☐ |

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. (Confirmation (including fees) must reach the receiving Office within the 15-month time limit.)

Box No. VI PRIORITY CLAIM		Further priority claims are indicated in the Supplemental Box ☐	
The priority of the following earlier application(s) is hereby claimed:			
Country <i>(in which, or for which, the application was filed)</i>	Filing Date <i>(day/month/year)</i>	Application No.	Office of filing <i>(only for regional or international application)</i>
item (1) EP (designating NL)	04-09-2001	01203327.0	EPO
item (2)			
item (3)			
Mark the following check-box if the certified copy of the earlier application is to be issued by the Office which for the purposes of the present international application is the receiving Office (a fee may be required): ☒ The receiving Office is hereby requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) identified above as item(s): 1			
Box No. VII INTERNATIONAL SEARCHING AUTHORITY			
Choice of International Searching Authority (ISA) (If two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used): ISA /EPO			
Earlier search Fill in where a search (international, international-type or other) by the International Searching Authority has already been carried out or requested and the Authority is now requested to base the international search to the extent possible, on the results of that earlier search. Identify such search or request either by reference to the relevant application (or the translation thereof) or by reference to the search request			
Country (or regional Office): EP		Date (day/month/year): 04-09-2001	Number: 01203327.0
Box No. VIII CHECK LIST			
This international application contains the following number of sheets: 1. request: 4 sheets 2. description: 19 sheets 3. claims: 2 sheets 4. abstract: 1 sheets 5. drawings: _____ sheets 6. sequence listing: _____ sheets Total: 26 sheets		This international application is accompanied by the item(s) marked below: 1. ☒ separate signed power of attorney 2. ☒ copy of general power of attorney 3. ☐ statement explaining lack of signature 4. ☐ priority document(s) identified in Box No VI as item(s): _____ 5. ☒ fee calculation sheet 6. ☐ separate indications concerning deposited microorganisms 7. ☐ nucleotide and/or amino acid sequence listing (diskette) 8. ☐ other (specify): Request refund Letter / Copy European Search Report.	
Figure No. _____ of the drawings (if any) should accompany the abstract when it is published.			
Box No. IX SIGNATURE OF APPLICANT OR AGENT			
Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request)  P van Wezenbeek			

For receiving Office use only	
1. Date of actual receipt of the purported international application:	2. Drawings: ☐ received ☐ not received
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:	
4. Date of timely receipt of the required corrections under PCT Article 11(2):	
5. International Searching Authority specified by the applicant: ISA/	6. ☐ Transmittal of search copy delayed until search fee is paid

For International Bureau use only
Date of receipt of the record copy by the International Bureau:

25/09

PCT

FEE CALCULATION SHEET

For receiving Office use only

Annex to the Request

International application No.

Applicant's or agent's
file reference

2001.647 WO

Date stamp of the receiving Office

Applicant

Akzo Nobel N.V.

CALCULATION OF PRESCRIBED FEES

1. TRANSMITTAL FEE EUR 100,= T

2. SEARCH FEE EUR 945,= S

International search to be carried out by EPO
(If two or more International Searching Authorities are competent in relation to the international application, indicate the name of the Authority which is chosen to carry out the international search.)

3. INTERNATIONAL FEE

Basic Fee

The international application contains 26 sheets

first 30 sheets EUR 444,= b₁

EUR 10,= b₂

remaining sheets additional amount

Add amounts entered at b₁ and b₂ and enter total at B EUR 444,= B

Designation Fees

The international application contains 58 designations

number of designation fees payable (maximum 5) amount of designation fee EUR 480,= D

Add amounts entered at B and D and enter total at I EUR 924,= I

(Applicants from certain States are entitled to a reduction of 75% of the international fee. Where the applicant is (or all applicants are) so entitled, the total to be entered at I is 25% of the sum of the amounts entered at B and D.)

4. FEE FOR PRIORITY DOCUMENT EUR 30,= P

5. TOTAL FEES PAYABLE

Add amounts entered at T, S, I and P,
and enter total in the TOTAL box

EUR 1999,=

TOTAL

☐ The designation fee is not paid at this time.

MODE OF PAYMENT

☒ authorization to charge
deposit account (see below)

☐ bank draft

☐ coupons

☐ cheque

☐ cash

☐ other (specify):

☐ postal money order

☐ revenue stamps

DEPOSIT ACCOUNT AUTHORIZATION (this mode of payment may not be available at all receiving Offices)

The RO/ EPO

☒

is hereby authorized to charge the total fees indicated above to my deposit account.

☒

is hereby authorized to charge any deficiency or credit any overpayment in the total fees indicated above to my deposit account.

☐

is hereby authorized to charge the fee for preparation and transmittal of the priority document to the International Bureau of WIPO to my deposit account.

2809 0081

28/08/2002

Deposit Account Number

Date (day/month/year)

Signature P van Wezenbeek

Form PCT/RO/101 (Annex) (January 1996; reprint January 1998)

See Notes to the fee calculation sheet

Power of Attorney
(Concerning a Given International Application)

PATENT CO-OPERATION TREATY
APPOINTMENT OF AGENT OR COMMON REPRESENTATIVE

POWER OF ATTORNEY

The undersigned applicant(s):

HANSSEN, R.G.J.M.
Robert Gerard Jules Marie
N.V. Organon
Postbus 20
5340 BH Oss
The Netherlands

TIMMERS, C.M.
Cornelis Marius
N.V. Organon
Postbus 20
5340 BH Oss
The Netherlands

hereby appoints (appoint) Mr. (Ms., Miss, Mrs.) (Name, address):

H. Kraak

M. Hogenbirk

P.M.G.F. van Wezenbeek

All residing at:
Postbus 20
5340 BH Oss
The Netherlands

☒ as agent

☐ as common representative

to act on his (her, their) behalf before the competent International Authorities in connection with the international application on [title of the invention, applicant's or agent's file reference, if any has been indicated in the request, international application number, if already available]:

Our ref.: 2001.647 WO

Title: "Thieno[2,3-d] pyrimidines with combined LH and FSH agonistic activity"

filed with the [name of the Office]: EPO
as receiving Office and to make or receive payments on his (her, their) behalf.

Place: Oss Date: 1/7/2002

Signature of the applicant (where there are several applicants, each of them must sign):

HANSSEN, R.G.J.M.

TIMMERS, C.M.

[Type the name under the (each) signature and add, in case of legal persons, an indication of the capacity in which the person signs]

ALLGEMEINE VOLLMACHT
GENERAL AUTHORISATION
POUVOIR GENERAL

Nur für amtlichen Gebrauch / For official use only
Cadre réservé à l'administration
Nr. der allgemeinen Vollmacht / General Authorisation No.
N° du pouvoir général

59 (rev.)

Ich (Wir) / I (We) / Je (Nous)

Akzo Nobel N.V.
Velperweg 76
6824 BM Arnhem
The Netherlands

bevollmächtige(n) hiermit / do hereby authorise / autorise (autorisons) par la présente

Schalkwijk, Pieter Cornelis
Van Deursen, Petrus Hubertus
Quelle-Fontijn, Monique
Hesselink, Dinah E.
Zonneveld, Hendrik Jan
De Vries, Adriaan Jacobus
Alferink, Petrus Johannes Theodorus
Van den Broek, Ludovicus, A.G.M.

Address of place of business:
Akzo Nobel N.V.
Intellectual Property Department (Dept. AIP)
P.O. Box 9300
6800 SB Arnhem
The Netherlands

mich (uns) in den durch das Europäische Patentübereinkommen geschaffenen Verfahren in allen meinen (unsere) Patentangelegenheiten zu vertreten, alle Handlungen für mich (Uns) vorzunehmen und Zahlungen für mich (Uns) in Empfang zu nehmen.

to represent me (us) in all proceedings established by the European Patent Convention and to act for me (us) in all patent transactions and to receive payments on my (our) behalf.

à me (nous) représenter pour ce qui concerne toutes mes (nos) affaires de brevet dans toute procédure instituée par la Convention sur le brevet européen et, à ce titre, à agir en mon (notre) nom et à recevoir des paiements pour mon (notre) compte.

☒ Die Vollmacht gilt auch für Verfahren nach dem Vertrag über die internationale Zusammenarbeit auf dem Gebiet des Patentrechts. This authorisation shall also apply to the same extent to any proceedings established by the Patent Cooperation Treaty. Ce pouvoir s'applique également à toute procédure instituée par le Traité de coopération en matière de brevets.

☒ Weitere Vertreter sind auf einem gesonderten Blatt angegeben. / Additional representatives indicated on supplementary sheet. Les autres mandataires sont mentionnés sur une feuille supplémentaire.

☒ Untervollmacht kann erteilt werden. / Sub-authorisation may be given. / Le pouvoir pourra être délégué.

☒ Bitte die gelbe Kopie, ergänzt um die Nr. der allgemeinen Vollmacht, an den Vollmachtgeber zurücksenden. Please return the yellow copy, supplemented by the General Authorisation No., to the authoriser. Prière de renvoyer la copie jaune au mandant, munie du n° du pouvoir général.

Ort/Place/Lieu Arnhem, the Netherlands

Datum / Date November 22, 2001

Unterschrift(en) / Signature(s)

P.C. Schalkwijk
(Holder of Proxy)

P.H. van Deursen
(Holder of Proxy)

Das Formblatt muß vom (von den) Vollmachtgeber(n) (bei juristischen Personen vom Unterschriftsberechtigten) eigenhändig unterschrieben sein. Nach der Unterschrift bitte den (die) Namen des (der) Unterzeichneten mit Schreibmaschine wiederholen (bei juristischen Personen die Stellung des Unterschriftsberechtigten innerhalb der Gesellschaft angeben).

The form must bear the personal signature(s) of the authoriser(s). (In the case of legal persons, that of the officer empowered to sign). After the signature, please type the name(s) of the signatory(ies) adding, in the case of legal persons, his (their) position within the company.

Le formulaire doit être signé de la propre main du (des) mandant(s) (dans le cas de personnes morales, de la personne ayant qualité pour signer). Veuillez ajouter à la machine, après la signature, le (les) nom(s) du (des) signataire(s) en mentionnant, dans le cas de personnes morales, ses (leurs) fonctions au sein de la société.

SUPPLEMENTARY SHEET

This sheet is part of:
concerning:
signed in the name of:
dated:

ÉPA/EPO/OEB Form 1004. 1 04.92
General Authorisation No. 59 (rev.)
Akzo Nobel N.V.
November 22, 2001

Additional representatives:Address of place of business:

KRAAK, Hajo
HOGENBIRK, Marijke
DE WEERD, Petrus Gerardus
Wilhelmus
VAN WEZENBEEK, Petrus Maria
Gerardus Franciscus
HERMANS, Franciscus G.M.

N.V. Organon
Patent Department
P.O. Box 20
5340 BH Oss
The Netherlands

MESTROM, Joannes Jozef Louis
VAN GENT, Marieke
KEUS, Jacobus Albertus Ronald

Intervet International B.V.
Patent Department
P.O. Box 31
5830 AA Boxmeer
The Netherlands

SCHÖLD, Zaid Olof
JÖNSSÉN, Christer

Eka Chemicals AB
Patent Department
Box 11556
S-100 61 Stockholm
Sweden

ANDERSSON, Rolf Erling

Akzo Nobel Surface Chemistry AB
Intellectual Property Department
S-444 85 Stenungsund
Sweden

The demand must be filed directly with the competent International Preliminary Examining Authority or, if two or more Authorities are competent, with the one chosen by the applicant. The full name or two-letter code of that Authority may be indicated by the applicant on the line below:

IPEA/ _____

33
CHAPTER II

PCT

DEMAND

under Article 31 of the Patent Cooperation Treaty:
The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty.

For International Preliminary Examining Authority use only

Identification of IPEA

Date of receipt of DEMAND

Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION

Applicant's or agent's file reference
2001.647 WO

International application No.

International filing date (day/month/year)

(Earliest) Priority date (day/month/year)

PCT/EP02/09647

29-08-2002

04-09-2001

Title of invention

"Thieno[2,3-d]pyrimidines with combined LH and FSH agonistic activity"

Box No. II APPLICANT(S)

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

Telephone No.:
0412-666380

**Akzo Nobel N.V.
Velperweg 76
6824 BM ARNHEM
The Netherlands**

Facsimile No.:
0412-650592

Teleprinter No.:

State (i.e. country) of nationality: **NL**

State (i.e. country) of residence: **NL**

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

**HANSSEN,
Robert, Gerard, Jules, Marie
N.V. Organon
Postbus 20
5340 BH OSS
The Netherlands**

State (i.e. country) of nationality: **NL**

State (i.e. country) of residence: **NL**

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

**TIMMERS,
Cornelis, Marius
N.V. Organon
Postbus 20
5340 BH OSS
The Netherlands**

State (i.e. country) of nationality: **NL**

State (i.e. country) of residence: **NL**



Further applicants are indicated on a continuation sheet.

Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The following person is ☒ agent ☐ common representative
 and ☒ has been appointed earlier and represents the applicant(s) also for international preliminary examination.
☐ is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.
☐ is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.

Name and address: *(Family name followed by given name; for a legal entity, full official designation.
 The address must include postal code and name of country.)*

P.M.G.F. van Wezenbeek
 P.O. Box 20
 5340 BH Oss
 The Netherlands

Telephone No.:

0412-666219

Facsimile No.:

0412-650592

Teleprinter No.:

☐ Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No. IV STATEMENT CONCERNING AMENDMENTS

The applicant wishes the international Preliminary Examining Authority*

(i) ☒ to start the international preliminary examination on the basis of the international application as originally filed.

(ii) ☐ to take into account the amendments under Article 34 of

☐ the description (amendments attached).

☐ the claims (amendments attached).

☐ the drawings (amendments attached).

(iii) ☐ to take into account any amendments of the claims under Article 19 filed with the International Bureau (a copy is attached).

(iv) ☐ to disregard any amendments of the claims made under Article 19 and to consider them as reversed.

(v) ☐ to postpone the start of the international preliminary examination until the expiration of 20 months from the priority date unless that Authority receives a copy of any amendments made under Article 19 or a notice from the applicant that he does not wish to make such amendments (Rule 69.1(d)). *(This check-box may be marked only where the time limit under Article 19 has not yet expired.)*

* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Box No. V ELECTION OF STATES

☒ The applicant hereby elects all eligible States *(that is, all States which have been designated and which are bound by Chapter II of the PCT) except*

(If the applicant does not wish to elect certain eligible States, the name(s) or country code(s) of those States must be indicated above.)

Box No. VI CHECK LIST

The demand is accompanied by the following documents for the purposes of international preliminary examination:

1. amendments under Article 34

description	:	sheets
claims	:	sheets
drawings	:	sheets

2. letter accompanying amendments under Article 34

: sheets

3. copy of amendments under Article 19

: sheets

4. copy of statement under Article 19

: sheets

5. other (specify):

: sheets

For International Preliminary
Examining Authority use only

received

not received

☐☐☐☐☐☐☐☐☐☐☐☐☐☐

The demand is also accompanied by the item(s) marked below:

1. ☐

separate signed power of attorney

4. ☒

fee calculation sheet

2. ☐

copy of general power of attorney

5. ☐

other (specify):

3. ☐

statement explaining lack of signature

Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).



P.M.G.F. van Wezenbeek

For International Preliminary Examining Authority use only

1. Date of actual receipt of DEMAND:

2. Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b):

3. ☐

The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply.

☐

The applicant has been informed accordingly.

4. ☐

The date of receipt of the demand is WITHIN the period of 19 months from the priority date as extended by virtue of Rule 80.5.

5. ☐

Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82.

For International Bureau use only

Demand received from IPEA on:

FEE CALCULATION SHEET

Annex to the Demand for international preliminary examination

International application No. PCT/EP02/09647 Applicant's or agent's file reference 2001.647 WO Applicant Akzo Nobel N.V.	For International Preliminary Examining Authority use only Date stamp of the IPEA
Calculation of prescribed fees 1. Preliminary examination fee..... EUR 1530,= P 2. Handling fee (Applicants from certain States are entitled to a reduction of 75% of the handling fee. Where the applicant is (or all applicants are) so entitled, the amount to be entered at H is 25% of the handling fee.)..... EUR 159,= H 3. Total of prescribed fees Add the amounts entered at P and H and enter total in the TOTAL box..... EUR 1689,= TOTAL	
Mode of Payment ☒ authorization to charge deposit account with the IPEA (see below) ☐ cash ☐ cheque ☐ revenue stamps ☐ postal money order ☐ coupons ☐ bank draft ☐ other (specify):	
Deposit Account Authorization (this mode of payment may not be available at all IPEAs) The IPEA / EPO ☒ is hereby authorized to charge the total fees indicated above to my deposit account. ☒ (this check-box may be marked only if the conditions for deposit accounts of the IPEA so permit) is hereby authorized to charge any deficiency or credit any overpayment in the total fees indicated above to my deposit account. 2809 0012 Deposit Account Number 30-01-2003 Date (day/month/year) P.M.G.F. van Wезenbeek Signature	
Form PCT/IPEA401 (Annex) (January 1996) See Notes to the fee calculation sheet	

PATENT COOPERATION TREATY

09 DEC. 2002

37

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT
OR THE DECLARATION

(PCT Rule 44.1)

To: VAN WEZENBEEK, P.M.G.F. P.O. Box 20 NL-5340 BH Oss NETHERLANDS	<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%;">Behandeld door</td> <td style="width: 50%; text-align: center;">PVL</td> </tr> <tr> <td>Adm. afzender</td> <td style="text-align: center;">✓</td> </tr> <tr> <td>Bericht d.d.</td> <td style="text-align: center;">✓</td> </tr> <tr> <td>aan:</td> <td></td> </tr> <tr> <td>Baan: d.d.</td> <td></td> </tr> <tr> <td>Afzender</td> <td style="text-align: center;">lw</td> </tr> </table>	Behandeld door	PVL	Adm. afzender	✓	Bericht d.d.	✓	aan:		Baan: d.d.		Afzender	lw
Behandeld door	PVL												
Adm. afzender	✓												
Bericht d.d.	✓												
aan:													
Baan: d.d.													
Afzender	lw												

Date of mailing (day/month/year)	10/12/2002
-------------------------------------	------------

Applicant's or agent's file reference 2001.647 WO	FOR FURTHER ACTION See paragraphs 1 and 4 below
International application No. PCT/EP 02/09647	International filing date (day/month/year) 29/08/2002
Applicant AKZO NOBEL N.V.	

1. ☒ The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. Further action(s): The applicant is reminded of the following:

Shortly after 18 months from the priority date, the International application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the International application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for International publication.

Within 19 months from the priority date, a demand for International preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within 20 months from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority  European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Sandrine Polenzani
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NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 18. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the letter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 18(1)" (see below, under "Statement under Article 18(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 2001.647 WO	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/EP 02/09647	International filing date (day/month/year) 29/08/2002	(Earliest) Priority Date (day/month/year) 04/09/2001
Applicant AKZO NOBEL N.V.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 03 sheets.



It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.



the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing:



contained in the international application in written form.



filed together with the international application in computer readable form.



furnished subsequently to this Authority in written form.



furnished subsequently to this Authority in computer readable form.



the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.



the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☐ Certain claims were found unsearchable (See Box I).

3. ☐ Unity of invention is lacking (see Box II).

4. With regard to the title,

the text is approved as submitted by the applicant.



the text has been established by this Authority to read as follows:

5. With regard to the abstract,

the text is approved as submitted by the applicant.



the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No.

as suggested by the applicant.



because the applicant failed to suggest a figure.



because this figure better characterizes the invention.



None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 02/09647

4/

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D495/04 A61K31/505 A61P15/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BIOSIS, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 00 61586 A (AKZO NOBEL NV ;ADANG ANTON EGBERT PETER (NL); GERRITSMA GERRILDINA) 19 October 2000 (2000-10-19) cited in the application page 3, line 9-16; claims 1,8,11,15; examples 111,116; table 1	1-6

☐ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *Z* document member of the same patent family

Date of the actual completion of the international search

2 December 2002

Date of mailing of the international search report

10/12/2002

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 apo nl,
Fax (+31-70) 340-3016

Authorized officer

Guspanova, J

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 02/09647

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0061586	A	19-10-2000	
		AU 3816600 A	14-11-2000
		BR 0009558 A	19-02-2002
		CN 1349535 T	15-05-2002
		CZ 20013605 A3	13-03-2002
		WO 0061586 A1	19-10-2000
		EP 1171443 A1	16-01-2002
		HU 0200653 A2	29-06-2002
		NO 20014824 A	04-10-2001
		TR 200102839 T2	22-04-2002

PATENT CO-OPERATION TREATY

[21 FEB. 2003

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From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To:

VAN WEZENBEEK, P.M.G.
P.O. Box 20
NL-5340 BH Oss
PAYS-BAS

Adm. opposition	
Bericht d.d. adm.	
Beantw. d.d.	
Aleggen	

NOTIFICATION OF RECEIPT OF DEMAND BY COMPETENT INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

(PCT Rules 59.3(e) and 61.1(b), first sentence
and Administrative Instructions, Section 601(a))

Date of mailing
(day/month/year)

19-02-2003

Applicant's or agent's file reference
2001.647 WO

IMPORTANT NOTIFICATION

International application No.

PCT/EP 02/09647

International filing date (day/month/year)

29/08/2002

Priority date (day/month/year)

04/09/2001

Applicant

AKZO NOBEL N.V. et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority considers the following date as the date of receipt of the demand for international preliminary examination of the international application:

03/02/2003

2. This date of receipt is:

- ☒ the actual date of receipt of the demand by this Authority (Rule 61.1(b)).
- ☐ the actual date of receipt of the demand on behalf of this Authority (Rule 59.3(e)).
- ☐ the date on which this Authority has, in response to the invitation to correct defects in the demand (Form PCT/IPEA/404), received the required corrections.

3. ☐ **ATTENTION:** That date of receipt is **AFTER** the expiration of 19 months from the priority date. Consequently, the election(s) made in the demand does (do) not have the effect of postponing the entry into the national phase until 30 months from the priority date (or later in some Offices) (Article 39(1)). Therefore, the acts for entry into the national phase must be performed within 20 months from the priority date (or later in some Offices) (Article 22). For details, see the *PCT Applicant's Guide*, Volume II.

- ☐ (If applicable) This notification confirms the information given by telephone, facsimile transmission or in person on:

4. Only where paragraph 3 applies, a copy of this notification has been sent to the International Bureau.

Name and mailing address of the IPEA/



European Patent Office
D-80298 Munich
Tel. (+49-89) 2399-0, Tx: 523656 epnu d
Fax: (+49-89) 2399-4465

Authorized officer

FERRO VASCONCELOS M

Tel (+49-89) 2399-7905



PATENT COOPERATION TREATY

21 FEB. 2003
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From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To:	
VAN WEZENBEEK, P.M.G.	Deanfield door D.W.
P.O. Box 20	Adm. opmerkingen A.v.l.
NL-5340 BH Oss	Bericht d.d.
PAYS-BAS	aan:
	Beantw. d.d.
	Afleggen

NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Applicant's or agent's file reference 2001.647 WO		IMPORTANT NOTIFICATION	
International application No. PCT/EP 02/09647	International filing date (day/month/year) 29/08/2002	Priority date (day/month/year) 04/09/2001	
Applicant AKZO NOBEL N.V. et al.			

- The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
- A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
- Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the IPEA/  European Patent Office D-80298 Munich Tel. (+49-89) 2399-0, Tx: 523656 eprmu d Fax: (+49-89) 2399-4465	Authorized officer FERRO VASCONCELOS M Tel. (+49-89) 2399 2828
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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

(Rationalised Report according to the Notice of the President of the EPO published in the OJ11/2001)

Applicant's or agent's file reference 2001.647 WO	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/EP 02/ 09647	International filing date (day/month/year) 29/08/2002	Priority date (day/month/year) 04/09/2001
International Patent Classification (IPC) or national classification and IPC C07D495/04		
Applicant AKZO NOBEL N.V. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 2 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consists of a total of _____ sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 03/02/2003	Date of completion of this report 14/02/2003
Name and mailing address of the IPEA/ European Patent Office D-80298 Munich Tel. (+49-89) 2399-0, Tx: 523656 epmu d Fax: (+49-89) 2399-4465	Authorized officer TZSCHOPPE D A Tel. (+49-89) 2399 2828



I. Basis of the report

The basis of this international preliminary examination is the application as originally filed.

V. Reasoned statement under Rule 66.2(a)(II) with regard to novelty, inventive step or industrial applicability

In light of the documents cited in the international search report, it is considered that the invention as defined in the claims meets the criteria mentioned in Article 33 (1) PCT, i.e. it appears to be novel, to involve an inventive step and to be industrially applicable.

Traducción

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**TRATADO DE COOPERACIÓN DE PATENTES
PCT
INFORME DE EXAMEN PRELIMINAR INTERNACIONAL
(Artículo 36 y Regla 70 del PCT)**

Referencia del expediente del agente o solicitante 2001.647 WO	PARA ACTUACIONES ADICIONALES Ver notificación de Transmisión del Reporte de Examen Preliminar (Formato PCT/PEA416)	
Solicitud Internacional No. PCT/EP02/00847	Fecha de presentación internacional (día/mes/año) 29/08/2002	Fecha de prioridad (día/mes/año) 04/09/2001
Clasificación Internacional de Patentes (IPC) o clasificación nacional e IPC C07D 495/04		
Solicitante AKZO NOBEL N.V. et al		

1. Este informe de examen preliminar internacional ha sido preparado por esta Administración encargada del Examen Preliminar Internacional y se envía al solicitante en concordancia con el artículo 36.

2. Este INFORME consta de una total de 2 hojas, incluyendo la portada

☐ Este informe también se acompaña de ANEXOS, esto es documentos de la descripción, reivindicaciones y/o dibujos que han sido corregidos y que son la base de este informe y/o documentos que contienen rectificaciones realizadas ante esta Administración (Ver Regla 70.16 y Sección 607 de las Instrucciones Administrativas según el PCT)

Estos anexos constan de un total de _____ hojas.

3. Este informe contiene indicaciones relativas a los siguientes aspectos:

- I ☒ Fundamentos del Informe
- II ☐ Prioridad
- III ☐ No se establece concepto relativo a la novedad, nivel inventivo y aplicación industrial
- IV ☐ Carencia de unidad de la invención
- V ☒ Declaración razonada según el artículo 35(2), en relación con la novedad, nivel inventivo o aplicación industrial; citaciones y explicaciones que soportan dicha declaración
- VI ☐ Ciertos documentos citados
- VII ☐ Ciertos defectos de la solicitud internacional
- VIII ☐ Ciertas observaciones respecto a la solicitud internacional

Fecha de presentación de la demanda 03/02/2003	Fecha de terminación de este reporte 14/02/2003
Nombre y dirección de correo de la autoridad encargada del examen preliminar  Oficina Europea de Patentes D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 apmu d Fax: +49 89 2399 - 4465	Funcionario Autorizado TZSCHOPPE D A Teléfono No. +49 89 2399-2782

Formato PCT/PEA409 (portada) (julio 1998)

I. Base del informe

La base de este examen preliminar internacional es la solicitud como originalmente fue presentada.

V. Declaración motivada según el Artículo 35(2) en cuanto a la novedad, el nivel inventivo y la aplicación industrial; citas y explicaciones que apoyan esta declaración.

A la luz de los documentos citados en el informe de búsqueda internacional, se considera que la invención tal y como esta definida en las reivindicaciones cumple con los criterios mencionados en el Artículo 33(1) PCT; es decir parece ser novedosa, tener nivel inventivo y tener aplicación industrial.

COLO 11214-841-014-8
PRP/WPC11214/ID-293

**Tieno[2,3-d]pirimidinas con actividad agonista combinada
de LH y FSH**

La invención se relaciona con compuestos que tienen actividad agonista de hormona glicoproteína, en particular con compuestos que tienen tanto actividad agonista de Hormona Luteinizante (LH) como de Hormona Estimulante del Folículo. La invención se relaciona además con composiciones farmacéuticas que contienen la misma así como también el uso de estos compuestos en terapia médica, particularmente para usos como un control de fertilidad.

Las gonadotropinas sirven para importantes funciones en una variedad de funciones del cuerpo que incluyen metabolismo, regulación de temperatura y el proceso reproductivo. Las gonodotropinas hipofíseas FSH y LH por ejemplo juegan un papel de pivote en la estimulación del desarrollo del folículo y la maduración mientras que el LH está involucrado en la inducción del proceso ovulatorio (Sharp, R.M. Clin. Endocrinol 33, 787-807, 1990; Dorrington y Armstrong, Recent Prog. Horm. Res

35,301-342, 1979; Levy et al, Human Reproduction 15, 2258-2265, 2000).

Habitualmente, el LH se aplica clínicamente, en combinación con el FSH, para estimulación del ovario es decir hiperestimulación del ovario para fertilización in vitro (IVF) e inducción de ovulación en mujeres anovulatorias infértiles (Insler, V., Int. J. Fertility 33, 85-97, 1988, Navot y Rosenwaks, J. Vitro Fert. Embryo Transfer 5, 3-13, 1988), así como también para hipogonadismo de machos e infertilidad de machos.

Las gonadotropinas actúan sobre tipos de célula de gónada específicos para iniciar la diferenciación y la esteroidogénesis del ovario y testicular.

Las acciones de estas hormonas pituitaria y de placenta son mediadas por receptores de membrana de plasma específicos que son miembros de la gran familia de los receptores acoplados G-proteína. Ellos consisten de un polipéptido simple con siete dominios de transmembrana y son capaces de interactuar con la proteína Gs, conduciendo a la activación de la adenil ciclasa.

Las gonadotropinas destinadas a propósitos terapéuticos se pueden aislar de las fuentes de orina humana y son de baja pureza (Morse et al, Amer. J. Reproduct. Immunol. and Microbiology 17, 143, 1988). Alternativamente, ellas se pueden preparar como gonadotropinas recombinantes. Además de estas proteínas, los receptores de gonadotropinas se pueden activar o desactivar mediante compuestos sintéticos de bajo peso molecular. Los compuestos heteroaromáticos Biciclitos se han descrito en la WO 00/61586. Mediante experimentos *in vitro* e *in vivo* ellos han mostrado ser útiles como agonistas LH.

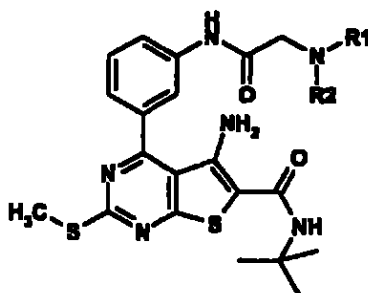
En hembras normales la liberación del LH y FSH de pituitaria se caracteriza por una ondulación de ciclo medio que precede la ovulación. La ovulación se caracteriza por tres distintos fenómenos fisiológicos es decir la maduración del oocito, ruptura folicular y luteinización. Aunque el papel de la ondulación de LH en la inducción *in vivo* de estos fenómenos no está en disputa, el papel de la ondulación de FSH es menos claro. Sin embargo, se ha mostrado recientemente que el FSH induce la maduración del oocito *in vitro* al inducir células cúmulos al producir un factor que soluciona

positivamente la detención meiótica inducida por hipoxantina (Lu et al. Mol. Cell. Endocrinol. 164, 191-196, 2000). Se cree que este factor es un esteroide activado por la meiosis (MAS).

En la inducción de ovulación, es deseable suministrar los efectos de LH como el componente principal. De acuerdo con la presente invención se han encontrado compuestos con propiedades particulares ventajosas cuando se utilizan en protocolos para fertilidad mejorada. En estos compuestos la actividad LH se acompaña mediante una actividad FSH.

De esta manera la presente invención suministra compuestos de bajo peso molecular que además de la actividad LH tienen inesperadamente también actividad FSH. En general estos compuestos son [2,3-d]pirimidinas las cuales en la posición 4 del anillo de pirimidinas son sustituidas por un grupo fenilo que a su vez es sustituido en la posición meta.

La presente invención está relacionada con derivados de tieno[2,3-d]pirimidina de acuerdo con la fórmula general I,



Fórmula I

o una sal farmacéuticamente aceptable de esta, en donde N(R1)R2 está unido en un anillo (2-6C)heterocicloalquilo.

Los compuestos más preferidos son tert-butil 5-amino-2-metiltio-4-(3-(2-(azetidín-1-il)-acetamido)-fenil)-tieno[2,3-d]pirimidina-6-carboxamida; tert-butil 5-amino-2-metiltio-4-(3-(2-(morfolín-4-il)-acetamido)-fenil)-tieno[2,3-d]pirimidina-6-carboxamida; tert-butil 5-amino-2-metiltio-4-(3-(2-(tiomorfolín-4-il)-acetamido)-fenil)-tieno[2,3-d]pirimidina-6-carboxamida; tert-butil 5-amino-2-metiltio-4-(3-(2-(piperidín-1-il)-acetamido)-fenil)-tieno[2,3-d]pirimidina-6-carboxamida; tert-butil 5-amino-2-metiltio-4-(3-(2-(pirrolidín-1-il)-acetamido)-fenil)-tieno[2,3-d]pirimidina-6-carboxamida y tert-butil

5-amino-2-metiltio-4-(3-(2-(piperazin-1-il)-acetamido)-fenil)-tieno[2,3-d]pirimidina-6-carboxamida.

El término unido en un anillo (2-6C) heterocicloalquilo en la definición de la fórmula I, significa que R1 y R2 junto con el átomo de nitrógeno al cual ellos están unidos forman un anillo que tiene 2-6 átomos de carbono, opcionalmente que contiene uno o más heteroátomos seleccionados de N, O y/o S. Ejemplos de tales anillos son azetidina, pirrolidina, piperidina, piperazina, morfolino, y tiomorfolino.

Se ha encontrado que los compuestos de la fórmula I anteriormente mencionada muestran actividad LH y FSH agonista. En un bioensayo *in vitro* utilizando células CHO establemente transfectadas con el receptor LH o FSH de humano, respectivamente, el EC₅₀ con relación al receptor LH Se encontró que era menor que $5,10^{-8}M$ mientras que con relación al receptor FSH el EC₅₀ era menor de $10^{-5}M$. Típicamente la actividad FSH varía desde una actividad de aproximadamente 1% de la estimulación agonista LH a aproximadamente 10% de la estimulación agonista LH.

La invención reside además en una composición farmacéutica que comprende un compuesto derivado de tieno[2,3-d]pirimidina o sales de estos que tienen la fórmula general I.

Así, los compuestos de acuerdo con la invención se pueden utilizar en terapia. Un aspecto adicional de la invención reside en el uso de un compuesto de tieno[2,3-d]pirimidina que tiene la fórmula general I para la elaboración de un medicamento para el control de fertilidad, más preferiblemente inducción de ovulación. Los presentes compuestos son utilizados para activar tanto los receptores LH como FSH. El compuesto de la presente invención se puede utilizar por lo tanto en un método para tratar hembras con problemas de fertilidad.

Para uso terapéutico, las sales de los compuestos de formula I son aquellas en donde el contraión es farmacéuticamente aceptable. Sin embargo, las sales de adición de ácido de bases de acuerdo con la fórmula I, también pueden encontrar uso, por ejemplo, en la preparación o purificación de un compuesto farmacéuticamente aceptable. Todas las sales, sean

farmacéuticamente aceptables o no, están incluidas dentro del ámbito de la presente invención.

Ejemplos de sales de adición de ácido incluyen aquellas derivadas de ácidos minerales tales como ácido clorhídrico, ácido fosfórico, ácido sulfúrico, preferiblemente ácido clorhídrico, y ácidos orgánicos como ácido cítrico, ácido tartárico, ácido acético, ácido láctico, ácido maleíco, ácido malónico, ácido fumárico, ácido glicólico, ácido succínico, y similares.

Las rutas de administración adecuadas para los compuestos de formula I o las sales farmacéuticamente aceptables de estas, también denominadas aquí como ingrediente activo son inyecciones intramusculares, inyecciones subcutáneas, inyecciones intravenosas o inyecciones intraperitoneales, administración oral o intranasal. Preferiblemente, los compuestos se pueden administrar oralmente. La dosis y el régimen exacto de administración del ingrediente activo o una composición farmacéutica de esta, necesariamente dependerá del efecto terapéutico a ser logrado (tratamiento de infertilidad; contracepción), y puede variar con el compuesto particular, la ruta de administración, y la edad y

condición del sujeto individual a quien el medicamento le va ser administrado.

En general, la administración parenteral requiere dosis más bajas que otros métodos de administración que son más dependientes de la absorción. Sin embargo, una dosis para humanos contiene preferiblemente 0,0001-25 mg por kg de peso de cuerpo. La dosis deseada puede ser presentada como una dosis o como subdosis múltiples administradas a intervalos apropiados a lo largo del día. En el caso de receptores hembras, las dosis se pueden administrar a intervalos apropiados diariamente a lo largo del ciclo menstrual para soporte folicular o como una dosis simple para inducción de ovulación. Las dosis así como el régimen de administración pueden diferir entre el receptor hembra y un macho.

En caso de aplicaciones *in vitro* o *ex vivo*, como en aplicaciones IVF, los compuestos de la invención se deben utilizar en el medio de incubación en una concentración de aproximadamente 0,01-5µg/ml.

La presente invención también se relaciona así con unas composiciones farmacéuticas que comprenden un

compuesto de tieno[2,3-d]pirimidina de acuerdo con la fórmula en mezcla con auxiliares farmacéuticamente aceptables, y opcionalmente otros agentes terapéuticos. Los auxiliares deben ser "aceptables" en el sentido de ser compatibles con los otros ingredientes de la composición y no deletéreos a los receptores de esta.

Las composiciones farmacéuticas incluyen a aquellas adecuadas para administración oral, rectal, nasal, tópica (incluyendo transdérmica, bucal y sublingual), vaginal o parenteral (incluyendo subcutánea, intramuscular, intravenosa, e intradérmica) Las composiciones se pueden preparar mediante cualquier método bien conocido en la técnica de farmacia, por ejemplo, utilizando métodos tales como aquellos descritos en Gennaro et al., Remington Pharmaceutical Sciences (18ed., Mack Publishing Company, 1990, ver especialmente Parte 8: *Pharmaceutical Preparations and Their Manufacture*).

Tales métodos incluyen la etapa de traer en asociación el ingrediente activo con cualquier agente auxiliar. El o los agentes auxiliares, también denominados ingredientes accesorios, incluyen aquellos convencionales en la técnica (Gennaro, *supra*), tales

como, llenadores, ligadores, diluyentes, desintegrantes, lubricantes, colorantes, agentes saborizantes y agentes humectantes.

Las composiciones farmacéuticas adecuadas para administración oral pueden estar presentes como unidades de dosis discretas tales como píldoras, tabletas o cápsulas, o un polvo o gránulos, o como una solución suspensión. El ingrediente activo también puede estar presente como un bolo o pasta. Las composiciones pueden además ser procesadas en un supositorio o enema para administración rectal.

Para administración parenteral, las composiciones adecuadas incluyen inyección estéril acuosa y no acuosa. Las composiciones pueden estar presentes en recipientes de dosis unitaria o de multidosis, por ejemplo frascos seriados y ampollas, y se pueden almacenar en una condición de secado en frío (liofilizado) que requiere solo la adición de un portador líquido estéril, por ejemplo, agua antes de uso.

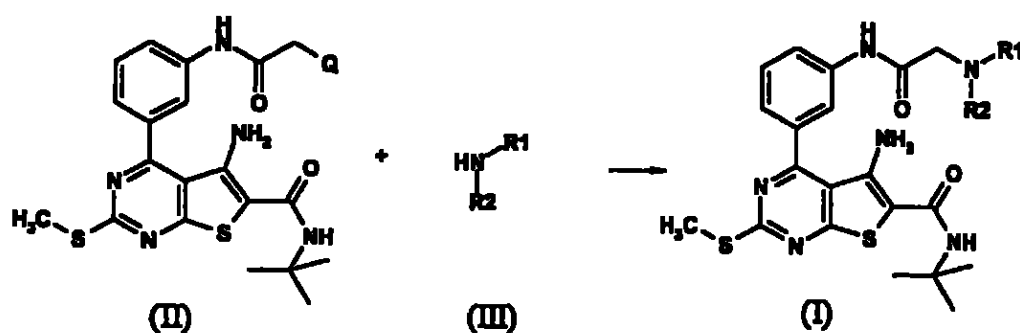
Las composiciones, o formulaciones, adecuadas para administración mediante inhalación incluyen polvos finos

o vapores que se pueden generar por medios de aerosoles presurizados con dosis medidas, nebulizadores o insufladores.

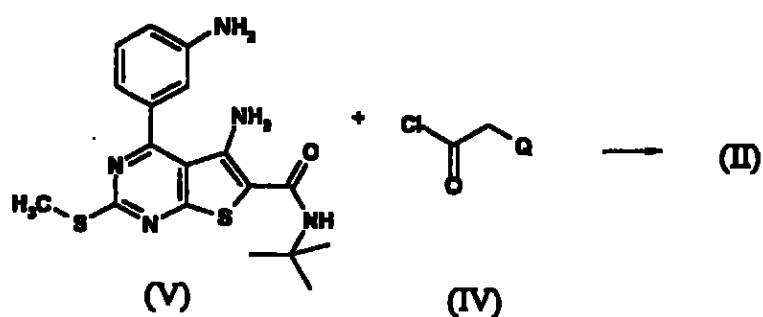
Los compuestos de tieno[2,3-d]pirimidina de la invención se pueden administrar en la forma de dispositivos farmacéuticos implantables, que consisten de un núcleo de material activo, recubierto por una membrana que regula la proporción de liberación. Tales implantes se deben aplicar subcutáneamente o localmente, y liberarán el ingrediente activo a una proporción aproximadamente constante durante largos periodos de tiempo, por ejemplo de semanas a años. Los métodos para preparación de los dispositivos farmacéuticos implantables como tales son conocidos en la técnica, por ejemplo como se describe en la Patente europea 0,303,306 (AKZO N.V.)

De esta manera, los compuestos de acuerdo con la presente invención se pueden utilizar con los mismos propósitos clínicos que el LH nativo, con la ventaja de que ellos poseen actividad FSH, muestran propiedades de estabilidad alterada y se pueden administrar de manera diferente.

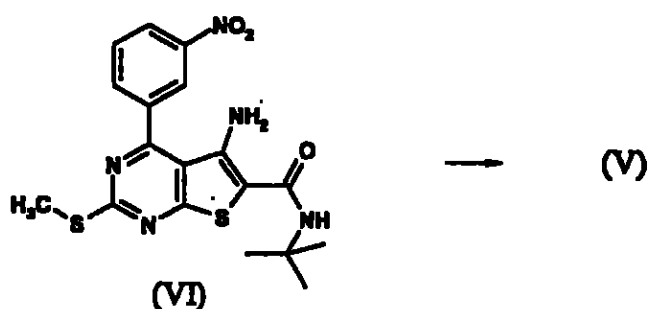
Los compuestos de la presente invención, representados por la fórmula (I) pueden ser preparados generalmente mediante sustitución nucleofélica de haluros (II) en donde Q = CL o Br con aminas secundarias (cíclicas) de la fórmula (III) en un solvente apropiado tal como N,N-dimetilformamida o THF a temperatura ambiente de cuarto en la presencia de una base terciaria tal como N,N-diisopropiletilamina (DIPEA).



Los derivados de formula (II) en donde Q = CL o Br se pueden preparar mediante acilación regioselectiva de un derivado de anilina (V) con cloruros de acilo del tipo (IV), en donde Q = CL o Br en la presencia de una base terciaria tal como N,N-diisopropiletilamina en un solvente adecuado tal como diclorometano o THF.

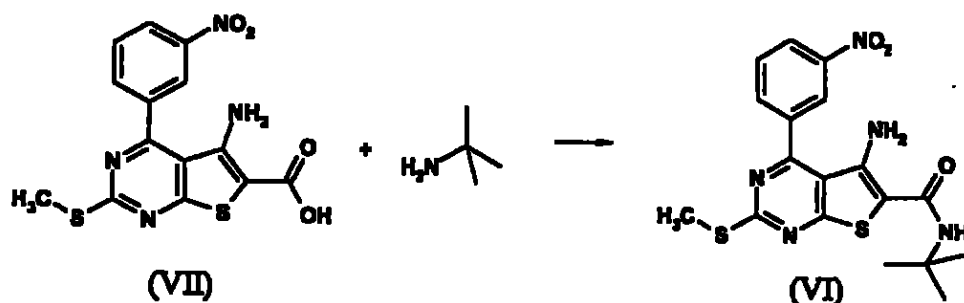


El compuesto (V) es accesible mediante reducción conocida en la técnica de la función nitro en derivado (VI) utilizando un agente reductor apropiado tal como cloruro de estaño (II) en un solvente propio tal como etanol en la presencia de ácido clorhídrico a temperatura elevada (J. Heilbron, J. Chem. Soc, 1279 (1940)).

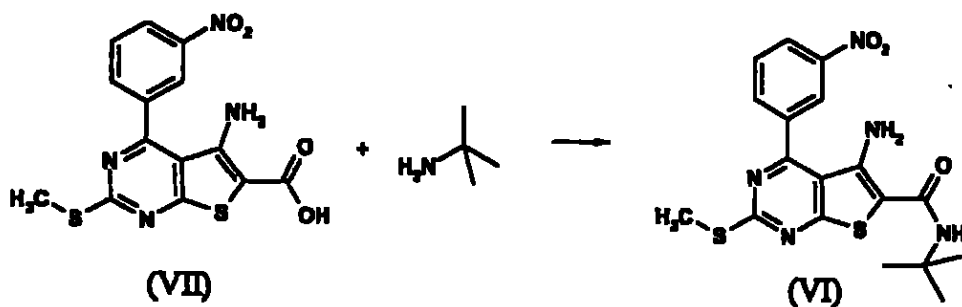


La tienopirimidina (VI) se puede preparar mediante condensación de ácido carboxílico (VII) con tert-

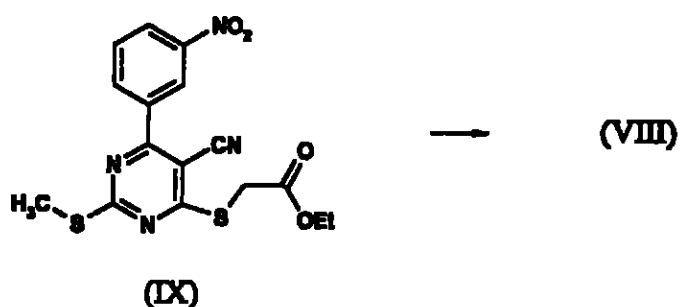
butilamina bajo la influencia del agente acoplante tal como O-(-benzotriazol-1-il)-N,N,N',N'-tretametiluronio tetrafluoroborato (TBTU) o bromotripirrolidinofosfonio hexafluorofosfato (PyBrOP) y una base terciaria, por ejemplo N,N-diisopropiletilamina.



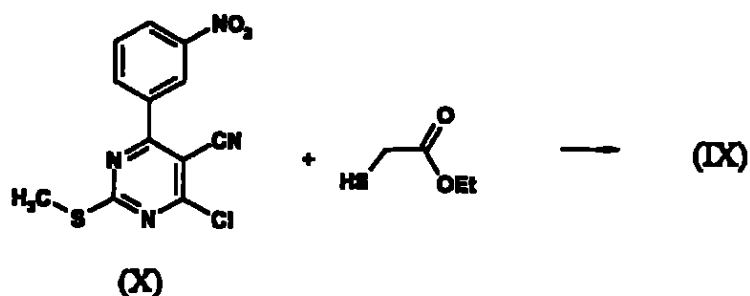
La saponificación del éster de etilo (VIII) al correspondiente ácido carboxílico (VII) tiene lugar en la presencia de una base tal como hidróxido de litio, hidróxido de potasio o hidróxido de sodio en dioxano acuoso a temperatura elevada (80°C a reflujo).



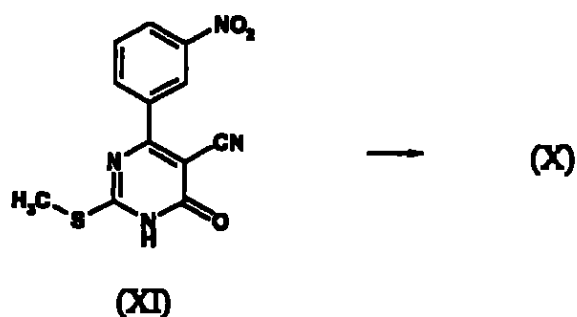
El biciclo (VIII) se forma mediante sustitución de cloruro (X) con etil mercaptoacetato bajo la agencia de N,N-diisopropiletilamina, seguida por el cierre de anillo catalizado por base del tioeter intermedio (IX). Este tipo de formaciones de anillo de tieno[2,3-d]pirimidina se ha descrito en: S.A. Abdel-Hady, M.A. Badaway, Y. A. Ibrahim, Sulfur, Lett. 9, 101 (1989) and S. Tumkevicius, Liebigs Ann, 1703 (1995).



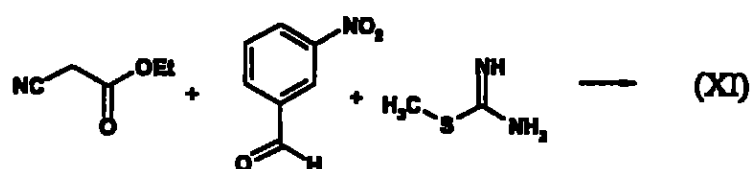
Las condiciones adecuadas para la reacción de ciclización son etóxido de sodio en etanol o N,N-diisopropiletilamina en tolueno/etanol (1/1, v/v) a temperatura a reflujo.



La cloroimina de requisito (II) se puede sintetizar siguiendo los procedimientos de la literatura como se describe por ejemplo en S.S. Santilli, D.H. Kim y S.V. Wanser, J. Heterociclo. Chem. 8,445, 1971. De acuerdo a este procedimiento, la lactama (XI) se trata con POCl₃ a temperatura elevada (80°C hasta reflujo) para dar cloruro (X). La adición de un solvente apropiado, por ejemplo, dioxano, y/o la adición de PCl₅ o N,N-dimetilanilina a la mezcla de reacción puede dar como resultado unos tiempos de reacción más cortos y una producción mayor de cloruro (X).



Una ruta apropiada hacia las lactamas (XI) comprenden la condensación multicomponente de etil cianoacetato con 3-nitro-benzaldehído y S-metil isotiourea en etanol bajo la agencia de una base tal como carbonato de potasio a temperatura elevada (60°C).



Los procedimientos relacionados se han descrito en: s. Kambe, K. Saito y H. Kishi, *Síntesis*, 287 (1979); A.M. Abd-Elfattah, S.M. Hussain y A.M. El-Reddy, *Tetrahedron* 39, 3197 (1983); S.M. Hussain, A.A. El-Barbary y S.A. Mansour, *J. Heterocycl. Chem.* 22, 169 (1985).

Los métodos para determinar la unión receptora así como también los ensayos *in vitro* e *in vivo* para determinar la actividad biológica de las gonadotropinas son bien conocidos. En general, el receptor expresado es puesto en contacto con el compuesto a ser ensayado y se

mide la unión o la estimulación o la inhibición de una respuesta funcional.

Para medir una respuesta funcional ADN aislado que codifica el gen receptor de LH o el FSH, preferiblemente el receptor humano se expresa en células hospederas adecuadas. Tal célula podía ser de célula de ovario de hámster chino, pero otras células también son adecuadas.

Preferiblemente las células son de origen mamífero (Jia et al, Mol. Endocrin., 5,759-776, 1991)

Los métodos para construir líneas de células recombinantes que expresan LH o FSH son bien conocidos en la técnica (Sambrook et al., Molecular Cloning: a Laboratory Manual, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, latest edition. La expresión del receptor se logra mediante la expresión del ADN que codifica la proteína deseada. Las técnicas para mutagénesis dirigida a sitio, ligación de secuencias adicionales, PCR, y construcción de sistemas de expresión adecuados son todas, por ahora, bien conocidas en la técnica. Las porciones o todo el ADN que codifica la proteína deseada se pueden construir sintéticamente

utilizando técnicas de fase sólida estándar, preferiblemente para incluir sitios de restricción para facilidad de ligación. Los elementos de control adecuados para la transcripción y la traducción de la secuencia de codificación incluida se pueden suministrar a las secuencias que codifican el ADN. Como es bien conocido, los sistemas de expresión que están ahora disponibles que son combatibles con una amplia variedad de hospederos, incluyen hospederos procarióticos tales como bacterias y hospederos eucarióticos tales como levaduras, células de plantas, células de insectos, células de mamíferos, células de aves y similares.

Las células que expresan el receptor son entonces puestas en contacto con el compuesto de ensayo para observar la unión, o estimulación o inhibición de una respuesta funcional.

Alternativamente las membranas de célula aislada que contienen el receptor expresado se pueden utilizar para medir la unión del compuesto.

Para la medición de la unión se pueden utilizar compuestos etiquetados radio activa o fluorescentemente.

Como compuesto de referencia se puede utilizar LH o FSH humano recombinante. En la alternativa también se pueden desarrollar ensayos de unión de competición.

Otros ensayos involucran el tamizado de compuestos agonistas de receptores de LH o FSH al determinar la estimulación del receptor mediado por acumulación de cAMP. De esta manera, tal método involucra la expresión del receptor de la superficie de célula de una célula hospedera y exponer la célula al compuesto de ensayo. La cantidad de cAMP es entonces medida. El nivel de cAMP se reducirá o incrementará, dependiendo del efecto inhibitorio o estimulante del compuesto de ensayo luego de la unión al receptor.

Además de la medición directa de por ejemplo los niveles de cAMP en la célula expuesta, las células se pueden utilizar las cuales además de la transfección con un ADN que codifica al receptor son también transfectadas con un segundo ADN que codifica un gen reportero cuya expresión responde al nivel de cAMP. Tales genes reporteros podrían ser cAMP inducibles o podrían ser contruidos de tal manera que ellos sean conectados a elementos de respuesta cAMP novedosos. En general, la

expresión del gen reportero se podría controlar mediante cualquier elemento de respuesta que reaccione con los niveles de cambio de cAMP. Genes reporteros adecuados son por ejemplo LacZ, fosfatasa alcalina, luciferaza de fuego y la proteína de fluorescencia verde. Los principales de tales ensayos de transactivación son bien conocidos en la técnica y son descritos por ejemplo en Estratowa, Ch, Himmeler, A y Czernilofski, A. P., Curr. Opin. Biotechnol. 6, 574, (1995).

Para Seleccionar compuestos activos en los receptores LH o FSH, ensayos a 10^{-5} M deben resultar en una actividad de más del 20% de la actividad máxima cuando LH o FSH es usado como referencia. Otro criterio puede ser el valor EC_{50} , que debe ser menor a 10^{-5} M, preferiblemente menor a 10^{-7} M.

La persona versada reconocerá que deseablemente los valores EC_{50} son dependientes del compuesto ensayado. Por ejemplo, un compuesto con un EC_{50} , que es menor de 10^{-5} M es generalmente, considerado un candidato para selección de droga. Preferiblemente este valor es inferior a 10^{-7} M. Sin embargo, un compuesto que tenga un EC_{50} mayor, pero es

selectivo para el receptor particular, puede aún ser un mejor candidato.

La escogencia o el tamizado para los compuestos agnósticos de receptor LH pueden también ser llevados a cabo usando un bioensayo de células de ratón Leydig (Van Damme, M., Robersen, D. Y Diczfalusy, E., Acta Endocrinol. 77: 655-671 (1974), Mannaerts, B. Kloosterboer, H. y Schuurs, A., Neuroendocrinología de la reproducción. R. Rolland et al. Ediciones., Elsevier Science Publishers B. V., 49-58 (1987)). En este ensayo, la estimulación de la producción de testosterona mediada por el receptor LH puede ser medida en células Leydig aisladas de ratones macho.

La actividad agonística del FSH de los compuestos puede también ser determinada en un modelo *ex vivo* usando folículos cultivados de ratón de acuerdo con Nayudu, P. Y Osborn, S. (J. Reproduction and Fertility 95, 349-362 (1992)). Por lo tanto, los folículos de ovario de ratón son aislados y cultivados en la presencia de compuestos agnósticos FSH para inducir el crecimiento folicular. Las mediciones del diámetro folicular y el estradiol en el

medio de cultivo son indicativos del crecimiento folicular.

Para medir la actividad *in vivo* de los compuestos LH, la inducción de ovulación en ratones inmaduros puede ser estudiada. En este ensayo los ratones hembras inmaduros son cebados con FSH urinario y aproximadamente 48 horas después tratados con un compuesto agnóstico LH. Los animales son sacrificados después del tratamiento agonista LH y el número de óvulos en el oviducto es accesado microscópicamente.

Para medir la actividad FSH *in vivo* de los compuestos en ratas inmaduras las ratas hembras inmaduras son tratadas en a 0, 8, 24 y 32 horas con un compuesto agnóstico FSH para inducir el crecimiento folicular. A las 52 horas después del inicio del experimento los animales son inyectados con hCG para inducir la ovulación. Los animales son sacrificados 72 horas después del inicio del experimento y el número de óvulos en el oviducto es accesado microscópicamente. En adición el peso del ovario es determinado.

Los compuestos de la presente invención pueden ser aplicados clínicamente en aquellos regímenes en donde ahora es usado el LH o el hCG. Estos incluyen la sustitución de LH entre sujetos con hipogonadismo hipogonadal sea en macho o hembra, la administración en ciclos medios para inducir la ovulación (inducción de ovulación (OI) o hiperestimulación controlada (COH) o estimulación del corpus luteum.

Los siguientes ejemplos son ilustrativos para la invención y no deben ser interpretados de ninguna manera como limitativos del alcance de la invención.

Ejemplos

Ejemplo 1

5-amino-2-metiltio-4-(3-(2-(azetidin-1-il)-acetamido)-
fenil)-tieno [2,3-d]pirimidina-6-carboxamida de tert-
butilo

(a). 5-clano-4-(3-nitrofenil)-2-metiltio-6-oxopirimidina

Una mezcla de sulfato de S-metilisotiurea (69,0 g), 3-nitrobenzaldehído (75,0 g) cianoacetato de etilo (56,0 ml) y carbonato de potasio (72,5 g) en EtOH absoluto (1500 ml) fueron agitados a 60°C durante 16 horas. La mezcla de reacción fue enfriada a 0°C en un baño de hielo. El precipitado resultante fue filtrado, lavado con EtOH absoluto y disuelto en agua caliente (100°C). La solución fue enfriada a temperatura ambiente, acidificada con HCL al 2N hasta un pH 2 y enfriada a 0°C en un baño de hielo. El precipitado resultante fue filtrado retirado y lavado con agua y hielo. El agua residual en el precipitado fue removida por coevaporación con 1,4-dioxano.

Producción: 54,0 mg

MS-ESI: $[M+H]^+ = 289,0$

TLC: $R_f = 0,3$, gel de sílice, DCM/MeOH = 9/1 (v/v).

(b). 6-cloro-5-ciano-4-(3-nitrofenil)-2-metiltio-pirimidina

POCl₃ (100 ml) fue agregado a una solución agitada de 5-ciano-4-(3-nitrofenil)-2-metiltio-6-oxopirimidina (ejemplo 1 (a), 25,0 g) en 1-4-dioxano seco (300 ml).

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Después de 3 horas a 90°C la mezcla fue enfriada a temperatura ambiente y concentrada bajo presión reducida. El residuo fue disuelto en 1,4-dioxano (100 ml) y la solución resultante fue enfriada a 0°C. Agua con hielo fue agregada cuidadosamente. El precipitado resultante fue filtrado retirado y lavado con agua. El agua residual en el precipitado fue removida por coevaporación con 1,4-dioxano.

Producción: 26,0 g

MS-ESI: $[M+H]^+ = 307,0$

TLC: $R_f = 0,5$, gel de sílice, heptano/EtOAc

=

3/2 (v/v).

(c) 5-ciano-4-(3-nitrofenil)-2-metiltio-6-(etoxicarbonilmetiltio)-pirimidina de etilo.

DIPEA (15,7 ml) fue agregado a una solución agitada de 2-mercaptoacetato de etilo (9,3 ml) y 6-cloro-5-ciano-4-(3-nitrofenil)-2-metiltio-pirimidina (ejemplo 1 (b), 26,0 g) en una mezcla de EtOH (250 ml) y DCM (250 ml). Después de 1 h a temperatura ambiente, se agregó HCl acuoso al 0,1 N (500 ml) a la mezcla la cual fue entonces extraída con

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76

DCM(3* 500 ml), secada (MgSO₄) y concentrada bajo presión reducida.

Producción: 28,0 g

MS-ESI: [M+H]⁺ = 390,4

TLC: R_f = 0,5, gel de sílice, heptano/EtOAc

=

3/2 (v/v).

(d). 5-amino-4-(3-nitrofenil)-2-metiltio-tieno [2,3-d]pirimidina-6-carboxilato de etilo

A una mezcla de 5-ciano-4-(3-nitrofenil)-2-metiltio-6-(etoxicarbonilmetiltio)-pirimidina de etilo (ejemplo 1(c), 28.0 g) y DIPEA (30 ml) en una mezcla de tolueno (150 ml) y EtOH (150 ml) fue agitado a temperatura de reflujo (100°C) durante 16 h. La mezcla fue entonces enfriada a temperatura ambiente y concentrada bajo presión reducida. El DIPEA residual fue removido por coevaporación con tolueno.

Producción: 28,0 g

MS-ESI: [M+H]⁺ = 391,2

TLC: R_f = 0,6, gel de sílice, heptano/EtOAc

=

3/2 (v/v).

(e). 5-amino-4-(3-aminofenil)-2-metiltio-tieno [2,3-d]pirimidina-6-carboxilato de etilo

EtOH (400 ml) fue agregado a una mezcla de 5-amino-4-(3-nitrofenil)-2-metiltio-tieno[2,3-d] pirimidina-6-carboxilato de etilo (ejemplo 1(d), 28,0 g) HCL acuoso concentrado (15 ml) y cloruro de estaño (II) (41,0 g) en 1,4-dioxano (400 ml). La mezcla fue agitada a 90°C durante 16 h. La mezcla fue entonces enfriada a temperatura ambiente y concentrada bajo presión reducida. El residuo fue suspendido en EtOAc (1000 ml). NaOH acuoso al 4N fue agregado para obtener un pH entre 10 y 11. La mezcla fue agitada vigorosamente y la capa orgánica fue separada, secada (MgSO₄) y concentrada bajo presión reducida.

Producción: 21,0 g

MS-ESI: [M+H]⁺ = 361,0

TLC: R_f = 0,6, gel de sílice, heptano/EtOAc

=

3/2 (v/v).

(F). Ácido 5-amino-4-(3-aminofenil)-2-metiltio-tieno
[2,3-d]pirimidina-6-carboxílico.

Hidróxido de potasio (32,4 g) fue agregado a una solución de 5-amino-4-(3-aminofenil)-2-metiltio-tieno[2,3-d]pirimidina-6-carboxilato de etilo (ejemplo 1(e), 21,0 g) en una mezcla de 1,4-dioxano(300 ml) y agua (100 ml). Después de 16 h a 90°C, la mezcla fue enfriada a 10°C y ácido cítrico acuoso al 2N (300 ml) fue agregado bajo agitación vigorosa. El precipitado resultante fue filtrado retirado, y lavado con agua (180 ml) y secado en vacío.

Producción: 14,0 g

MS-ESI: $[M+H]^+ = 333,0$

TLC: $R_f = 0,5$, gel de sílice, dcm/MeOH= 9/1
(v/v).

(g). 5-amino-4-(3-aminofenil)-2-metiltio-tieno [2,3-
d]pirimidina-6-carboxamida de tert-butilo

TBTU (16,1 g) fue agregado a una solución de ácido 5-amino-4-(3-aminofenil)-2-metiltio-tieno[2,3-d]pirimidina-6-carboxílico (ejemplo 1(f), 14,0 g), DIPEA (17,4 ml) y

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tert-butilamina (7,3 g) en DCM/DMF (1/1, v/v, 250 ml). Después de 3 h a una temperatura ambiente, la mezcla fue lavada con NaHCO₃ acuoso saturado (3*100 ml), HCl acuoso al 0,1 N (100 l) y agua (100 ml). La capa orgánica fue concentrada bajo presión reducida. El producto crudo fue purificado por cristalización a partir de EtOH absoluto caliente (300 ml).

Producción: 10,5 g

MS-ESI: [M+H]⁺ = 388,2

HPLC: R_t = 30,72 min, Luna C-18(2), 5µm, 250*2,0 mm, detección de UV=210 nm, temperatura de horno = 40°C, flujo = 0,25 ml/min eluyente agua/ACN/MeOH = 90/9,5/0,5 a 0/95-5, tiempo de corrida = 50 min.

(h). 5-amino-2-metiltio-(4)-(3-(2-bromoacetamido)-fenil)-tieno [2,3-d]pirimidina-6-carboxamida de tert-butilo

Bromoacetilcloruro (615 mg) fue agregado a una solución de 5-amino-2-metiltio-4-(3-aminofenil)-tieno[2,3-d]-pirimidina-6-carboxamida de tert-butilo (ejemplo 1(g), 1,08 g) DIPEA (2,43 ml) en DCM seco (20 ml). Después de 3 h a una temperatura ambiente, la mezcla fue diluida con

DCM, lavada con NaHCO_3 acuoso saturado, secada (MgSO_4) y concentrada bajo presión reducida. El producto crudo fue purificado por cromatografía sobre gel de sílice usando heptano/EtOAc = 3/2 (v/v) como eluyente.

Producción: 910 mg

MS-ESI: $[\text{M}+\text{H}]^+ = 510,2$

TLC: $R_f = 0,3$ gel de sílice heptano/EtOAc = 3/2 (v/v).

(i). 5-amino-2-metiltio-(4)-(3-(2-acetidin-1-il)-acetamido)-fenil)-tieno[2,3-d]pirimidina-6-carboxamida de tert-butilo

5-amino-4-(3-(2-bromoacetamido)-fenil)-2-metiltio-tieno [2,3-d]pirimidina-6-carboxamida de tert-butilo (ejemplo 1 (h), 91 mg) fue agregado a una solución de hidrocloruro de acetidina (120 mg) y N,N-diisopropiletilamina (0,25 ml) en DCM (5 ml). Después de 16 h a temperatura ambiente, la mezcla fue lavada con NaHCO_3 , acuoso saturado, secada (MgSO_4) y concentrada bajo presión reducida. El producto crudo fue purificado por HPLC usando una columna Luna C-18 con el siguiente gradiente: TFA acuoso al 0,1% + ACN acuoso al 10%/ACN = 90/10 a 10/90 en 30 min. El compuesto

titulado fue entonces liofilizado a partir de agua con TFA al 0,1%.

Producción: 56 mg (TFA-sal)

MS-ESI: $[M+H]^+ = 485,2$

HPLC: $R_t = 13,45$ min, columna Luna C-18(2), $3\mu\text{m}$, $100 \times 2,0$ mm, detección de UV = 210 nm, temperatura de horno = 40°C , flujo = 0,25 ml/min amortiguador del fosfato como eluyente 50 mM pH 2,1/agua/ACN/ = 10/70/20 a 10/10/80 (v/v), tiempo de corrida = 20 min.

Ejemplo 2

5-amino-2-metiltio-4-(3-(2-(morfolin-4-il)-acetamido)-fenil)-tieno[2,3-d]pirimidina-6-carboxamida de tert-butilo

Morfolina (5,0 ml) fue agregada a una solución de 5-amino-4-(3-(2-bromoacetamido)-fenil)-2-metiltio-tieno[2,3-d]pirimidina-6-carboxamida de tert-butilo (ejemplo 1(h), 1,0 g) en THF (50 ml). Después de 16 h a temperatura ambiente, la mezcla fue concentrada bajo presión reducida. El residuo fue purificado por

cromatografía de columna sobre gel de sílice usando DCM/MeOH = 9/1 como eluyente. El producto crudo fue purificado adicionalmente por HPLC usando una columna Luna C-18 con el siguiente gradiente: TFA acuoso al 0,1%/agua/ACN = 3/97/0 a 3/7/90 en 30 min. El compuesto titulado puro fue liofilizado de una mezcla de TFA acuoso al 0,1% y agua.

Producción: 215 mg (TFA-sal)

MS-ESI: $[M+H]^+ = 515,2$

HPLC: $R_t = 20,62$ min, Luna C-18(2), 5 μ m, 150*2 mm, detección de UV = 210 nm, temperatura de horno = 40°C, flujo = 0,25 ml/min amortiguador del fosfato como eluyente 50 mM pH 2,1/agua/ACN//MeOH = 10/72/17/1 a 10/18/68/4 (v/v), tiempo de corrimiento = 40 min.

Ejemplo 3

5-amino-2-metiltio-4-(3-(2-(tiomorfolin-4-il)-acetamido)-fenil)-tieno[2,3-d]pirimidina-6-carboxamida de tert-butilo

Tiomorfolina (2,16 ml) fue agregado a una solución de 5-amino-2-metiltio-4-(3-(2-bromoacetamido)-fenil)-

tieno[2,3-d]pirimidina-6-carboxamida de tert-butilo (ejemplo 1(h), 1,09 g) en DCM (50 ml). Después de 16 h a temperatura ambiente la mezcla fue diluida con DCM, lavada con NaHCO₃ acuoso saturado, secada, MgSO₄) y concentrado bajo presión reducida. El producto crudo fue purificado por HPLC usando una columna luna C-18 con el siguiente gradiente: TFA acuoso al 0,1%+ ACN acuoso al 10%/ACN = 100/0 a 10/90 en 30 min. El compuesto titulado puro fue liofilizado a partir de agua acidificada con HCL al 1N acuoso.

Producción: 816 mg

MS-ESI: [M+H]⁺ = 531,2

HPLC: R_t = 14,72 min, columna Luna C-18(2), 3 µm, 100*2 mm, detección de UV = 210 nm, + 254 nm temperatura de horno = 40°C, flujo = 0,25 ml/min eluyente de amortiguador del fosfato 50 mM pH 2,1/agua/ACN//MeOH = 10/72/17/1 a 10/18/68/4 (v/v), tiempo de corrida = 20 min.

Ejemplo 4

5-amino-2-metiltio-4-(3-(2-(piperidin-1-il)-acetamido)-
fenil)-tieno[2,3-d]pirimidina-6-carboxamida de tert-
butilo

Piperidina (3,0 ml) fue agregada a una solución de 5-amino-4-(3-(2-bromoacetamido)-fenil)-2-metiltio-tieno[2,3-d]pirimidina-6-carboxamida de tert-butilo (ejemplo 1(h), 1,0 g) en CH₂Cl₂ (50 ml). Después de 16 h a temperatura ambiente, la mezcla fue concentrada bajo presión reducida. El residuo fue purificado por cromatografía de columna sobre gel de sílice usando DCM/MeOH = 9/1 como eluyente. El producto crudo fue purificado adicionalmente por HPLC usando una columna Luna C-18 con el siguiente gradiente: TFA al 0,1% acuoso/ACN = 100/0 a 10/90 en 30 min. El compuesto puro titulado fue liofilizado a partir de una mezcla de TFA acuoso al 0,1% y agua.

Producción: 851 mg (TFA-sal)

MS-ESI: [M+H]⁺ = 513,2

HPLC: R_t = 37,3 min, Luna C-18(2), 5µm, 150*2 mm, detección de UV = 210 nm, temperatura de horno =

40°C, flujo = 0,25 ml/min eluyente amortiguador del fosfato 50 mM pH 2,1/agua/ACN = 20/60/20 a 20/0/80 (v/v), tiempo de corrida = 40 min.

Ejemplo 5

5-amino-2-metiltio-4-(3-(2-(pirrolidin-1-il)-acetamido)-fenil)-tieno[2,3-d]pirimidina-6-carboxamida de tert-butilo

Pirrolidina (3,0 ml) fue agregada a una solución de 5-amino-4-(3-(2-bromoacetamido)-fenil)-2-metiltio-tieno[2,3-d]pirimidina-6-carboxamida de tert-butilo (ejemplo 1(h), 1,0 g) en CH₂Cl₂ (50 ml). Después de 16 h a temperatura ambiente, la mezcla fue concentrada bajo presión reducida. El residuo fue purificado por cromatografía de columna sobre gel de sílice usando DCM/MeOH = 9/1 como eluyente. El producto crudo fue purificado adicionalmente por HPLC usando una columna Luna C-18 con el siguiente gradiente: TFA acuoso al 0,1%/ACN = 100/0 a 10/90 en 30 min. El compuesto puro titulado fue liofilizado a partir de una mezcla de TFA acuoso al 0,1% y agua.

Producción: 2,616 mg (TFA-sal)
MS-ESI: $[M+H]^+ = 499,2$
HPLC: $R_t = 37,5$ min, Luna C-18(2), 5 μ m, 150*2 mm, detección de UV = 210 nm, temperatura de horno = 40°C, flujo = 0,25 ml/min eluyente amortiguador del fosfato 50 mM pH 2,1/agua/ACN = 20/60/20 a 20/0/80 (v/v), tiempo de corrida = 40 min.

Ejemplo 6

5-amino-2-metiltio-4-(3-(2-(piperidin-1-il)-acetamido)-fenil)-tieno[2,3-d]pirimidina-6-carboxamida de tert-butilo

Piperazina (2,5 g) fue agregada a una solución de 5-amino-4-(3-(2-bromoacetamido)-fenil)-2-metiltio-tieno[2,3-d]pirimidina-6-carboxamida de tert-butilo (ejemplo 1(h), 1,0 g) en CH₂Cl₂ (50 ml). Después de 16 h a temperatura ambiente, la mezcla fue concentrada bajo presión reducida. El residuo fue purificado por cromatografía de columna sobre gel de sílice usando DCM/MeOH = 7/1 como eluyente. El producto crudo fue purificado adicionalmente por HPLC usando una columna Luna C-18 con el siguiente gradiente: TFA acuoso al

0,1%/ACN = 100/0 a 10/90 en 30 min. El compuesto puro titulado fue liofilizado a partir de una mezcla de TFA acuoso al 0,1% y agua.

Producción: 766 mg (bis TFA-sal)

MS-ESI: $[M+H]^+ = 514,4$

HPLC: $R_t = 33.7$ min, Luna C-18(2), 5 μ m, 150*2 mm, detección de UV = 210 nm, temperatura de horno = 40°C, flujo = 0,25 ml/min eluyente amortiguador del fosfato 50 mM pH 2,1/agua/ACN = 20/60/20 a 20/0/80 (v/v), tiempo de corrida = 40 min.

Ejemplo 7

Bioactividad *in vitro* de CHO-LH y AHO-FSH

La actividad agonística del LH de los compuestos fueron ensayadas en células de ovario de hámster chino (CHO) transfectadas establemente con el receptor humano y cotransfectadas con un elemento que responde al cAMP (CRE)/promotor que dirige la expresión de un gen reporter de luciferaza de fuego. De la unión del ligando al receptor LH acoplado por GS resultará en un incremento de cAMP. Lo que a su vez inducirá una transactivación

incrementada de la construcción del reportero de luciferaza. La señal luciferaza fue cuantificada usando un contador de luminiscencia. Para los compuestos de ensayo, los valores EC_{50} (concentración del compuesto de ensayo que causa la máxima mitad (50%) de estimulación) fueron calculadas. Para este propósito el programa de software GraphPad PRISM versión 3.0 (GraphPad software Inc., San Diego) fue usado.

De una manera similar la actividad agonística del FSH de los compuestos fue ensayada en células CHO transfectadas con el gen reportero de luciferaza y el receptor humano de FSH. Los resultados se dan en la tabla 1.

Bioactividad in vivo

Para medir la actividad in vivo de los compuestos agonísticos de receptor LH/FSH en la inducción de ovulación en ratones inmaduros se estudio. En este ensayo los ratones hembra inmaduros fueron cebados con FSH urinario (Humegon 12,5 IU/animal). Aproximadamente 48 horas después los animales fueron tratados con un compuesto agnóstico de LH/FSH a un nivel de dosis de 50

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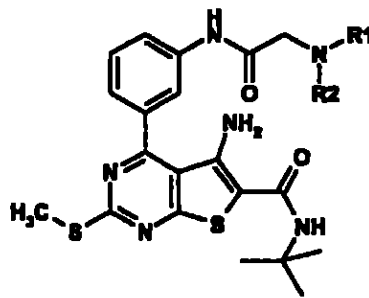
mg/kg. Los animales fueron sacrificados 24 horas después del tratamiento con el agonista LH/FSH y el número de óvulos en el oviducto fue accesado microscópicamente. Los resultados son mostrados en la tabla 1.

Tabla 1

Ejemplo No.	Nombre	EC50 CHO LHR (M)	EC50 CHO FSHR (M)	No. animales ensayados	No. Promedio de óvulos (50 mg/kg p.o)
1	<u>5-amino-2-metiltio-4-(3-(2-(azetidin-1-il)-acetamido)-fenil)-tieno [2,3-d]pirimidina-6-carboxamida de tert-butilo</u>	3,86E-09	4,62E-07	15	1,6
2	<u>5-amino-2-metiltio-4-(3-(2-(morfolin-4-il)-acetamido)-fenil)-tieno[2,3-d]pirimidina-6-carboxamida de tert-butilo</u>	2,24E-09	4,20E-08	10	9,3
3	<u>5-amino-2-metiltio-4-(3-(2-(tiomorfolin-4-il)-acetamido)-fenil)-tieno[2,3-d]pirimidina-6-carboxamida de tert-butilo</u>	8,03E-09	1,04E-06	10	19,8
4	<u>5-amino-2-metiltio-4-(3-(2-(piperidin-1-il)-acetamido)-fenil)-tieno[2,3-d]pirimidina-6-carboxamida de tert-butilo</u>	6,63E-09	2,01E-07		
5	<u>5-amino-2-metiltio-4-(3-(2-(pirrolidin-1-il)-acetamido)-fenil)-tieno[2,3-d]pirimidina-6-carboxamida de tert-butilo</u>	6,68E-09	4,80E-07		
6	<u>5-amino-2-metiltio-4-(3-(2-(piperidin-1-il)-acetamido)-fenil)-tieno[2,3-d]pirimidina-6-carboxamida tert butilo</u>	3,17E-09	1,50E-07		

REIVINDICACIONES

1. Un derivado de tieno[2,3-]pirimidina de acuerdo con la fórmula general 1,



(Fórmula I)

O una sal farmacéuticamente aceptable de la misma, en donde R1 y R2 juntos con el átomo de nitrógeno al cual ellos están unidos forman un anillo que tiene 2 a 6 átomos de carbono, opcionalmente contiene uno o más heteroátomos seleccionados de N, O y/o S.

2. Un compuesto seleccionado del grupo de 5-amino-2-metiltio-4-(3-(2-(azetidín-1-il)-acetamido)-fenil)-tieno[2,3-d]pirimidina-6-carboxamida de tert-butilo; 5-amino-2-metiltio-4-(3-(2-(morfolín-4-il)-acetamido)-fenil)-tieno[2,3-d]pirimidina-6-carboxamida de tert-

butilo; 5-amino-2-metiltio-4-(3-(2-(tiomorfolin-4-il)-acetamido)-fenil)-tieno[2,3-d]pirimidina-6-

carboxamida de tert-butilo;

5-amino-2-metiltio-4-(3-(2-(piperidin-1-il)-acetamido)-fenil)-tieno[2,3-d]pirimidina-6-carboxamida de tert-butilo

5-amino-2-metiltio-4-(3-(2-(pirrolidin-1-il)-acetamido)-fenil)-tieno[2,3-d]pirimidina-6-carboxamida de tert-butilo;

5-amino-2-metiltio-4-(3-(2-(piperazin-1-il)-acetamido)-fenil)-tieno[2,3-d]pirimidina-6-carboxamida de tert-butilo.

3. Un compuesto de acuerdo con las reivindicaciones 1 y 2 para uso en terapia

4. Una composición farmacéutica que comprende un compuesto de tieno[2,3-d]pirimidina de acuerdo con las reivindicaciones 1 o 2 o una sal farmacéuticamente aceptable de los mismos o un solvato de los mismos, en mezcla con un auxiliar farmacéuticamente aceptable.

5. El uso de compuestos de tieno[2,3-d]pirimidina de acuerdo con las reivindicaciones 1 o 2 o una sal o solvato farmacéuticamente aceptable de la misma para la fabricación de un medicamento para el control de la fertilidad.

6. Un método para tratar los desórdenes de fertilidad en pacientes que los necesitan por la administración de una cantidad efectiva de un compuesto de acuerdo con las reivindicaciones 1 y 2.

Expediente No		04020062	No de Folia
Item		No de unidades	
1	CD		
2	DVD		
3	REVISTA		
4	LIBRO		
5	PERIODICO		
6	DISQUETES		
7	SOBRE DE MANILA		
8	SOBRE BLANCO TAMAÑO CARTA	1	
9	SOBRE BLANCO TAMAÑO OFICIO		
10	OTROS:		

Observaciones:

Contiene una figura de arte Final.

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↔

MIT : 800176089-2

SUPERINDUSTRIA Y COMERCIO

Radicacion : 04020062 00000000

Valios: 95

Fecha (AND): 2004-03-04 17:02:35

Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC

Dependencia: 2820 DIVISION DE NUEVAS CREACIONES

RECIBO OFICIAL DE CAJA : 04 - 16,320
FECHA : MARZO 1 DE 2004

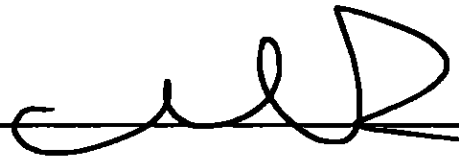
***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	Vr. PAGO
CAVELIER ABOGADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	20338560	01/03/2004	31,169,400.00

***** CONCEPTO *****

CANT. RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1 50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	422,000.00
	TOTAL :	422,000.00

SOM: CUATROCIENTOS VEINTIDOS MIL PESOS

RESPONSABLE : 

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

Cdo 11214-841-014-8

014-8 ARZO NOBEL

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SUPERINTENDENCIA Y COMISIÓN
Indicación: PATENTE DE INVENCION
Fecha (MM): 2014-03-01 17:04:55
Trámite : 011 MC-PATENT 379 FASE MULT 411 PRESENTAL
Asistencia: 2000 DIVISION DE NUEVAS CREACIONES

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

	USUARIO	RADICADOR	
PATENTE DE INVENCION			
MODELO DE UTILIDAD	()	(/)	
- Indicación de que se solicita la concesión de una patente.	()	(/)	
- Datos de identificación del solicitante o de la persona que se presenta la solicitud.	()	(/)	
- Descripción de la invención.	()	(/)	
- Dibujos de ser estos pertinentes.	()	(/)	
- Comprobante de Pago de las tasas establecidas.	()	(/)	
COMPLETA ()			INCOMPLETA ()
DISEÑO INDUSTRIAL ()			
- Indicación de que se solicita el registro de Diseño Industrial	()	()	
- Datos de identificación del solicitante o de la persona que presenta la solicitud.	()	()	
- Representación gráfica y fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño.	()	()	
- Comprobante de pago de las tasas establecidas	()	()	
COMPLETA ()			INCOMPLETA ()
ESQUEMA DE TRAZADO ()			
- Indicación de que solicita el registro de un Esquema de trazado.	()	()	
- Datos de identificación del solicitante o de la persona que presenta La solicitud.	()	()	
- Representación gráfica del esquema de trazado	()	()	
- Comprobante de pago de las tasas establecidas.	()	()	
COMPLETA ()			INCOMPLETA ()

Firma Responsable:

Claudia M. Nena

Fecha:



2020
Bogotá DC

Doctor
EMILIO FERRERO
Apoderado
AKZO NOVEL M.V.

REFERENCIA:	Radicación No.	04 20062
	Solicitud Internacional	PCT/EP2002/09647
	Fecha Inicio fase nacional	04/04/2004
	Trámite	011
	Evento	379
	Actuación	416
	Oficio No.	650
	Folios	001

Teniendo en cuenta que la solicitud de privilegio de patente que se tramita bajo el expediente indicado en la referencia, reúne los requisitos de forma establecidos en la Decisión 486 de la Comisión de la Comunidad Andina, el Tratado de Cooperación en Materia de Patentes (PCT), el Reglamento y la Circular Unica de la Superintendencia de Industria y Comercio, se envía el extracto de la solicitud a la Oficina de Comunicaciones para efecto de su publicación en la Gaceta de Propiedad Industrial.

Cúmplase
Dado en Bogotá DC, 12 MAYO 2004


ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones

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