Industria y Comercio
SUPERINTENDENCIA

PETITORIO

SUPERINTENDENCIA Y COMERCIO
Radicacion : 03107046 00000000 Folios: 141
Fecha (AMD): 2003-12-04 17:11:50
Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

03 107046 00

FORMULARIO UNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL

1 SOLICITUD DE:

☒ Patente de Invención. ☐ Patente de Modelo de Utilidad.
☐ Capítulo I. ☒ Capítulo II.

2 SOLICITANTE (71)

Nombre: **AKZO NOBEL N. V.**
sociedad constituida y existente bajo las leyes de Holanda.
Dirección: Velperweg 76/ 6824 BM
NL-6824 BM Arnhem,
Holanda
Domicilio: Arnhem,
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@camvp.com.
Domicilio: Bogotá, Colombia.

IDENTIFICACIÓN
C.C. ☒ NIT ☐
C.E. ☐ Otro ☐
Cual ____
Número 438.019 T.P 31.929

4 INVENTOR (ES) (72)

1. **GROVE, Simon, James, Anthony**
c/o Organon Laboratories Ltd.
New Edinburg Road,
Newhouse, Lanarkshire
Scotland, ML1 5SH,
Reino Unido
2. **ZHANG, Mingqiang**
260 rue Sherbrooke Est,
Montreal, H2X 1E1,
Canadá
3. **SHAHID, Mamad,**
c/o Organon Laboratories Ltd.
New Edinburg Road,
Newhouse, Lanarkshire
Scotland, ML1 5SH,
Reino Unido

5 PCT (86)

Solicitud Internacional No. PCT/EP02/06185 Fecha: 5 de Junio de 2002
Publicación Internacional No. WO 02/100865 A1 Fecha : 19 de Diciembre de 2002

6 Título (54)

DERIVADOS DE BENZOXAZEPINA Y SU USO COMO ESTIMULADORES DEL RECEPTOR AMPA

7 Clasificación Internacional (51) C07D 498/04, A61K31/553

8 Prioridad SI☒ NO☐

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
EP	11 de Junio de 2001	01202215.8

9 Comprobante de pago No.: 03-85,519 Fecha: Noviembre 24 de 2003

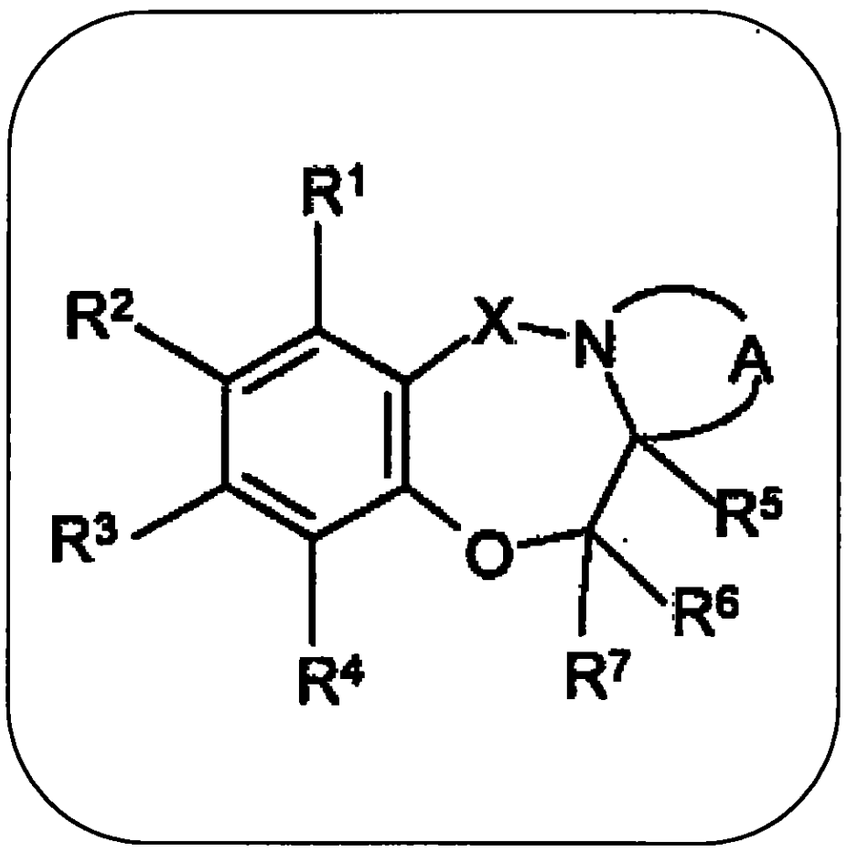
10

Anex s:

- [x] Comprobante de pago de la tasa de presentación de la solicitud por $ 400.000.oo.
- [ ] Comprobante de pago por reivindicación de prioridad.
- [x] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- [x] Poderes, si fuere el caso.
- [ ] Documento de cesión del inventor al solicitante o a su causante.
- [ ] Declaraciones.
- [x] Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- [x] Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- [x] Copia del examen preliminar efectuado por la IPEA.
- [x] 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.
- [x] 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

CAVELIER

ABOGADOS

CAR.

BOGOTÁ

0197301 CO

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.

21

REPRESENTACION Y PODER

REPRESENTATION AND POWER OF ATTORNEY

33234
1538

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 Nº 72-35, Bogotá, Colombia, en obedecimiento 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 primero o segundo suplentes, 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, desistir, 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 Nº 72-35, 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, for which purpose I (we) authorize the said attorneys to represent me (us) before any authorities or persons, with or without jurisdiction, specially those administrative, administrative contentious and judicial, 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/Dado y firmado hoy 6 AUG 1998

F.G.M. Hermans — Director Patents Pharma

E.H. Reerink — Deputy Director Legal Affairs

in/en

AKZO NOBEL N.V.

Signature/Firma

CAVELIER ABOGADOS
WPPODERE-179 (MINUTA Nº 12.1.1.2.5)

TRADUCCION No.: 18.11.98
MARIA ELVIRA MARCELO
Traductora e Intérprete Oficial
Inglés - Español - Inglés
Res. No. 2579 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 *cons* ... on (1) the legal existence of the company ... nts, the Power-of-Attorney, (2) that it is in ac... ...ise of its company purposes, and (3) that the persons who execute the Power of Attorney is autorized to do so. To this effect, please 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.

Mr M. P. M. PHILIPS
NOTARIS te OSS

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)
EXCLUSIVELY BEING FOR LEGALIZATION OF
THE ABOVE/AFOREMENTIONED SIGNATURE(S)
27 AUG 1998
KAMER VAN KOOPHANDEL
OOST-BRABANT
's-HERTOGENBOSCH
J. Schellekens

Gezien voor legalisatie van de handtekening
van de heer/mw J. Schellekens
's-Gravenhage, 09 SEP 1998
De Minister van
Buitenlandse Zaken
voor deze,
Leges f 20,= H.H. van POORTEN

CONSUL NOTARIO SEXTO DEL CIRCULO
DE BOGOTA, HAGO CONSTAR QUE LA
FOTOCOPIA COINCIDE CON EL ORIGINAL
QUE HE TENIDO A LA VISTA
02 DIC 2003
JUAN MANUEL GOTERO MEDINA
NOTARIO

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

C.N.D. 112 19-201-001-3

5

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 constituída 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 Guillelmus 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).

COMO NOTARIO SEXTO DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA.
02 DIC 2003
JUAN MANUEL [illegible] DINA
NOTARIO

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

MINISTERIO DE RELACIONES EXTERIORES

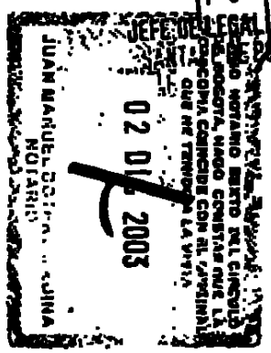
300803

CUYA FIRMA APARECE EN EL DOCUMENTO DESEMPEÑA LAS FUNCIONES INDICADAS

NO SE ASUME RESPONSABILIDAD DEL TEXTO

98 NOV 19 AM 11:56

JEFE DE LEGALIZACIONES SANTAFE DE BOGOTA D.C.



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 OST BRABANT (PAÍSES BAJOS). Visto exclusivamente para la legalización de la(s) firma(s) que antecede(n). Agosto 27NO de 1998 (Firma ilegible) J. Schellenkens.

(Sello en holandés).

COMO NOTARIO SEXTO DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
02 DIC 2003
JUAN MANUEL LOPEZ GUZMAN

(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 No.

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 ficina para su confrontación.

COLO 11214-801-001-3

Id. 6

Nov. 20/98

María E. Martelo
TRADUCCION No. 16.11.98
MARIA ELVIRA MARTELO
Traductora e Interprete Oficial
Inglés - Español - Inglés
Res. No. 2879 Min. Justicia

COMO NOTARIO SEXTO DEL CIRCULO DE SANTAFE DE BOGOTA, HAGO CONSTAR QUE LA(S) ANTERIOR(ES) FIRMA(S) PUESTA(S) POR 23 NOV 1998
IDENTIFICADOS CON C.C. No.(s)
ES(SON) AUTENTICA(S)
SANTAFE DE BOGOTA, 23 NOV. 1998

COMO NOTARIO SEXTO DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
02 DIC 2003
JUAN MANUEL GUTIERREZ MEDINA
NOTARIO

MINISTERIO DE RELACIONES EXTERIORES
198457
CUYA FIRMA APARECE EN EL DOCUMENTO DESEMPEÑA LAS FUNCIONES INDICADAS
98 NOV 24 PM 12:06
JEFE DE LEGALIZACIONES
SANTAFE DE BOGOTA D.C.
NO SE ASUME RESPONSABILIDAD DEL TEXTO

2

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
19 December 2002 (19.12.2002)

PCT

(10) International Publication Number
WO 02/100865 A1

(51) International Patent Classification[7]: C07D 498/04, 515/04, A61K 31/553, 31/554, A61P 25/00

(21) International Application Number: PCT/EP02/06185

(22) International Filing Date: 5 June 2002 (05.06.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
01202215.8 11 June 2001 (11.06.2001) EP

(71) Applicant *(for all designated States except US)*: AKZO NOBEL N.V. [NL/NL]; Velperweg 76, NL-6824 BM Arnhem (NL)

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: GROVE, Simon, James, Anthony [GB/GB]; c/o Organon Laboratories Ltd., New Edinburgh Road, Newhouse, Lanarkshire, Scotland ML1 5SH (GB). ZHANG, Mingqiang [NL/CA]; 260, rue Sherbrooke Est, Montreal H2X 1E1 (CA). SHAHID, Mohammad [GB/GB]; c/o Organon Laboratories Ltd., New Edinburgh Road, Newhouse, Lanarkshire, Scotland ML1 5SH (GB).

(74) Agents: VAN WEZENBEEK, P., M., G., F. et al.; P.O. Box 20, NL-5340 BH Oss (NL).

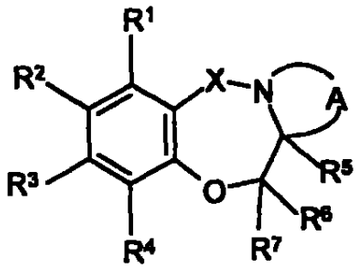
(81) Designated States *(national)*: AE, AG, AL, AU, BA, BB, BG, BR, BZ, CA, CN, CO, CR, CU, CZ, DM, DZ, EC, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KE, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, MZ, NO, NZ, PH, PL, RO, RU, SG, SI, SK, TT, UA, US, UZ, VN, YU, ZA.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

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

(54) Title: BENZOXAZEPINE DERIVATIVES AND THEIR USE AS AMPA RECEPTOR STIMULATORS



(I)

(57) Abstract: The present invention relates to benzoxazepine derivative having the general formula I, wherein X represents CO or SO_2; R^1, R^2, R^3 and R^4 are independently selected from H, (C_{1-4})alkyl, (C_{1-4})alkyloxy, (C_{1-4})alkyloxy(C_{1-4})alkyl, halogen, nitro, cyano, NR^8R^9, NR^8COR^{10}, and $CONR^8R^9$, R^5, R^6 and R^7 are independently H or (C_{1-4})alkyl; R^8 and R^9 are independently H or (C_{1-4})alkyl; or R^8 and R^9 form together with the nitrogen atom to which they are bound a 5- or 6-membered saturated heterocyclic ring, optionally containing a further heteroatom selected from O, S or NR^{11}; R^{10} is (C_{1-4})alkyl; R_{11} is (C_{1-4})alkyl; A represents the residue of a 4-7 membered saturated heterocyclic ring, optionally containing an oxygen atom, the ring being optionally substituted with 1-3 substituents selected from (C_{1-4})alkyl, (C_{1-4})alkyloxy, hydroxy, halogen and oxo; or a pharmaceutically acceptable salt thereof. The invention also relates to pharmaceutical compositions comprising said derivatives, and to the use of these benzoxazepine derivatives in the treatment of neurological diseases and psychiatric disorders which are responsive to enhancement of synaptic responses mediated by AMPA receptors in the central nervous system.

WO 02/100865 A1

BENZOXAZEPINE DERIVATIVES AND THEIR USE AS AMPA RECEPTOR STIMULATORS

The present invention relates to benzoxazepine derivatives, to pharmaceutical compositions comprising the same and to the use of these benzoxazepine derivatives in the teatment of neurological and psychiatric diseases.

In the mammalian central nervous system (CNS), the transmission of nerve pulses is controlled by the interaction between a neurotransmitter, that is released by a sending neuron, and a surface receptor on a receiving neuron, which causes excitation of this receiving neuron. L-Glutamate is the most abundant neurotransmitter in the CNS. It mediates the major excitatory pathway in mammals and is referred to as an excitatory amino acid (EAA). The excitatory amino acids are of great physiological importance, playing a role in a variety of physiological processes, such as learning and memory, the development of synaptic plasticity, motor control, respiration, cardiovascular regulation and sensory perception.

The receptors that respond to glutamate are called excitatory amino acid receptors (EAA receptors). These receptors are classified into two general types: (1) "ionotropic" receptors that are directly coupled to the opening of cation channels in the cell membrane of the neurons, and (2) G-protein linked "metabotropic'" receptors which are coupled to multiple secondary messenger systems that lead to enhanced phosphoinositide hydrolysis, activation of phospholipase D, increases or decreases in c-AMP formation and changes in ion channel function.

The ionotropic receptors can be pharmacologically subdivided into three subtypes, which are defined by the depolarizing actions of the selective agonists N-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA), and kainic acid (KA).

Activation of synaptic AMPA receptors mediates a voltage independent fast (~ 1 ms to peak response) excitatory postsynaptic current (the fast EPSC), whereas activation of synaptic NMDA receptors generates a voltage-dependent, slow (~ 20 ms to peak response) excitatory current. The regional distribution of AMPA receptors in the brain suggests that AMPA receptors mediate synaptic transmission in those areas likely responsible for cognition and memory.

Activation of AMPA receptors by agonists is thought to lead to a conformational change in the receptor causing rapid opening and closing of the ion channel. The extent and duration of channel activation can either be decreased by a drug, which thereby acts as a negative allosteric modulator (e.g. GYKI 52466), or it can be enhanced by a drug, which is then acting as a positive allosteric modulator.

A structural class of AMPA receptor positive modulators derived from aniracetam (e.g. CX 516) are called Ampakines. Positive modulators of the AMPA receptor can thus bind to the glutamate receptor and, upon subsequent binding of a receptor agonist, allow an ion flux through the receptor of increased duration.

Defects in glutamatergic neurotransmission may be associated with many human neurological and psychiatric diseases. The therapeutic potential of positive AMPA receptor modulators in the treatment of neurological and psychiatric diseases has been reviewed by Yamada, K.A. (*Exp. Opin. Invest. Drugs*, 2000, 9, 765-777), by Lees, G.J. (*Drugs*, 2000, 59, 33-78) and by Grove S.J.A. et al. (*Exp. Opin. Ther. Patents*, 2000, 10, 1539-1548).

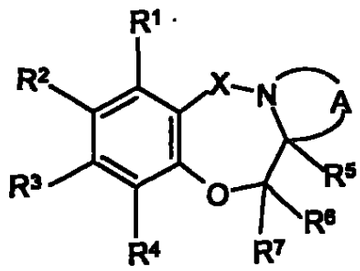
Various classes of compounds that increase AMPA receptor function have been recognized and were recently reviewed by Grove S.J.A. et al. (supra). N-anisoyl-2-pyrrolidinone (aniracetam; Roche) is regarded as an ampakine prototype (Ito, I. et al., *J. Physiol.* 1990, 424, 533-543), shortly thereafter followed by the discovery of certain sulphonamides (exemplified by cyclothiazide; Eli Lilly & Co) as AMPA modulators (Yamada, K.A. and Rothman, S.M., J. *Physiol.*, 1992, 458, 385-407). On the basis of the structure of aniracetam, derivatives thereof having improved potency and stability were developed by Lynch, G.S. and Rogers, G.A. as disclosed in International Patent Application WO 94/02475 (The Regents of the University of California). Additional ampakines in the form of benzoylpiperidines and pyrrolidines were subsequently disclosed in WO 96/38414 (Rogers, G.A. and Nilsson, L.; CORTEX Pharmaceuticals), followed by compounds wherein the amide function was conformationally restricted in a benzoxazine ring system, as disclosed in WO 97/36907 (Rogers G.A. and Lynch. G., The Regents of the University of California; CORTEX Pharmaceuticals), or in an acylbenzoxazine ring system, as disclosed in WO 99/51240 (Rogers G.A. and Johnström, P., The Regents of the University of California). Structurally related benzoxazine derivatives and especially 1,2,4-benzothiadiazine-1,2-dioxides, structurally derivatives of cyclothiazide™, have been disclosed in WO 99/42456 (NEUROSEARCH A/S) as positive modulators of the AMPA receptor.

Positive AMPA receptor modulators have many potential applications in humans. For example, increasing the strength of excitatory synapses could compensate for losses of synapses or receptors associated with ageing and brain disease (Alzheimer's disease, for example). Enhancing AMPA receptor-mediated activity could cause more rapid processing by multisynaptic circuitries found in higher brain regions and thus could produce an increase in perceptual motor and intellectual performance. Ampakines have further been suggested to be potentially useful as memory enhancers, to improve the performance of subjects with sensory-motor problems and

of subjects impaired in cognitive tasks dependent upon brain networks utilizing AMPA receptors, in treating depression, alcoholism and schizophrenia, and in improving the recovery of subjects suffering from trauma.

It has been observed on the other hand that sustained AMPA receptor activation in experimental animals (for example, at high doses of some AMPA modulators, especially those that are potent inhibitors of receptor desensitization), can cause seizures and potentially also other proconvulsant side effects (Yamada, K.A., *Exp. Opin. Invest. Drugs*, 2000, 9, 765-777). In view of the potential of excitotoxicity on AMPA receptor activation (particularly by modulators of the thiadiazide class), there remains a need for the development of modulators having a sufficient therapeutic index.

To this end the present invention provides benzoxazepine derivatives having the general formula I



Formula I

wherein

X represents CO or SO_2;

R^1, R^2, R^3 and R^4 are independently selected from H, (C_{1-4})alkyl, (C_{1-4})alkyloxy, (C_{1-4})alkyloxy(C_{1-4})alkyl, CF_3, halogen, nitro, cyano, NR^8R^9, NR^8COR^{10}, and $CONR^8R^9$;

R^5, R^6 and R^7 are independently H or (C_{1-4})alkyl;

R^8 and R^9 are independently H or (C_{1-4})alkyl; or R^8 and R^9 form together with the nitrogen atom to which they are bound a 5- or 6-membered saturated heterocyclic ring, optionally containing a further heteroatom selected from O, S or NR^{11};

R^{10} is (C_{1-4})alkyl;

R^{11} is (C_{1-4})alkyl

A represents the residue of a 4-7 membered saturated heterocyclic ring, optionally containing an oxygen atom, the ring being optionally substituted with 1-3 substituents selected from (C_{1-4})alkyl, (C_{1-4})alkyloxy, hydroxy, halogen and oxo; or a pharmaceutically acceptable salt thereof;

with the proviso that
the compounds of formula I wherein X is CO; each of R^1-R^7 is H, and A represents $(CH_2)_3$ or $(CH_2)_4$;
the compound of formula I wherein X is CO; R^1 is H; R^2 is methyl; each of R^3-R^7 is H; and A represents $(CH_2)_3$;
the compound of formula I wherein X is CO; R^1 and R^2 are H; R^3 is methyl; each of R^4-R^7 is H; and A represents $(CH_2)_3$;
the compound of formula I wherein X is CO; each of R^1-R^3 is H; R^4 is methyl; each of R^5-R^7 is H; and A represents $(CH_2)_3$; and
the compound of formula I wherein X is CO; each of R^1-R^4 is H; R^5 is methyl; R^6 and R^7 are H; and A represents $(CH_2)_3$; are excluded.

The benzoxazepines for which no protection *per se* is sought relates to a disclosure by Schultz, A.G. et al (*J. Am. Chem Soc.* 1988, 110, 7828-7841) wherein these benzoxazepinone derivatives are described as synthetic intermediates, without any pharmacological activity.

The benzoxazepines of formula I, including the prior art benzoxazepinones described by Schultz et al. (supra), have been found to be positive AMPA receptor modulators, which can be useful in the treatment of neurological and psychiatric diseases where an enhancement of synaptic responses mediated by AMPA receptors is required.

The term (C_{1-4})alkyl as used in the definition of formula I means a branched or unbranched alkyl group having 1-4 carbon atoms, like butyl, isobutyl, tertiary butyl, propyl, isopropyl, ethyl and methyl.
In the term (C_{1-4})alkyloxy, (C_{1-4})alkyl has the meaning as defined above.
The term (C_{1-4})alkyloxy(C_{1-4})alkyl means a (C_{1-4})alkyl group which is substituted with (C_{1-4})alkyloxy, both having the meaning as defined above.
The term halogen means F, Cl, Br or I.
In the definition of formula I R^8 and R^9 may form together with the nitrogen atom to which they are bound a 5- or 6-membered saturated heterocyclic ring, optionally containing a further heteroatom selected from O, S or NR^{11}. Examples of such heterocyclic ring substituents are piperidino, pyrrolidino, morpholino, N-methyl-piperazino, N-ethyl-piperazino and the like.
In the definition of formula I A represents the residue of a 4-7 membered saturated heterocyclic ring, optionally containing an oxygen atom, meaning that A is a bivalent radical containing 2-5 carbon atoms, such as ethylene, 1,3-propylene, 1,4-butylene,

1,5-pentylene, one carbon atom of which may be substituted by oxygen. Examples of 4-7 membered heterocyclic rings formed by residue A together with the nitrogen and carbon atom to which A is bonded are azetidine, pyrrolidine, piperidine, oxazolidine, isoxazolidine, morpholine, and azacycloheptane.

Preferred are the benzoxazepine derivative of formula I , wherein X is CO, which compounds are benzoxazepinones.

More prefered are the benzoxazepine derivatives of formula I, wherein X is CO and wherein R^5, R^6 and R^7 are H; and A represents $(CH_2)_3$.

Especially preferred are the benzoxazepine derivatives of formula I, wherein X is CO, one or more of R^1, R^2, R^3 and R^4 is halogen, preferably fluoro, and wherein R^5, R^6 and R^7 are H; and A represents $(CH_2)_3$.

Particular preferred compounds of the invention are:

(R)-7-Fluoro-2,3,11,11a-tetrahydro-1H,5H-pyrrolo[2,1-c][1,4]benzoxazepine-5-one;

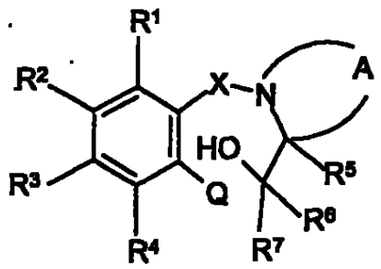
(S)-7-Fluoro-2,3,11,11a-tetrahydro-1H,5H-pyrrolo[2,1-c][1,4]benzoxazepine-5-one

(S)-9-fluoro-2,3,11,11a-tetrahydro-1H,5H-pyrrolo[2,1-c][1,4]benzoxazepine-5-one;

(R)-9-fluoro-2,3,11,11a-tetrahydro-1H,5H-pyrrolo[2,1-c][1,4]benzoxazepine-5-one;

(S)-6-Fluoro-2,3,11,11a-tetrahydro-1H,5H-pyrrolo[2,1-c][1,4]benzoxazepine-5-one.

The benzoxazepine derivatives of the invention may be prepared by methods known in the art of organic chemistry in general. More specifically such compounds can be prepared using procedures outlined by A. G. Schultz *et al* (*J. Am. Chem. Soc.* 1988, 110, 7828-7841) or by modification of those routes.



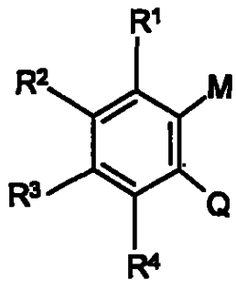
Formula II

Benzoxazepine derivatives of Formula I can for instance be prepared by cyclization of a compound according to formula II, wherein X, A and R^1-R^7 have the meaning as previously defined, any functional group with an acidic hydrogen being protected with a suitable protecting group, and wherein Q represents hydroxy, halogen or (C_{1-4})-alkyloxy, after which any protecting group, when present, is removed. The cyclization reaction for compounds wherein Q is halogen or (C_{1-4})alkyloxy can be carried out in

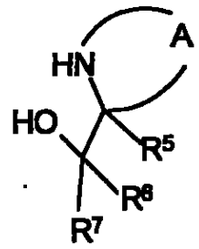
the presence of a base such as sodium hydride or caesium carbonate in a solvent such as dimethylformamide and at a temperature of 0-200 °C, preferably 25-150 °C.

For compounds of formula II wherein Q is a hydroxy group, cyclization can be effected under Mitsunobu conditions (Mitsunobu, O., *Synthesis* 1981, 1) using triphenyl phosphine and a dialkyl azodicarboxylate, such as diisopropyl azodicarboxylate, in a solvent such as tetrahydrofuran.

Suitable protecting groups for functional groups which are to be temporarily protected during syntheses, are known in the art, for example from Wuts, P.G.M. and Greene, T.W.: *Protective Groups in Organic Synthesis*, Third Edition, Wiley, New York, 1999.



Formula III



Formula IV

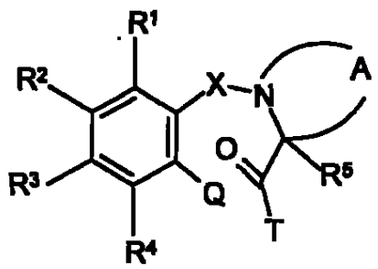
Compounds of formula II can be prepared from the condensation of a compound of formula III, wherein R^1 - R^4 and Q have the meaning as previously defined and M represents a carboxylic acid or an activated derivative thereof, such as a carboxylic ester or a carboxylic acid halide, preferably a chloride or a bromide, or M represents a sulfonyl halide, such as fluoride, chloride or bromide, with a compound of formula IV where R^6 - R^7 and A have the meaning as previously defined.

When M represents a carboxylic acid the condensation reaction, i.e. an acylation, can be effected with the aid of a coupling reagent, such as for example carbonyl diimidazole, dicyclohexylcarbodiimide and the like, in a solvent such as dimethylformamide or dichloromethane.

When M represents a carboxylic acid halide or a sulphonyl halide the condensation with the amine derivative IV can be carried out in the presence of a base, for example triethylamine, in a solvent such as methylene chloride.

When M represents a carboxylic acid ester derivative a direct condensation with the amine derivative of Formula IV can be carried out at an elevated temperature, for example at about 50 to 200 °C. This condensation can also be performed using a Lewis acid, for example aluminium trichloride as described by D. R. Bam *et al* (*Biorg. Med. Chem. Lett.*, 1999, 9, 1329-34).

The preparation of compounds of formula I can be performed using the methods described above by employing a one pot two step procedure, meaning that a compound of formula II, which results from a condensation reaction between a compound of formula III with a compound of formula IV, is not isolated from the reaction mixture but further treated with a base to give compounds of formula I.



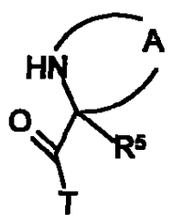
Formula V

Compounds of formula II may also be prepared from the reaction of a compound of formula V where R^1 to R^5, X and A are as defined above and T represents hydrogen, $C_{(1-4)}$alkyl, or alkyloxy, with a $C_{(1-4)}$alkylmetal reagent, for example a Grignard reagent, in a solvent such as tetrahydrofuran.

A compound of formula II where R^6 represents a hydrogen and R^7 represents a $C_{(1-4)}$alkyl group may be prepared from a compound of formula V where T represents a $C_{(1-4)}$alkyl group by a reduction, for example sodium borohydride, in a solvent such as ethanol.

A compound of formula V where X is CO and T represents an alkyloxy group may be prepared from a compound of formula III where M represents a carboxylic acid chloride and an alkanolamine imine derived from an alkyl glycolate as described by D. E. Thurston et al (*J. Chem. Soc., Chem. Commun.*, 1990, 874-876).

A compound of formula V may be prepared by coupling a compound of formula III, wherein R^1-R^4, M and Q have the meaning as previously defined, with a compound of formula VI, wherein R^5, A and T have the meaning as previously defined employing the methods described above for the coupling of compounds of formula III and IV.



Formula VI

Compounds of formula III, IV and VI can be obtained from commercial sources, prepared by literature procedures or modifications of literature procedures known to those persons skilled in the art.

The skilled person will likewise appreciate that various compounds of Formula I can be obtained by appropriate conversion reactions of functional groups corresponding to certain of the substituents R^1-R^4.

For example, the reaction of a (C_{1-4})alkyl alcohol with a compound of formula I, wherein X, A and R^5-R^7 are as defined above, and wherein one of R^1 to R^4 is a leaving group such as, but not limited to, fluoro or chloro in the presence of a base such as sodium hydride gives compounds of formula I where one of R^1 to R^4 is (C_{1-4})alkyloxy.

Compounds of formula I where one or more of R^1 to R^4 are $CONR^8R^9$ may be prepared by conversion of a compound of formula I where one or more of R^1 to R^4 are bromo or iodo into the corresponding carboxylic acid ester using a palladium (II), for example dichlorobis(triphenylphosphine)palladium, catalysed carbonylation reaction as descibed by A. Schoenberg *et al* (*J. Org. Chem.* 1974, 39, 3318). The saponification of the ester to the carboxylic acid, using for example sodium hydroxide in tetrahydrofuran-water, and coupling of the carboxylic acid with an amine of formula NHR^8R^9 using, for example carbonyl diimidazole as coupling agent, gives compounds of formula I where one or more of R^1 to R^4 are $CONR^8R^9$. The carboxylic acid precursor to compounds of formula I where one or more of R^1 to R^4 are $CONR^8R^9$ may be prepared by the oxidation of a compound of formula I where one or more of R^1 to R^4 is a methyl group using an oxidant, for example chromium trioxide. Compounds of formula I where one or more of R^1 to R^4 are $CONR^8R^9$ may be prepared by a palladium (II), such as dichlorobis(triphenylphosphine)palladium, catalysed carbonylation of a compound of formula I where one or more of R^1 to R^4 are bromo or iodo in the presence of an amine of formula NHR^8R^9 using the method descibed by A. Schoenberg and R. F. Heck (*J. Org. Chem.* 1974, 39, 3327).

A compound of formula I where one or more of R^1 to R^4 are CN may be prepared from a compound of formula I where one or more of R^1 to R^4 is $CONH_2$ by dehydration with a dehydrating agent, for example phosphorus oxychloride. A compound of formula I where one or more of R^1 to R^4 are CN may be prepared from a compound of formula I where one or more of R^1 to R^4 is bromo or iodo using a palladium (0) catalysed cyanation reaction as descibed by M. Alterman and A. Hallberg (*J. Org. Chem.* 2000, 65, 7984).

A compound of formula I where one or more of R^1 to R^4 are NR^8R^9 may be prepared from a compound of formula I where one or more of R^1 to R^4 is fluoro or chloro by displacement of the halogen with an amine of formula NHR^8R^9. A compound of formula I where one or more of R^1 to R^4 are NR^8R^9 may be prepared from a compound of formula I where one or more of R^1 to R^4 is chloro, bromo or iodo by a palladium catalysted amination reaction with an amine of formula NHR^8R^9 as described by J. P. Wolfe *et al* (*J. Org. Chem.* 2000, 65, 1158). A compound of formula I where one or more of R^1 to R^4 are NR^8R^9 and one of R^8 or R^9 is hydrogen may be prepared from a compound of formula I where one or more of R^1 to R^4 are NR^8R^9 and both R^8 and R^9 are H by alkylation of the nitrogen atom with an alkylating agent of formula R^8Y where Y is a leaving group such as an alkyl or aryl sulfonate, chloro, bromo or iodo. A compound of formula I where one or more of R^1 to R^4 are NR^8R^9 and both R^8 and R^9 are H may be prepared from a compound of formula I where one or more of R^1 to R^4 are nitro by a reduction for example a palladium catalysed reduction with hydrogen. A compound of formula I where one or more of R^1 to R^4 are NR^8COR^{10} may be prepared from a compound of formula I where one or more of R^1 to R^4 are NHR^8 by treatment with an acylating agent such as a $C_{(1-5)}$acid chloride or anhydride, for example acetic anhydride, in a solvent, for example pyridine.

Treatment of a compound of formula I, where A represents a residue of a 4-7 membered saturated heterocyclic ring substituted with 1-3 hydroxy groups, with a base, such as sodium hydride, in a solvent, such as tetrahydrofuran, with an alkylating agent of formula $C_{(1-4)}$alkylY where Y is defined as above gives a compound of formula I where A represents a residue of a 4-7 membered saturated heterocyclic ring optionally substituted with 1-3 alkyloxy groups.

In a compound of formula I, where A represents a residue of a 4-7 membered saturated heterocyclic ring substituted with 1-3 hydroxy groups, the hydroxy group(s) can be substituted by halogen by treatment with a halogenating reagent such as (diethylamino)sulfur trifluoride (DAST) or with the carbon tetrahalide-triphenylphosphine combination.

Similarly, a compound of formula I where A represents a residue of a 4-7 membered saturated heterocyclic ring optionally substituted with 2 halogen groups at the same carbon atom may be prepared from the corresponsing oxo-derivative by treatment with a halogenating agent, such as DAST.

The oxidation of compound of formula I, where A represents a residue of a 4-7 membered saturated heterocyclic ring optionally substituted with 1-3 hydroxy groups, with an oxidising agent, such as in the Swern oxidation as described by R. E. Ireland and D. W. Norbeck (*J. Org. Chem.* 1985, 50, 2198-2200), gives compounds of formula I where A represents a residue of a 4-7 membered saturated heterocyclic ring optionally substituted with 1-3 oxo groups.

The benzoxazepine derivatives of Formula I and their salts contain at least one centre of chirality, and exist therefore as stereoisomers, including enantiomers, and when appropriate, diastereomers. The present invention includes the aforementioned stereoisomers within its scope and each of the individual R and S enantiomers of the compounds of formula I and their salts, substantially free, i.e. associated with less than 5%, preferably less than 2 %, in particular less than 1 % of the other enantiomer, and mixtures of such enantiomers in any proportions including the racemic mixtures containing substantially equal amounts of the two enantiomers. Methods for asymmetric synthesis whereby the pure stereoisomers are obtained are well known in the art, e.g. synthesis with chiral induction or starting from chiral intermediates, enantioselective enzymatic conversions, separation of stereoisomers or enantiomers using chromatography on chiral media. Such methods are for example described in *Chirality in Industry* (edited by A.N. Collins, G.N. Sheldrake and J. Crosby, 1992; John Wiley). Specific methods applicable for the stereoselective preparation of benzoxazepine derivatives of this invention are those described by Schultz, A.G. et al. (*J. Am. Chem Soc.* 1988, 110, 7828-7841).

Pharmaceutically acceptable salts may be obtained by treating a free base of a compound according to formula I with a mineral acid such as hydrochloric acid, hydrobromic acid, phosphoric acid and sulphuric acid, or an organic acid such as for example ascorbic acid, citric acid, tartaric acid, lactic acid maleic acid, malonic acid, fumaric acid, glycolic acid, succinic acid, propionic acid, acetic acid, methane sulphonic acid, and the like.

The compounds of the invention may exist in unsolvated as well as in solvated forms with pharmaceutically acceptable solvents such as water, ethanol and the like. In general, the solvated forms are considered equivalent to the unsolvated forms for the purpose of the invention.

The present invention further provides pharmaceutical compositions comprising a benzoxazepine derivative having the general formula I, or a pharmaceutically acceptable salt thereof, in admixture with pharmaceutically acceptable auxiliaries, and optionally other therapeutic agents. The term "acceptable" means being compatible with the other ingredients of the composition and not deleterious to the recipients thereof. Compositions include e.g. those suitable for oral, sublingual, subcutaneous, intravenous, intramuscular, local, or rectal administration, and the like, all in unit dosage forms for administration.

For oral administration, the active ingredient may be presented as discrete units, such as tablets, capsules, powders, granulates, solutions, suspensions, and the like.

For parenteral administration, the pharmaceutical composition of the invention may be presented in unit-dose or multi-dose containers, e.g. injection liquids in predetermined amounts, for example in sealed vials and ampoules, and may also be stored in a freeze dried (lyophilized) condition requiring only the addition of sterile liquid carrier, e.g. water, prior to use.

Mixed with such pharmaceutically acceptable auxiliaries, e.g. as described in the standard reference, Gennaro, A.R. et al., Remington: *The Science and Practice of Pharmacy* (20th Edition., Lippincott Williams & Wilkins, 2000, see especially Part 5: Pharmaceutical Manufacturing), the active agent may be compressed into solid dosage units, such as pills, tablets, or be processed into capsules or suppositories. By means of pharmaceutically acceptable liquids the active agent can be applied as a fluid composition, e.g. as an injection preparation, in the form of a solution, suspension, emulsion, or as a spray, e.g. a nasal spray.

For making solid dosage units, the use of conventional additives such as fillers, colorants, polymeric binders and the like is contemplated. In general any pharmaceutically acceptable additive which does not interfere with the function of the active compounds can be used. Suitable carriers with which the active agent of the invention can be administered as solid compositions include lactose, starch, cellulose derivatives and the like, or mixtures thereof, used in suitable amounts. For parenteral administration, aqueous suspensions, isotonic saline solutions and sterile injectable solutions may be used, containing pharmaceutically acceptable dispersing agents and/or wetting agents, such as propylene glycol or butylene glycol.

The invention further includes a pharmaceutical composition, as hereinbefore described, in combination with packaging material suitable for said composition, said packaging material including instructions for the use of the composition for the use as hereinbefore described.

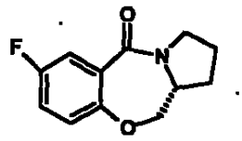
The benzoxazepines of the invention are AMPA receptor stimulators, as can be determined by an increase in steady state current induced by application of glutamate in a conventional whole cell patch clamp method when a benzoxazepine of the invention is present (see Example 30 and Table I). The compounds may be used in the treatment of neurological and psychiatric diseases where an enhancement of synaptic responses mediated by AMPA receptors is required, such as neuro-degenerative disorders, cognitive or memory dysfunction, memory and learning disorders such as can result from ageing, attention disorder, trauma, stroke, epilepsy, Alzheimer's disease, depression, schizophrenia, psychotic disorders, anxiety, sexual dysfunctions, autism, or a disorder or disease resulting from neurotic agents or substance abuse, and alcohol intoxication.

The compounds of the invention may be administered for humans in a dosage of 0.001-50 mg per kg body weight, preferably in a dosage of 0.1-20 mg per kg body weight.

The invention is illustrated by the following Examples.

Example 1.

(R)-7-Fluoro-2,3,11,11a-tetrahydro-1H,5H-pyrrolo[2,1-c][1,4]benzoxazepine-5-one

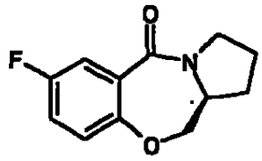


To a solution of 2,5-difluorobenzoic acid (1.0 g; 6.325 mmol) in dimethylformamide (5 ml) was added 1,1'-carbonyldiimidazole (1.07 g; 6.64 mmol) and the solution stirred at room temperature for 1 h, followed by the addition of (R)-(-)-2-pyrrolidinemethanol (0.655 ml; 6.64mmol). The reaction was stirred at room temperature overnight whereupon 60% sodium hydride in mineral oil (0.507g; 12.7 mmol) was carefully added and the mixture was heated to 120 °C for 2h. The reaction was cautiously diluted with water and extracted with ethyl acetate and the organic layer washed with water then dried (Na_2SO_4) and evaporated to give the crude product. Trituration with ether and filtration afforded the title compound (0.29 g).

M.p.: 85-86 °C; EIMS: m/z = 222.2 $[M+H]^+$

Example 2.

(S)-7-Fluoro-2,3,11,11a-tetrahydro-1H,5H-pyrrolo[2,1-c][1,4]benzoxazepine-5-one



The title compound was prepared following the method of Example 1 using (S-(+)-2-pyrrolidinemethanol. M.p.: 80-82 °C; EIMS: m/z = 222.2 $[M+H]^+$

Example 3.

The procedure described under Example 1 was further used to prepare the following compounds:

3A: (R)-9-Fluoro-2,3,11,11a-tetrahydro-1H,5H-pyrrolo[2,1-c][1,4]benzoxazepine-5-one was obtained from 2,3-difluorobenzoic acid and (R)-(-)-2-pyrrolidinemethanol. M.p.: 94-95 °C; EIMS: m/z = 222.1 $[M+H]^+$

3B: (S)-9-Fluoro-2,3,11,11a-tetrahydro-1H,5H-pyrrolo[2,1-c][1,4]benzoxazepine-5-one was obtained from 2,3-difluorobenzoic acid and (S)-(+)-2-pyrrolidinemethanol. M.p.: 92-93 °C; EIMS: m/z = 222.2 $[M+H]^+$

3C: (R)-8-Trifluoromethyl-2,3,11,11a-tetrahydro-1H,5H-pyrrolo[2,1-c][1,4]benzoxazepine-5-one was obtained from 2-fluoro-4-trifluoromethylbenzoic acid and (R)-(-)-2-pyrrolidinemethanol. M.p.: 92-94 °C; EIMS: m/z = 272.2 $[M+H]^+$

3D: (S)-8-Trifluoromethyl-2,3,11,11a-tetrahydro-1H,5H-pyrrolo[2,1-c][1,4]benzoxazepine-5-one was obtained from 2-fluoro-4-trifluoromethylbenzoic acid and (S)-(+)-2-pyrrolidinemethanol. M.p., 95-96 °C; EIMS: m/z = 272.1 $[M+H]^+$

3E:(R)-6-Fluoro-2,3,11,11a-tetrahydro-1H,5H-pyrrolo[2,1-c][1,4]benzoxazepine-5-one was obtained from 2,6-difluorobenzoic acid and (R)-(-)-2-pyrrolidinemethanol, m.p., 146-148 °C; EIMS: m/z = 222.2 $[M+H]^+$

3F:(S)-8-chloro-2,3,11,11a-tetrahydro-1H,5H-pyrrolo[2,1-c][1,4]benzoxazepine-5-one was obtained from 2,4-dichlororobenzoic acid and (S)-(+)-2-pyrrolidinemethanol. M.p., 105-106 °C; EIMS: m/z = 238.2 $[M+H]^+$

3G:(S)-7-chloro-2,3,11,11a-tetrahydro-1H,5H-pyrrolo[2,1-c][1,4]benzoxazepine-5-one was obtained from 2,5-dichlororobenzoic acid and (S)-(+)-2-pyrrolidinemethanol. M.p., 124-126 °C; EIMS: m/z = 238 $[M+H]^+$

3H: (±)-3-Fluoro-6,6a,7,8,9,10-hexahydro-12H-pyrido[2,1-c][1,4]benzoxazepine-12-one was obtained from 2,5-difluorobenzoic acid and 2-piperidinemethanol and isolated as a gum. EIMS: m/z = 236 $[M+H]^+$

3I: (R)-7-Bromo-2,3,11,11a-tetrahydro-1H,5H-pyrrolo[2,1-c][1,4]benzoxazepine-5-one was obtained from 5-bromo-2-chlorobenzoic acid and (R)-(-)-2-pyrrolidinemethanol. M.p. 115-116 °C; EIMS: m/z = 284 $[M+H]^+$

3J:(S)-7-Bromo-2,3,11,11a-tetrahydro-1H,5H-pyrrolo[2,1-c][1,4]benzoxazepine-5-one was obtained from 5-bromo-2-chlorobenzoic acid and (S)-(+)-2-pyrrolidinemethanol. M.p. 115-116 °C; EIMS: m/z = 284 $[M+H]^+$

3K: (R)-7-Nitro-2,3,11,11a-tetrahydro-1H,5H-pyrrolo[2,1-c][1,4]benzoxazepine-5-one was obtained from 5-nitro-2-chlorobenzoic acid and (R)-(-)-2-pyrrolidinemethanol. M.p. 169-170 °C; EIMS: m/z = 249 $[M+H]^+$

3L: (S)-7-Nitro-2,3,11,11a-tetrahydro-1H,5H-pyrrolo[2,1-c][1,4]benzoxazepine-5-one was obtained from 5-nitro-2-chlorobenzoic acid and (S)-(+)-2-pyrrolidinemethanol. M.p. 170-171 °C; EIMS: m/z = 249 $[M+H]^+$

Example 4.

(R)-8-chloro-2,3,11,11a-tetrahydro-1H,5H-pyrrolo[2,1-c][1,4]benzoxazepine-5-one

To a solution of 2,4-dichlorobenzoic acid (1.21 g; 6.325 mmol) in dimethylformamide (5 ml) was added 1,1'-carbonyldiimidazole (1.07 g; 6.64 mmol) and the solution stirred at room temperature for 1 h before the addition of (R)-(-)-2-pyrrolidinemethanol (0.655 ml; 6.64mmol). The reaction was stirred at room temperature overnight then the solvent was removed in vacuo and the residue purified by chromatography on silica (eluting with 5% methanol in dichloromethane) to give the intermediate amide which was not characterised but taken directly onto the next step. To a solution of this amide (0.6 g) in dimethylformamide was added caesium carbonate (1.5 g). The mixture was heated at 150 °C for 2 h, then cooled to room temperature. The reaction was diluted with water and extracted with ethyl acetate. The organic layer was washed with water and dried (Na_2SO_4). Evaporation of the solvent and the solvent removed. The crude product was purified by chromatography on silica (eluting with 5% methanol in dichloromethane). The resulting clear oil crystallised on standing and was triturated with heptane. Filtration afforded the title compound (0.22 g). M.p., 92-94 °C; EIMS: m/z = 238.1 $[M+H]^+$

Example 5.

The procedure described under Example 4 was further used to prepare:

(S)-8-fluoro-2,3,11,11a-tetrahydro-1H,5H-pyrrolo[2,1-c][1,4]benzoxazepine-5-one was obtained from 2,4-difluorobenzoic acid and (S)-(+)-2-pyrrolidinemethanol. M.p., 75-76 °C; EIMS: m/z = 222.2 $[M+H]^+$

16

Example 6.

(±)-3-Trifluoromethyl-6,6a,7,8,9,10-hexahydro-12H-pyrido[2,1-c][1,4]benzoxazepine-12-one

To a solution of 2-fluoro-4-(trifluoromethyl)-benzoic acid (1.31g; 6.325 mmol) in dimethylformamide (5mL) was added 1,1'-carbonyldilmidazole (1.08 g; 6.64 mmol) and the solution stirred at room temperature for 1h, whereupon 2-piperidinemethanol (0.765 g; 6.64 mmol) was added. The reaction was stirred at room temperature overnight then caesium carbonate (4.12 g) was added and the mixture heated to 120 °C for 4 h. Diluted with water the product was extracted into ethyl acetate and washed with water. Organic layer was dried (Na_2SO_4) and evaporation of the solvent *in vacuo* gave the crude product which crystallised from 5% ether in heptane to give the title compound (0.83 g), M.p.: 103-104 °C; EIMS: m/z = 286 $[M+H]^+$

Example 7.

The procedure described under Example 6 was further used to prepare the following compounds:

7A: (±)-4-Fluoro-6,6a,7,8,9,10-hexahydro-12H-pyrido[2,1-c][1,4]benzoxazepine-12-one was obtained from 2,3-difluorobenzoic acid and 2-piperidinemethanol as a gum. EIMS: m/z = 235.8 $[M+H]^+$

7B: (±)-3-Fluoro-6,6a,7,8,9,10-hexahydro-12H-pyrido[2,1-c][1,4]benzoxazepine-12-one was obtained from 2,4-difluorobenzoic acid and 2-piperidinemethanol as a gum, EIMS: m/z = 236.2 $[M+H]^+$

7C: (±)-1-Fluoro-6,6a,7,8,9,10-hexahydro-12H-pyrido[2,1-c][1,4]benzoxazepine-12-one was obtained from 2,6-difluorobenzoic acid and 2-piperidinemethanol. M.p., 133-134 °C; EIMS: m/z = 236.2 $[M+H]^+$

Example 8.

(S)-9-Chloro-2,3,11,11a-tetrahydro-1H,5H-pyrrolo[2,1-c][1,4]benzoxazepine-5-one

To a solution of 3-chloro-2-fluorobenzoyl chloride (2.2 g; 11.4 mmol) in dimethylformamide (5 ml) was added triethylamine (1.7 mL; 11.7 mmol) and (S)-(+)-2-pyrrolidinemethanol (1.13 mL; 11.4 mmol). The mixture was stirred for 1h then caesium carbonate (7.4 g; 22.7 mmol) was added and the reaction heated at 120 °C for 5 hours. The reaction was cooled to room temperature then diluted with water and extracted with ethyl acetate The organics were washed with water and dried (Na_2SO_4) evaporated *in vacuo*. The crude product was purified by chromatography on silica (eluting with 5% methanol in dichloromethane). On removal of solvent the

pure amide crystallised and heptane/ether was added and the title compound collected (0.26 g). M.p., 89-90 °C; EIMS: m/z = 238 $[M+H]^+$

Example 9.

The procedure described under Example 8 was further used to prepare the following compounds:

9A: (S)-6-Fluoro-2,3,11,11a-tetrahydro-1H,5H-pyrrolo[2,1-c][1,4]benzoxazepine-5-one was obtained from 2,6-difluorobenzoyl chloride and (S)-(+)-2-pyrrolidinemethanol. M.p., 149-150 °C; EIMS: m/z = 222.2 $[M+H]^+$

9B: (S)-6-Chloro-2,3,11,11a-tetrahydro-1H,5H-pyrrolo[2,1-c][1,4]benzoxazepine-5-one was obtained from 2,6-dichlorobenzoyl chloride and (S)-(+)-2-pyrrolidinemethanol. M.p., 113-115 °C; EIMS: m/z = 238.2 $[M+H]^+$

9C: (S)-6-Trifluoromethyl-2,3,11,11a-tetrahydro-1H,5H-pyrrolo[2,1-c][1,4]benzoxazepine-5-one was obtained from 2-fluoro-6-trifluoromethylbenzoyl chloride and (S)-(+)-2-pyrrolidinemethanol. M.p., 175-176 °C; EIMS: m/z = 272.2 $[M+H]^+$

9D: (S)-7-Trifluoromethyl-2,3,11,11a-tetrahydro-1H,5H-pyrrolo[2,1-c][1,4]benzoxazepine-5-one was obtained from 2-fluoro-5-trifluoromethylbenzoyl chloride and (S)-(+)-2-pyrrolidinemethanol. M.p., 120-121 °C; EIMS: m/z = 272.4 $[M+H]^+$

9E: (S)-8,9-Difluoromethyl-2,3,11,11a-tetrahydro-1H,5H-pyrrolo[2,1-c][1,4]benzoxazepine-5-one was obtained from 2,3,4-trifluorobenzoic acid and (S)-(+)-2-pyrrolidinemethanol. M.p., 142-143 °C; EIMS: m/z = 272.2 $[M+H]^+$

Example 10

(S)-2,3,11,11a-tetrahydro-1H,5H-pyrrolo[2,1-c][5,1,4]benzthiaoxazepine-5-dioxide

To a solution of 2-fluorobenzenesulfonyl chloride (1.7 g; 8.8 mmol) in methylenechloride (50 mL) was added triethylamine (1.8 mL; 12.9 mmol) and (S)-(+)-2-pyrrolidinemethanol (1.07 mL; 10.7 mmol). The mixture was stirred for 7 hours then diluted with methylene chloride and washed with 2M hydrochloric acid and the organic layer was dried (Na_2SO_4). Evaporation of the solvent gave the crude sulfonamide which was taken up in 100 ml of dimethylformamide and 1.0 g of 60% sodium hydride in mineral oil was added. The mixture was stirred overnight and then evaporation of the solvent and aqueous work up followed by purification by chromatography on silica (eluting with ethyl acetate) afforded the title compound as a gum; ^1H NMR (400MHz; $CDCl_3$) δ 1.93-2.00 (m, 3H), 2.20-2.27 (m, 1H), 3.05-3.09 (m, 1H), 3.58-3.63 (m, 1H), 3.94 (dd, 1H), 4.18-4.21 (m, 1H), 4.76 (dd, 1H), 7.09 (dd, 1H), 7.19 (dd, 1H), 7.43 (dd, 1H), 7.84 (dd, 1H); EIMS: m/z = 240 $[M+H]^+$

Example 11

(S)-8-Methoxy-2,3,11,11a-tetrahydro-1H,5H-pyrrolo[2,1-c][1,4]benzoxazepine-5-one

A solution of (S)-8-fluoro-2,3,11,11a-tetrahydro-1H,5H-pyrrolo[2,1-c][1,4]-benzoxazepine-5-one (0.5 g; 2.14 mmol), prepared as described in Example 5A, and sodium methoxide (0.244 g; 4.52 mmol) in dimethylformamide (2 mL) was heated at 110 °C for 3h. The reaction was diluted with water and extracted with ethyl acetate and the organic layer washed with water then dried (Na_2SO_4) and evaporated *in vacuo*. The crude product was purified by chromatography on silica (eluting with 5% methanol in dichloromethane) to give the title product, m.p. 104-106 °C; EIMS: m/z = 234 $[M+H]^+$

Example 12

(S)-8-(1-Pyrrolo)-2,3,11,11a-tetrahydro-1H,5H-pyrrolo[2,1-c][1,4]benzoxazepine-5-one hydrochloride salt

A solution of (S)-8-fluoro-2,3,11,11a-tetrahydro-1H,5H-pyrrolo[2,1-c][1,4]-benzoxazepine-5-one (0.5 g; 2.14 mmol), prepared as described in Example 5A, in pyrrolidine (1 ml) was heated under reflux for 4h. Reaction was diluted with water and extracted with ethyl acetate and washed with water then dried (Na_2SO_4) and evaporated *in vacuo*. The crude product was chromatographed on silica (eluting with 5% methanol in dichloromethane) and then crystallised from 5% dichloromethane in ether. The pure product was dissolved in dichloromethane and converted to the hydrochloride salt with HCl in ether then ether was added to precipitate the title product (0.18 g). M.p.,169-176 °C; EIMS: m/z = 273 $[M+H]^+$

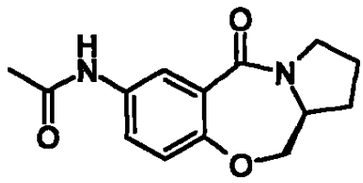
Example 13

(S)-7-amino-2,3,11,11a-tetrahydro-1H,5H-pyrrolo[2,1-c][1,4]benzoxazepine-5-one

A solution of (S)-7-nitro-2,3,11,11a-tetrahydro-1H,5H-pyrrolo[2,1-c][1,4]benz-oxazepine-5-one (7.4 g), prepared as described in Example 3L, in ethanol (100 ml) and methanol (50 ml) was hydrogenated over 10% palladium on activated carbon under 2 bar hydrogen, until the uptake of hydrogen ceased. The mixture was filtered to remove the catalyst and evaporated to dryness *in vacuo*. The crude product was passed through a short silica column (eluting with 10% methanol in dichloromethane) to give the title product (6.1 g). EIMS: m/z = 219 $[M+H]^+$

Example 14

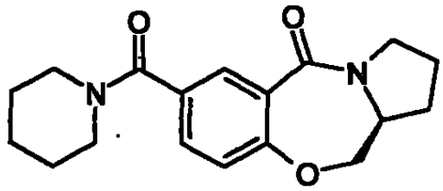
(S)-N-(2,3,11,11a-tetrahydro-5-oxo-1H,5H-pyrrolo[2,1-a][1,4]benzoxazepin-7-yl)-acetamide



A solution of the material from Example 13 (2.29 mmol) and acetic anhydride (0.237 ml; 2.5 mmol) in pyridine (5 ml) was allowed to stand at room temperature overnight. Reaction diluted with water and extracted into ethyl acetate, washed with water then dried (Na_2SO_4) and evaporated *in vacuo*. The crude product was crystallised from 5% dichloromethane in heptane to give the title product (140 mg). M.p. 185-187 °C; EIMS: m/z = 261 $[M+H]^+$

Example 15

(S)-7-(piperidinocarbonyl)-2,3,11,11a-tetrahydro-1H,5H-pyrrolo[2,1-c][1,4]benzoxazepine-5-one



A solution of (S)-7-Bromo-2,3,11,11a-tetrahydro-1H,5H-pyrrolo[2,1-c][1,4]-benzoxazepine-5-one (0.56 g; 2 mmoles), prepared as described in Example 3J, together with piperidine (2 ml) and dichlorobis(triphenylphosphine)palladium (II) (63 mg) was heated at 110 °C under an atmosphere of carbon monoxide overnight. Evaporation, partioning of residue between water and dichloromethane and evaporation of the organic layer followed by chromatographic purification eluting with 5% methanol in dichloromethane and crystallisation from ethyl acetate/petroleum ether gave 400 mg of the title product. M.p. 140-140.5 °C; EIMS: m/z = 315 $[M+H]^+$

Example 16

The procedure described under Example 15 was further used to prepare the following compounds:

16A: (S)-7-(morpholinocarbonyl)-2,3,11,11a-tetrahydro-1H,5H-pyrrolo[2,1-c][1,4]-benzoxazepine-5-one

The title compound was obtained using morpholine in place of piperidine as the reactant. M.p. 158-161 °C; EIMS: m/z = 317 $[M+H]^+$

16B: (S)-7-(N-ethylpiperazinocarbonyl)-2,3,11,11a-tetrahydro-1H,5H-pyrrolo[2,1-c]-[1,4]benzoxazepine-5-one hydrochloride salt

The title compound was obtained using N-ethylpiperazine in place of piperidine as the reactant and isolated as the hydrochloride salt by crystallisation from acetone-ether. M.p. >200 °C; EIMS: m/z = 344 $[M+H]^+$

Example 17.

17A: (S)-7-(aminocarbonyl)-2,3,11,11a-tetrahydro-1H,5H-pyrrolo[2,1-c][1,4]benzoxazepine-5-one

To a solution of (S)-7-Bromo-2,3,11,11a-tetrahydro-1H,5H-pyrrolo[2,1-c][1,4]-benzoxazepine-5-one (5 g; 17.76 mmol), prepared as described in Example 3J, in dimethylsulfoxide (80 ml) was added palladium acetate (225 mg; 1 mmol), 1,3-bis-(diphenylphosphino)propane (413 mg; 1mmol), triethylamine (5 ml; 36 mmol) and methanol (4 ml). After stirring under argon until all solids had dissolved the reaction vessel was purged several times with carbon monoxide and placed under an atmosphere of carbon monoxide (balloon). The mixture was then heated to 100 °C and stirred overnight. Further portions of palladium acetate (0.50 mmol) and 1,3-bis-(diphenylphosphino)propane (0.50 mmol) were added and the mixture stirred at 100 °C for a further 6h. After cooling water (200 ml) was added and the aqueous solution was extracted with three 75 ml portions of ethyl acetate. The combined extracts were dried (Na_2SO_4) and solvent evaporated under reduced pressure. The resulting brown oil was purified by column chromatography eluting with ethyl acetate. Further purification by recrystallisation from diethyl ether gave methyl (S)-2,3,11,11a-tetra-hydro-1H,5H-pyrrolo[2,1-c][1,4]benzoxazepine-5-one-7-carboxylate (3.13 g) as a white crystalline solid.

To a solution of this methyl ester (2.54 g; 9.73mmol) in methanol (40 ml) was added 4M sodium hydroxide (12 ml). The mixture was heated under reflux for 1.5 h and then allowed to cool to room temperature. The methanol was evaporated under reduced pressure and the aqueous solution was acidified with aqueous 1M HCl. The resulting precipitate was filtered off and dried under vacuum to give (S)-2,3,11,11a-tetrahydro-1H,5H-pyrrolo[2,1-c][1,4]benzoxazepine-5-one-7-carboxylic acid (2.39 g) as an off white solid.

A solution of the above carboxylic acid derivative (2.38 g; 9.64mmol) in thionyl chloride (10 ml) was heated under reflux for 1.5h. The excess thionyl chloride was

evaporated under reduced pressure to giving (S)-2,3,11,11a-tetrahydro-1H,5H-pyrrolo[2,1-c][1,4]benzoxazepine-5-one-7-carboxylic acid chloride (2.56 g) as a pale yellow solid.

A solution of the acid chloride (1.02 g; 3.85 mmol) in dichloromethane (8 ml) was added to a stirred solution of 38% aqueous ammonia (5 ml). After stirring for 20 min the dichloromethane was removed under reduced pressure. The white precipitate that had formed was collected by filtration and dried under vacuum to give the title compound (886 mg) as a white solid. M.p. 287-290°C; EIMS: m/z = 247.4 $[M+H]^+$

17B: (R)-7-(Aminocarbonyl)-2,3,11,11a-tetrahydro-1H,5H-pyrrolo[2,1-c][1,4]benzoxazepine-5-one was obtained following the method of Example 18A starting from the material prepared in Example 3I. M.p. 290-295°C EIMS: m/z = 247.2 $[M+H]^+$

Example 18.

(R)-7-(Methylaminocarbonyl)-2,3,11,11a-tetrahydro-1H,5H-pyrrolo[2,1-c][1,4]benzoxazepine-5-one

A solution of (R)-2,3,11,11a-tetrahydro-1H,5H-pyrrolo[2,1-c][1,4]benzoxazepine-5-one-7-carboxylic acid chloride (0.330 g; 1.24 mmol), prepared as described in Example 17A, starting from the material described in Example 3I, in dichloromethane (3 ml) was added dropwise to a stirred 10% solution of methylamine in tetrahydrofuran. The mixture was stirred at room temperature for a further 1h and then evaporated to dryness under reduced pressure. The residue was taken up in dichloromethane (20 mL) and washed with 0.5M HCl (2 x 20 mL). The dichloromethane layer was dried ($MgSO_4$) and solvent evaporated under reduced pressure. Recrystallisation of the crude product from ethylacetate /diethylether gave the title compound (0.262 g) as a white solid. M.p. 186-189 °C; EIMS: m/z = 261.0 $[M+H]^+$

Example 19.

(R)-7-Cyano-2,3,11,11a-tetrahydro-1H,5H-pyrrolo[2,1-c][1,4]benzoxazepine-5-one

To a stirred solution of the material prepared in Example 17B (1.57 mmol) in dimethylformamide (5 ml) under a nitrogen atmosphere was added phosphorous oxychloride (731 µl; 7.85 mmol). The mixture was stirred for 0.5 h at 80 °C. After cooling water (20 ml) was added and upon stirring a white precipitate formed. The precipitate was collected by filtration, washed with water and dried under vacuum to give the title compound (261 mg). M.p. 164-165 °C; EIMS: m/z = 229.0 $[M+H]^+$

Example 20.

20A: (11*R*, 11a*S*)-11-Ethyl-2,3,11,11a-tetrahydro-1H,5H-pyrrolo[2,1-c][1,4]benzoxazepine-5-one

To 2-chlorobenzoic acid (10 g; 63.9 mmol) in dimethylformamide (100 ml) under nitrogen was added carbonyldiimidazole (10.9 g; 67.1 mmol) and the solution stirred for 1h at room temperature. (*S*)-(+)-2-Pyrrolidinemethanol (7.56 ml, 76.6 mmol) was added and the mixture stirred at 40 °C for 18h. The solvent was removed under reduced pressure and the crude product purified by chromatography on silica (eluting with 50% to 75% ethyl acetate in heptane) to afford (*S*)-1-(2-chlorobenzoyl)-2-pyrrolidinemethanol (10.2 g), which was used directly in the next step.

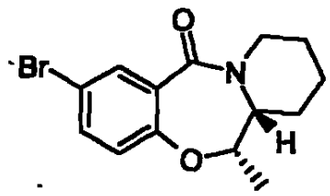
Tetrahydrofuran (24 ml) was cooled to -60°C with stirring and oxalyl chloride (1.15 ml, 13.2 mmol) was added. Dimethylsulfoxide (0.98 ml, 13.8 mmol) was then added dropwise. The mixture was stirred for 20 minutes, then a solution of 1-(2-chlorobenzoyl)-2-pyrrolidinemethanol (3.0 g, 12.5 mmol) in tetrahydrofuran (24 ml) was added dropwise over 15 minutes. After a further 15 minutes, the mixture was treated with triethylamine (7.0 ml, 50.1 mmol). The mixture was warmed briefly to 0°C before re-cooling to -78°C. Ethylmagnesium bromide (3.0 M in diethyl ether; 16.7 ml, 50.1 mmol) was added dropwise to the vigorously stirred reaction mixture. The reaction was warmed to -40°C for 1h, re-cooled to -78°C and then cautiously treated with ethanol (5 ml) followed by saturated ammonium chloride solution. The mixture was allowed to warm to room temperature, and then extracted with ethyl acetate (*ca.* 150 ml). The organic layer was dried (Na_2SO_4) and concentrated to afford crude (2*S*, α*RS*)-1-(2-chlorobenzoyl)-α-ethyl-2-pyrrolidinemethanol as a mixture of diastereoisomers. The crude product was dissolved in dimethylformamide (100 ml) under nitrogen. Sodium hydride (60% dispersion in mineral oil; 1.0 g, 25.0 mmol) was added, portionwise. The reaction was stirred at room temperature for 30 minutes and then heated to 120°C for 5 h, after which the temperature was reduced to 80°C for a further 16 h. The reaction was allowed to cool to room temperature and then quenched with methanol (10 ml) and stirred for 10 minutes. The solvents were removed under reduced pressure. The residue was taken up in water (50 ml) and extracted with dichloromethane (2 x 50 ml) to afford the product as a crude mixture of diastereoisomers (ratio approx. 30:70). Flash chromatography on silica (eluting with 0% to 80% ethyl acetate in heptane) afforded the title compound (80 mg) as a colourless oil; ^{1}H NMR (400MHz; $CDCl_3$) δ 4.24 (1H, dt, *J* 10.5, 2.3 Hz, 11-H); EIMS: m/z = 232 $[M+H]^+$

20B: (11*S*, 11a*S*)-11-Ethyl-2,3,11,11a-tetrahydro-1H,5H-pyrrolo[2,1-c][1,4]benzoxazepine-5-one

Further elution of the mixture prepared in Example 20A gave the title compound, which was recrystallised from ethyl acetate/heptane to afford a white crystaline product. M.p. 118-119 °C; ^{1}H NMR (400MHz; $CDCl_3$) δ 4.04 (1H, td, *J* 9.8, 2.5Hz, 11-H); EIMS: m/z = 232 $[M+H]^+$.

Example 21.

21A: (6*RS*,6a*SR*)-2-Bromo-6-methyl-6,6a,7,8,9,10-hexahydro-12H-pyrido[2,1-c][1,4]-benzoxazepine-12-one

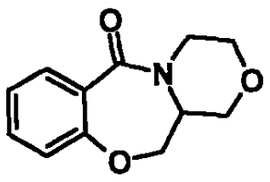


The title compound was prepared following the method of Example 20A, using 5-bromo-2-chlorobenzoic acid, (*RS*)-2-piperidinemethanol and methylmagnesium bromide. M. p. 105-106°C; EIMS: m/z = 312 $[M+H]^+$

21B: (6*RS*,6a*RS*)-2-Bromo-6-methyl-6,6a,7,8,9,10-hexahydro-12H-pyrido[2,1-c][1,4]-benzoxazepine-12-one

This enantiomer was obtained on further elution of the mixture obtained from Example 21A gave the title product, M. p. 105-107 °C; EIMS: m/z = 312 $[M+H]^+$.

Example 22. 6,6a-Dihydro-12*H*-Morpholino[3,4-c][1,4]benzoxazepin-12-one



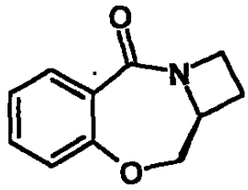
A solution of morpholine-3-carboxylic acid (4.035 g; 30.8 mmol) in ethanol (250 ml) was saturated with gaseous HCl, then stirred for a week. The solvent was evaporated and the residue taken up in water and made basic (pH ~10) with sodium hydrogen carbonate and sodium carbonate. The mixture was then extracted with dichloromethane (7x), the combined extracts dried (Na_2SO_4) and the solvent evaporated to give ethyl morpholine-3-carboxylate (746 mg). EIMS: m/z = 160.4 $[M+H]^+$. This ester derivative and lithium aluminium hydride (1 M in THF, 9.4 ml, 9.4 mmol) were carefully combined under a nitrogen atmosphere and following addition

were heated to reflux. After 5 h the reaction was cooled to room temperature and carefully quenched using dropwise water addition with ice cooling, then filtered and washed with dichloromethane. The solvent was evaporated to give 3-(hydroxymethyl)morpholine (409 mg). EIMS: m/z = 118.2 $(M+H)^+$.

To a solution of 3-(hydroxymethyl)morpholine (345 mg; 2.95 mmol) in dichloromethane (10 mL) was carefully added 2-fluorobenzoyl chloride (0.35 mL; 2.95 mmol) and triethylamine (0.62 mL; 4.42 mmol) and the reaction stirred for 0.5h. The product was combined with 4 N NaOH (10 mL) to hydrolyse any ester and the organic layer extracted (dichloromethane, 3 x). The combined organic layers were dried (Na_2SO_4) and the solvent evaporated to give an oil, which was purified by flash column chromatography on silica (gradient elution, dichloromethane-methanol 1:0 to 9:1) to give 4-(2-fluorobenzoyl)-3-(hydroxymethyl)morpholine (165 mg; 0.69 mmol), EIMS: m/z = 240.2 $(M+H)^+$.This product and caesium carbonate (0.544 g) were heated to 120 °C in dimethylformamide (10 ml) solution under nitrogen for 4 hours. The solvent was evaporated, and the residue taken up in water and extracted with dichloromethane (3 x). The combined dichloromethane extracts were dried (Na_2SO_4) and the solvent evaporated to give a crude solid which was purified by flash column chromatography on silica, eluting with ether to give the title compound (77 mg).
M.p. 105-107 °C; EIMS: m/z = 220.2 $(M+H)^+$.

4Example 23.

(S)-1,2,10,10a-Tetrahydroazetidinyl[2,1-c][1,4]benzoxazepin-4-one



N-Methylmorpholine (1.35 ml, 12 mmol) was added to a stirred solution of (S)-azetidine-2-carboxylic acid (1.08 g; 10 mmol) and di-*tert*-butyl-dicarbonate (3.03 g; 14 mmol) in 1,4-dioxane: water (1:1, 30 ml) cooled to 0 °C. The system was allowed to stir for 18h with the temperature being allowed to rise slowly to room temperature. Saturated sodium bicarbonate solution (15 ml), cooled to 5°C was added and the system was washed with ethyl acetate (3 x 75ml). The aqueous phase was then acidified to pH 3 by the addition of potassium hydrogen sulfate. The aqueous phase was then extracted with ethyl acetate (3 x 100ml), these organic layers were combined, dried ($MgSO_4$), filtered and solvent removed *in vacuo* to give the product (S)-N-*tert*-butoxycarbonyl-azetidine-2-carboxylic acid (2.15 g) as a viscous oil. EIMS:

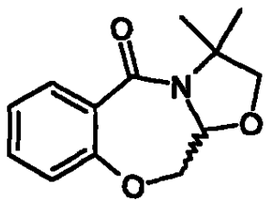
m/z = 201 $(M+H)^+$. Borane-THF complex (1M sol, 35 ml, 35 mmol) was added slowly to a stirred solution of the above carboxylic acid in dry tetrahydrofuran cooled to <5°C under nitrogen. The reaction was allowed to stir for 18h, with the temperature being allowed to slowly rise to room temperature. 10% Aqueous potassium hydrogen sulfate (10 ml) was then added dropwise. Volatile components were evaporated *in vacuo* and the remaining slurry was extracted with ethyl acetate (3 x 75 ml). The combined organic phase was dried ($MgSO_4$), filtered and solvent removed *in vacuo* to give the product (S)-N-*tert*-Butoxycarbonyl-2-hydroxymethylazetidine as a viscous oil (1.48 g, 74%), *m/z* $[M+Na]^+$ 210.

Trifluoroacetic acid (5ml) in dichloromethane (5ml) was added to a stirred solution of (S)-N-*tert*-butoxycarbonyl-azetidin-2-ylmethanol (1.17 g, 6.25 mmol) in dichloromethane (8 ml) cooled to ~5°C under nitrogen. The reaction was stirred for 18h with the temperature being allowed to rise slowly to RT. Solvent and excess acid were removed *in vacuo* to give the product (S)-2-hydroxymethylazetidine, trifluoroacetate salt as a viscous oil (1.26 g). Triethylamine (0.61 ml, 4.38 mmol) was added slowly to a solution of 0.19 g of (S)-2-hydroxymethylazetidine trifluoroacetate salt (0.94 mmol) and 2-fluorobenzoyl chloride (0.16 ml, 1.30 mmol) in dichloromethane (8 ml) cooled to ~5 °C and under nitrogen. The reaction was stirred for 18 h with the temperature being allowed to rise slowly to room temperature. Water (15 ml) and dichloromethane (20 ml) were added and the layers were separated. The aqueous layer was washed with more dichloromethane (20 ml) and the combined organic layers were dried ($MgSO_4$), filtered and solvent removed *in vacuo*. The crude residue was purified by chromatography on silica gel using ethyl acetate:petroleum ether (40/60) 1:1, as eluant giving (S)-N-(2-fluorobenzoyl)-2-hydroxymethylazetidine (0.15 g; 0.72 mmol) as a viscous oil, EIMS: m/z = 192 $[(M+H)-H_2O]^+$

The crude product was dissolved in dry dimethylformamide (5 ml) and anhydrous caesium carbonate (0.28 g, 0.87 mmol) was added to the stirred solution. The temperature was increased to 110 °C and the reaction was stirred for 18 h. After cooling, dimethylformamide was removed *in vacuo*. The residue was then taken up in water (20 ml) and extracted with dichloromethane (2 x 25 ml). The combined organic layers were dried ($MgSO_4$), filtered and solvent removed *in vacuo*. The crude residue was purified by chromatography on silica gel using ethyl acetate:petroleum ether (40/60) 4:1, as eluant, giving the title product (50 mg) as a white solid. M. p. 148-149 °C; ^1H NMR (400MHz; $CDCl_3$) δ 2.11-2.17 (m, 2H), 2.54-2.58 (m, 2H), 4.07-4.16 (m, 1H), 4.19 (dd, 1H), 4.28-4.32 (m, 1H), 4.45 (dd, 1H), 4.65-4.79 (m, 1H), 6.97 (d, 1H), 7.05 (dd, 1H), 7.38 (ddd, 1H), 8.11 (dd, 1H); EIMS: m/z = 190 $[M+H]^+$

Example 24.

2,11,11a-Trihydro-3,3-dimethyloxazolidinyl[2,1-c][1,4]-benzoxazepin-5-one



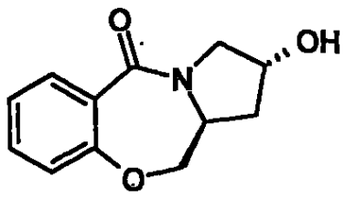
2-Amino-2-methyl-1-propanol (9.54 ml, 0.10 mol) was added to a stirred solution of ethyl glyoxylate (50% soln. in toluene, 21 ml, 0.10 mol) in dichloromethane (100 ml) in the presence of 4Å molecular sieves. The reaction was stirred under nitrogen for 16 h whereupon the system was filtered through Dicalite® and washed with more dichloromethane. Evaporation of the solvent *in vacuo* gave (1,1-dimethyl-2-hydroxy-ethylimino)-acetic acid ethyl ester (17.0 g) as an oil (EIMS: m/z = 174 $[M+H]^+$). 2-Fluorobenzoyl chloride (0.60 ml, 5.00 mmol) and then pyridine (0.96 ml, 12.0 mmol) were added to a stirred solution of the above described ethyl ester (0.87 g, 5.00 mmol) in dichloromethane (8 ml) cooled to ~5 °C and under nitrogen. After 1.5 h water (20ml) was added, the layers separated and the aqueous phase washed with more dichloromethane (30 ml). The combined organic phase was then washed with 1N hydrochloric acid (25 ml) before being dried ($MgSO_4$), filtered and solvent removed *in vacuo*. The crude residue was purified by chromatography on silica using dichloromethane as eluant, to give 3-(2-fluorobenzoyl)-4,4-dimethyl-oxazolidine-2-carboxylic acid ethyl ester (0.64 g) as an oil, EIMS: m/z = 296 $[M+H]^+$

Excess lithium borohydride was added to a stirred solution of 3-(2-fluorobenzoyl)-4,4-dimethyl-oxazolidine-2-carboxylic acid ethyl ester (0.47 g; 1.58 mmol) in dry diethyl-ether (5 ml). Dry toluene (8 ml) was then added and the system was heated to 100 °C. After 2 h, the diethylether was distilled off as described by H. C. Brown *et al* (*J. Org. Chem.*, 1982, 47(24), 4702). After 6 h heating, the system was allowed to cool and then the toluene was removed *in vacuo*. Aqueous acid (5N HCl:H_2O= 1:3 v/v; 8 ml) was then added and the system was stirred at room temperature for 1h. Potassium carbonate was then added to saturate the aqueous solution which was then extracted with diethylether (2 x 25 ml). The combined organic layers were dried ($MgSO_4$), filtered and solvent removed *in vacuo*. The crude residue was purified by chromatography on silica gel using dichloromethane:methanol 19:1 as eluant. This gave (±)-3-(2-fluorobenzoyl)-4,4-dimethyl-2-hydroxymethyl-oxazolidine (0.30 g) as a viscous oil, EIMS: m/z = 254 $[M+H]^+$

Caesium carbonate (0.60 g, 1.85 mmol) was added to a stirred solution of the above described oxazolidine (0.31 g, 1.23 mmol) in dry dimethylformamide (5 ml). The reaction mixture was heated to 130 °C and stirred for 18 h. After cooling, dimethylformamide was removed in vacuo, water (10 ml) was added to the residue which was then extracted with dichloromethane (3 x 30 ml). The combined organic layers were dried ($MgSO_4$), filtered and solvent removed *in vacuo*. The crude residue was purified by chromatography on silica gel using petroleum ether (40/60): ethyl acetate 4:1 (v/v) as eluent to give the title product (0.23 g) as a white waxy solid.
M.p. 65.5-66.5°C °C; ^1H NMR (400MHz; $CDCl_3$) δ 1.59 (s, 3H), 1.64 (s, 3H), 3.76 (d, 1H), 3.90 (d, 1H), 4.02 (dd, 1H), 4.54 (dd, 1H), 5.18 (dd, 1H), 6.96 (d, 1H), 7.08 (ddd, 1H), 7.36 (ddd, 1H), 8.06 (dd, 1H); EIMS: m/z = 234 $[M+H]^+$

Example 25.

(2R,11aS)-2-Hydroxy-2,3,11,11a-tetrahydro-1H,5H-pyrrolo[2,1-c][1,4]benzoxazepine-5-one

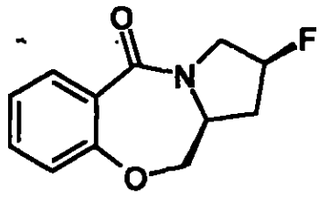


To a stirred slurry of (3R, 5,S)-3-hydroxy-5-hydroxymethylpyrrolidine (3.67 g; 23.9 mmol) (M. W. Reed *et al*, *J.Med.Chem.*, 1995, 38, 4587-4596) and diisopropyl-ethylamine (9.3 ml; 52.58mmol) in anhydrous dichloromethane (30 ml) under a nitrogen atmosphere was added dropwise 2-fluorobenzoylchloride (3.8 g; 23.9mmol) while maintaining the temperature below 25 °C by means of an ice bath.The mixture was allowed to stir at room temperature overnight and then evaporated under reduced pressure.The resultant mixture was taken up in ethyl acetate (100 ml), washed with water (2 x 50ml) and dried (Na_2SO_4). The solvent was evaporated under reduced pressure and the residue purified by flash chromatography eluenting with 1:9 methanol in dichloromethane to give the intermediate amide (5.2 g) as a colour-less oil, EIMS: m/z = 240.2 $[M+H]^+$. This amide (21.76 mmol) was suspended in di-methylformamide (70 ml) and caesium carbonate (8.5 g; 26.1 mmol) was added and the suspension was stirred under a nitrogen atmosphere at 110 °C for 16 hrs. The mixture was then evaporated to dryness under reduced pressure and the residue was then taken up in 100 ml of ethyl acetate. The solution was washed with water (80 ml) and the water layer then re-extracted with further ethyl acetate (100 ml). The combined organic extracts were then washed with brine (2 x 50 ml) and dried

(Na_2SO_4). The solvent was evaporated under reduced pressure and the residue further purified by flash chromatography eluting with 7% MeOH in methylene chloride to give the title compound (2.2 g) as a white crystalline solid. ^1H NMR (400MHz; $CDCl_3$) δ 2.75 to 2.87 (m, 1H), 2.02 (d, 1H), 2.2 to 2.30 (m, 1H), 3.857 (d, 2H), 4.03 to 4.07 (m, 1H), 4.24 (q, 1H), 4.48 (d, 1H), 4.55 (s, 1H), 6.97 (d, 1H), 7.06 (t, 1H), 7.36 (t, 1H), 8.109 (t, 1H); EIMS: m/z = 220.2 $[M+H]^+$

Example 26.

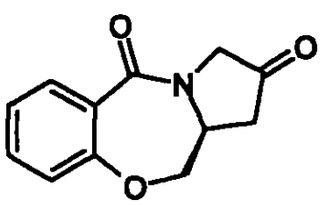
(2S,11aS)-2-Fluoro-2,3,11,11a-tetrahydro-1H,5H-pyrrolo[2,1-c][1,4]benzoxazepine-5-one



A solution of the material prepared in Example 25 (200 mg; 0.91 mmol) in dry ethyl acetate (10 ml) was cooled to –50 °C and (diethylamino)sulphur trifluoride (191 mg; 1.19 mmol) was added dropwise. The resultant solution was stirred at –50°C for 1 h and then allowed to slowly warm to room temperature over a period of 3 h. The mixture was then poured onto a saturated aqueous $NaHCO_3$ solution (50 ml) and further ethyl acetate (50 ml) added. After thorough mixing the organic layer was separated, washed sequentially with water (50 ml) and brine (50 ml), and dried (Na_2SO_4). The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography to give the title compound as a pale yellow crystalline solid (60 mg). ^1H NMR ($CDCl_3$) δ 2.13 to 2.48 (m, 2H), 3.79 (qd, 1H), 4.09 (t, 1H), 4.25 to 4.35 (m, 2H), 4.43-4.49 (m, 1H), 5.333 (d, 1H), 7.04 (d, 1H), 7.15 (t, 1H), 7.41 (dd, 1H), 7.88 (dd, 1H); EIMS: m/z = 222.2 $[M+H]^+$

Example 27.

(S)-2-Oxo-2,3,11,11a-tetrahydro-1H,5H-pyrrolo[2,1-c][1,4]benzoxazepine-5-one

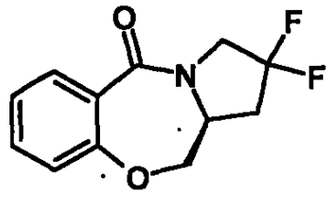


To a stirred solution of oxalyl chloride (0.52 ml; 5.94 mmol) in dry dichloromethane (15 ml) cooled to -78°C was added a solution of dimethylsulfoxide (0.81 ml, 11.42 mmol) in dry dichloromethane (2 ml). Stirring was continued for 10

minutes followed by dropwise addition of a solution of the material (1 g) prepared in Example 25 (4.57 mmol) in dry dichloromethane (10 ml). The mixture was stirred for a further 15 minutes then triethylamine (3.8 ml; 27.3 mmol) was added. After stirring at –78 °C for a further 10 minutes the mixture was allowed to warm to 0 °C before ethyl acetate (50 ml) and water (50 ml) were added. After thorough mixing the organic layer was separated, washed sequentially with 1M HCl (50 ml) and brine (50 ml), and dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue purified by flash chromatography eluting with 3% MeOH in methylene chloride to give the title product (220 mg) which was recrystallised once from the minimum of hot ethyl acetate, ^1H NMR ($CDCl_3$) δ 2.41 (dd, 1H), 2.87-2.93 (m, 1H), 4.15-4.33 (m, 3H), 4.45-4.49 (m, 2H), 7.06 (d, 1H), 7.18 (t, 1H), 7.44 (dd, 1H), 8.03 (dd, 1H); EIMS: m/z = 218.4 $[M+H]^+$

Example 28.

(2S)-2,2-Difluoro-2,3,11,11a-tetrahydro-1H,5H-pyrrolo[2,1-c][1,4]benzoxazepine-5-one



To a solution of the material prepared in Example 27 in methylene chloride (5 ml) was added diethylaminosulfur trifluoride ((245 mg; 1.5 mmol). The reaction was stirred for 2 days at room temperature then quenched by the addition of ice and washed with water (10 ml) and saturated sodium bicarbonate solution (10 ml) and dried (Na_2SO_4). Evaporation and purification by flash chromatography eluting with 19:1 methylene chloride-ether afforded the title compound as an off-white solid (63 mg). M.p. 116-5-119.5 °C; EIMS: m/z = 240.0 $[M+H]^+$

Example 29: Patch Clamp Whole Cell Electrophysiology.

A: Cell culture.

Hippocampal neurons were prepared from embryonic or 1-3 day old Sprague-Dawley rats which were decapitated and the heads immediately placed in ice cold HBS (HEPES Buffered Solution: 130 mM NaCl, 5.4 mM KCl, 10 mM HEPES, 1.0 mM $MgCl_2$, 1.8 $CaCl_2$, 25 mM glucose, adjusted to pH 7.4). The whole brain was excised and placed on pre-sterilised filter paper, soaked in HBS and the cerebellum was removed. The brain was chopped and an enzyme solution (0.5 mg/ml protease X and

0.5 mg/ml protease in HBS) was added and subsequently left for 40 minutes at room temperature to digest before trituration. Cells were resuspended and then counted to give a final concentration of $1.5x10^6$ per ml. Cells were aliquoted onto poly-D-lysine- and Matrigel®-treated coverslips and left to incubate at 37 °C for 1-2 hours. When incubation was complete, 1 ml of growth medium was added to each well containing a coverslip and the cells were returned to the incubator. After 3-5 days the mitotic inhibitor cytosine arabinoside (5 μM) was added and the cells returned to the incubator until required.

B: Patch clamp recording.

The whole cell configuration of the patch clamp technique (Hamill et al., *Pflügers Arch.* 1981, 39, 85-100) was used to measure glutamate-evoked currents from postnatal hippocampal neurons maintained in culture for 4-7 days. A glass coverslip containing the culture was transferred to the recording chamber (Warner Instrument Corp., Hamden, CT) mounted on the stage of an inverted microscope (Nikon, Kingston, UK). The recording chamber contained 1-2 ml extracellular solution (145 mM NaCl, 5.4 mM KCl, 10 mM HEPES, 0.8 mM $MgCl_2$, 1.8 $CaCl_2$, 10 mM glucose and 30 mM sucrose, adjusted to pH 7.4 with 1M NaOH) and was constantly perfused at a rate of 1 ml/min. Recordings were performed at room temperature (20-22 °C) using an Axopatch 200B amplifier (Axon Instruments Ltd., Foster City, CA). Data acquisition and analysis was performed using Signal software (Cambridge electronic Design Ltd., Cambridge, UK). Pipettes were manufactured from GC120F-10 glass (Harvard Apparatus, Edenbridge UK) using a model P-87 electrode puller (Sutter Instruments Co., Novarto, CA). The patch electrodes had typical resistances of between 3-5 MΩ when filled with intracellular solution (140 mM potassium gluconate, 20 mM HEPES, 1.1 mM EGTA, 5 mM phosphocreatine, 3 mM ATP, 0.3 mM GTP, 0.1 mM $CaCl_2$, 5 mM $MgCl_2$, adjusted to pH 7.4 with 1M KOH).

Cells were voltage clamped at a holding potential of –60 mV and glutamate (0.5 mM) was applied using a 12 channel semi-rapid drug application device (DAD-12. Digitimer Ltd., Welwyn Garden City, UK). The agonist glutamate was applied for 1 s every 30 s. The response did not "run-down" over time using the whole-cell configuration. Between applications saline flowed to clear any dead volume in the system. For each application steady-state currents were plotted from the difference in baseline and steady state current and averaged over 300 ms.

Two solutions of the compound in extracellular solution were made up, one with glutamate and one without. The protocol was: 10 second application of compound, 1 second application of compound + glutamate and then 10 second wash with saline,

then a 10 second delay. When the compound was not soluble, 0.5% DMSO was used as a co-solvent. Results are presented in Table I as the percentage increase in steady state current at 10 μM concentration of the compound of the invention in extracellular solution.

Example 30.

Differential Reinforcement of Low Rates of Responding, 72 seconds (DRL72)

Rats are pretrained in a standard operant chamber to perform a DRL72 procedure according to Andrews et al (Andrews JS, Jansen JHM, Linders S, Princen A, Drinkenburg WHIM, Coenders CJH and Vossen JHM (1994). Effects of imipramine and mirtazapine on operant performance in rats. Drug Development Research, 32:58-66). The test session lasts for 60 minutes with no limit to the number of trials. Each trial begins with the stimulus light on above the active lever. A response on the lever only results in delivery of a pellet if 72 seconds has elapsed. A response on the lever before 72 seconds has elapsed resets the timer and is not rewarded. The number of pellets earned and the number of lever presses is recorded and used to calculate an efficiency score. Test compounds are administered via the intraperitoneal route 30 minutes before the start of the test session. Antidepressants increase the number of pellets earned and decrease the number of lever presses (Andrews et al, 1994).

(S)-9-Fluoro-2,3,11,11a-tetrahydro-1H,5H-pyrrolo[2,1-c][1,4]benzoxazepine-5-one (Example 3B) exhibited an antidepressant like profile.

Example 31.

Inhibition of amphetamine-induced hyperlocomotion.

Mice were injected sc with drug or vehicle control. 30 Minutes later mice were injected sc with 1.5 mg/kg d-amphetamine sulphate or saline and immediately placed in infra red locomotor boxes where locomotor activity (long duration beam breaks of two adjacent beams) and stereotypic behaviour (repetitive short-duration beam breaks) were measured for a period of 60 minutes. The experiment was analysed using a 3-Way ANOVA with experimental session, infra red locomotor boxes and treatment as factors, and in the case of treatment, significant effects were followed up using a Tukey (HSD) test. (S)-2,3,11,11a-tetrahydro-1H,5H-pyrrolo[2,1-c][1,4]-benzoxazepine-5-one and (R)-9-fluoro-2,3,11,11a-tetrahydro-1H,5H-pyrrolo[2,1-c]-[1,4]benzoxazepine-5-one (Example 3A) showed antipsychotic like activity as shown by inhibited amphetamine induced hyperlocomotion.

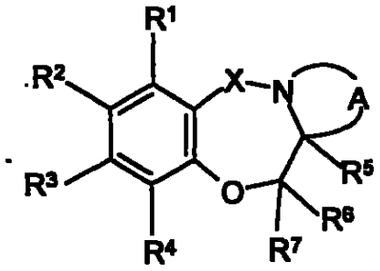
TABLE I

Compound	% Increase in steady state current at 10 μM
(S)-2,3,11,11a-tetrahydro-1H,5H-pyrrolo[2,1-c][1,4]benzoxazepine-5-one*	53
(R)-2,3,11,11a-tetrahydro-1H,5H-pyrrolo[2,1-c][1,4]benzoxazepine-5-one	24
(R)-7-Fluoro-2,3,11,11a-tetrahydro-1H,5H-pyrrolo[2,1-c][1,4]-benzoxazepine-5-one (Example 1)	17
(S)-7-Fluoro-2,3,11,11a-tetrahydro-1H,5H-pyrrolo[2,1-c][1,4]-benzoxazepine-5-one (Example 2)	19
(R)-9-Fluoro-2,3,11,11a-tetrahydro-1H,5H-pyrrolo[2,1-c][1,4]-benzoxazepine-5-one (Example 3A)	23
(S)-9-Fluoro-2,3,11,11a-tetrahydro-1H,5H-pyrrolo[2,1-c][1,4]-benzoxazepine-5-one (Example 3B)	20
(S)-2,3,11,11a-tetrahydro-1H,5H-pyrrolo[2,1-c][5,1,4]benzthiaoxazepine-5-dioxide (Example 10)	7
(S)-8-Methoxy-2,3,11,11a-tetrahydro-1H,5H-pyrrolo-[2,1-c][1,4]benzoxazepine-5-one (Example 11)	21
(S)-N-(2,3,11,11a-tetrahydro-5-oxo-1H,5H-pyrrolo[2,1-a][1,4]benzoxazepin-7-yl)acetamide (Example 14)	49
(S)-7-(morpholinocarbonyl)-2,3,11,11a-tetrahydro-1H,5H-pyrrolo[2,1-c][1,4]benzoxazepine-5-one (Example 16A)	24
(R)-7-(aminocarbonyl)-2,3,11,11a-tetrahydro-1H,5H-pyrrolo[2,1-c][1,4]benzoxazepine-5-one (Example 17A)	8
(11*R*, 11a*S*)-11-Ethyl-2,3,11,11a-tetrahydro-1H,5H-pyrrolo[2,1-c][1,4]benz-oxazepine-5-one (Example 20A)	31
(11*S*, 11a*S*)-11-Ethyl-2,3,11,11a-tetrahydro-1H,5H-pyrrolo[2,1-c][1,4]benzoxazepine-5-one (Example 20B)	28
6,6a-Dihydro-12*H*-Morpholino[3,4-c][1,4]benzoxazepin-12-one (Example 22)	31
(S)-1,2,10,10a-Tetrahydroazetidinyl[2,1-c][1,4]benzoxazepin-4-one (Example 23)	16
2,11,11a-Trihydro-3,3-dimethyloxazolidinyl[2,1-c][1,4]-benzoxazepin-5-one (Example 24)	18
(2R,11aS)-2-Hydroxy-2,3,11,11a-tetrahydro-1H,5H-pyrrolo[2,1-c][1,4]benzoxazepine-5-one (Example 25)	31
(2S,11aS)-2-Fluoro-2,3,11,11a-tetrahydro-1H,5H-pyrrolo[2,1-c][1,4]benzoxazepine-5-one (Example 26)	24
(2S,11aS)-2,2-Difluoro-2,3,11,11a-tetrahydro-1H,5H-pyrrolo[2,1-c][1,4]benzoxazepine-5-one (Example 28)	9

*: this compound was prepared as described by Schultz, A.G. et al (*J. Am. Chem Soc.* 1988, 110, 7828-7841) who use the naming: (3aS)-2,3,3a,4-tetrahydro-1H,1H-pyrrolo[2,1-c]benzoxazepin-10-one.

Claims.

1. A benzoxazepine derivative having the general formula I



Formula I

wherein

X represents CO or SO_2;

R^1, R^2, R^3 and R^4 are independently selected from H, (C_{1-4})alkyl, (C_{1-4})alkyloxy, (C_{1-4})alkyloxy(C_{1-4})alkyl, CF_3, halogen, nitro, cyano, NR^8R^9, NR^8COR^{10}, and $CONR^8R^9$;

R^5, R^6 and R^7 are independently H or (C_{1-4})alkyl;

R^8 and R^9 are independently H or (C_{1-4})alkyl; or R^8 and R^9 form together with the nitrogen atom to which they are bound a 5- or 6-membered saturated heterocyclic ring, optionally containing a further heteroatom selected from O, S or NR^{11};

R^{10} is (C_{1-4})alkyl;

R^{11} is (C_{1-4})alkyl

A represents the residue of a 4-7 membered saturated heterocyclic ring, optionally containing an oxygen atom, the ring being optionally substituted with 1-3 substituents selected from (C_{1-4})alkyl, (C_{1-4})alkyloxy, hydroxy, halogen and oxo; or a pharmaceutically acceptable salt thereof;

with the proviso that

the compounds of formula I wherein X is CO; each of R^1-R^7 is H, and A represents $(CH_2)_3$ or $(CH_2)_4$;

the compound of formula I wherein X is CO; R^1 is H; R^2 is methyl; each of R^3-R^7 is H; and A represents $(CH_2)_3$;

the compound of formula I wherein X is CO; R^1 and R^2 are H; R^3 is methyl; each of R^4-R^7 is H; and A represents $(CH_2)_3$;

the compound of formula I wherein X is CO; each of R^1-R^3 is H; R^4 is methyl; each of R^5-R^7 is H; and A represents $(CH_2)_3$; and

the compound of formula I wherein X is CO; each of R^1-R^4 is H; R^5 is methyl; R^6 and R^7 are H; and A represents $(CH_2)_3$; are excluded.

A represents the residue of a 4-7 membered saturated heterocyclic ring, optionally containing an oxygen atom, the ring being optionally substituted with 1-3 substituents selected from (C_{1-4})alkyl, (C_{1-4})alkyloxy, hydroxy, halogen and oxo; for use in therapy.

7. A pharmaceutical composition comprising a benzoxazepine derivatives of formula I as defined in claim 4, together with a pharmaceutically acceptable carrier therefore.

8. Use of a benzoxazepine derivative of formula I as defined in claim 4, in the preparation of a medicament for the treatment of neurological diseases and psychiatric disorders which are responsive to enhancement of synaptic responses mediated by AMPA receptors in the central nervous system.

9. The use according to claim 6, wherein the disease or disorder is selected from neurodegenerative disorders, cognitive or memory dysfunction, memory and learning disorders such as can result from ageing, attention disorder, trauma, stroke, epilepsy, Alzheimer's disease, depression, schizophrenia, psychotic disorders, anxiety, sexual dysfunctions, autism, or a disorder or disease resulting from neurotic agents or substance abuse, and alcohol intoxication.

10. A method of treating a neurological disease or a psychiatric disorder, which disease or disorder is responsive to enhancement of synaptic responses mediated by AMPA receptors in the central nervous system, which method comprises administering of a therapeutically effective amount of a benzoxazepine derivative according to Formula I of claim 1.

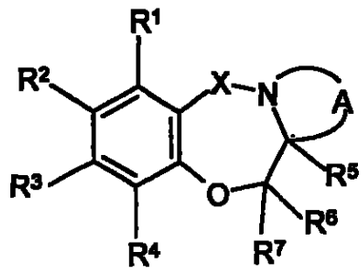
2. The benzoxazepine derivative of claim 1, wherein X is CO.

3. The benzoxazepine derivative of claim 2, wherein R^6, R^6 and R^7 are H; and A represents $(CH_2)_3$.

4. The benzoxazepine derivative of claim 3, wherein one or more of R^1, R^2, R^3 and R^4 is halogen.

5. A benzoxazepine derivative which is selected from:
(R)-7-Fluoro-2,3,11,11a-tetrahydro-1H,5H-pyrrolo[2,1-c][1,4]benzoxazepine-5-one;
(S)-7-Fluoro-2,3,11,11a-tetrahydro-1H,5H-pyrrolo[2,1-c][1,4]benzoxazepine-5-one
(S)-9-fluoro-2,3,11,11a-tetrahydro-1H,5H-pyrrolo[2,1-c][1,4]benzoxazepine-5-one;
(R)-9-fluoro-2,3,11,11a-tetrahydro-1H,5H-pyrrolo[2,1-c][1,4]benzoxazepine-5-one; and
(S)-6-Fluoro-2,3,11,11a-tetrahydro-1H,5H-pyrrolo[2,1-c][1,4]benzoxazepine-5-one.

6. A benzoxazepine derivative having the general formula I



Formula I

wherein

X represents CO or SO_2;

R^1, R^2, R^3 and R^4 are independently selected from H, (C_{1-4})alkyl, (C_{1-4})alkyloxy, (C_{1-4})alkyloxy(C_{1-4})alkyl, CF_3, halogen, nitro, cyano, NR^8R^9, NR^8COR^{10}, and $CONR^8R^9$;

R^5, R^6 and R^7 are independently H or (C_{1-4})alkyl;

R^8 and R^9 are independently H or (C_{1-4})alkyl; or R^8 and R^9 form together with the nitrogen atom to which they are bound a 5- or 6-membered saturated heterocyclic ring, optionally containing a further heteroatom selected from O, S or NR^{11};

R^{10} is (C_{1-4})alkyl;

R^{11} is (C_{1-4})alkyl;

These documents represent confirmation of an application filed by facsimile.

Date of facsimile: 29/10/2002

Name of authority with which facsimile was filed: EPO Munchen

competent International Preliminary Examining Authority or, if two or more Authorities are competent, with the or two-letter code of that Authority may be indicated by the applicant on the line below:

EP

PCT

CHAPTER II

DEMAND

under Article 31 of the Patent Cooperation Treaty:

ned 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 *2001.650 WO*
International application No. *PCT/EP02/06185*	International filing date *(day/month/year)* *05-06-2002*	(Earliest) Priority date *(day/month/year)* *11-06-2001*

Title of invention

" BENZOXAZEPINE DERIVATIVES AND THEIR USE AS AMPA RECEPTOR STIMULATORS"

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

GROVE, Simon, James, Anthony
c/o Organon Laboratories Ltd.
New Edinburgh Road
Newhouse, Lanarkshire
Scotland, ML1 5SH United Kingdom

State *(i.e. country)* of nationality:	State *(i.e. country)* of residence:
GB	*GB*

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.)*

ZHANG, Mingqiang
260 rue Sherbrooke Est
Montreal, H2X 1E1
Canada

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

[X] Further applicants are indicated on a continuation sheet.

9The 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: 27

IPEA/ _____

PCT

CHAPTER II

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 *2001.650 WO*
International application No. *PCT/EP02/06185*	International filing date *(day/month/year)* *05-06-2002*	(Earliest) Priority date *(day/month/year)* *11-06-2001*

Title of invention

" BENZOXAZEPINE DERIVATIVES AND THEIR USE AS AMPA RECEPTOR STIMULATORS"

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.)*

GROVE, Simon, James, Anthony
c/o Organon Laboratories Ltd.
New Edinburgh Road
Newhouse, Lanarkshire
Scotland, ML1 5SH United Kingdom

State *(i.e. country)* of nationality: *GB*	State *(i.e. country)* of residence: *GB*

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.)*

ZHANG, Mingqiang
260 rue Sherbrooke Est
Montreal, H2X 1E1
Canada

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

[X] Further applicants are indicated on a continuation sheet.

28

Sheet No.... 2...

International application No.
PCT/EP02/06185

Continuation of Box No. II **APPLICANT(S)**

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

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.)*

SHAHID, Mohammad
c/o Organon Laboratories Ltd.
New Edinburgh Road
Newhouse, Lanarkshire
Scotland, ML1 5SH United Kingdom

State *(i.e. country)* of nationality:	State *(i.e. country)* of residence:
GB	GB

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.)*

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

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.)*

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

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.)*

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

☐ Further applicants are indicated on another continuation sheet.

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

The following person is [X] agent [ ] common representative

and [X] 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) [X] 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 preliminaryexamination 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

[X] 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.)

Sheet No. 4

International application No.
PCT/EP02/06185

Box No. VI CHECK LIST

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

			For International Preliminary Examining Authority use only: received	not received
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	☐	☐

The demand is also 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. ☒ fee calculation sheet
5. ☐ other *(specify)*:

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:

31

PCT

CHAPTER II

FEE CALCULATION SHEET

Annex to the Demand for international preliminary examination

International application No. *PCT/EP02/06185*	For International Preliminary Examining Authority use only Date stamp of the IPEA
Applicant's or agent's file reference *2001.650 WO*	
Applicant *Akzo Nobel N.V.*	

Calculation of prescribed fees

1. Preliminary examination fee	*Euro 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.)*	*Euro 159,=*	H
3. Total of prescribed fees Add the amounts entered at P and H and enter total in the TOTAL box	*Euro 1689,=* TOTAL	

Mode of Payment

[X] 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*

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

[X] *(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	*29 Oktober 2002*	*P.M.G.F. van Wezenbeek*
Deposit Account Number	Date *(day/month/year)*	Signature

See Notes to the fee calculation sheet

PCT

REQUEST

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

For receiving Office use only

International Application No. (B)

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference *(if desired) (12 characters maximum)* *2001.650 WO*

32

Box No. I TITLE OF INVENTION

"Benzoxazepine derivatives."

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)*

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

☐ This person is also inventor

Telephone No. *0485-585284*

Facsimile No. *0485-585287*

Teleprinter No.

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

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(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. 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)*

GROVE, Simon, James, Anthony
c/o Organon Laboratories Ltd.
New Edinburgh Road
Newhouse, Lanarkshire
Scotland, ML1 5SH United Kingdom

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: *GB*

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

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 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.*

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.

33

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)*

ZHANG, Mingqiang
260 rue Sherbrooke Est
Montreal, H2X 1E1
Canada

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: *CA*

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)*

SHAHID, Mohammad
c/o Organon Laboratories Ltd.
New Edinburgh Road
Newhouse, Lanarkshire
Scotland, ML1 5SH United Kingdom

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: *GB*

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

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: ☐ 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

☒ **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		☒ SI Slovenia
☒ BZ Belize	☒ KR Republic of Korea	☒ SK Slovakia
☒ CA Canada	☐ KZ Kazakhstan	☐ SL Sierra Leone
☐ CH & LI Switzerland and Liechtenstein	☒ LC Saint Lucia	☐ TJ Tajikistan
☒ CN China	☒ LK Sri Lanka	☐ TM Turkmenistan
☒ CO Colombia	☒ LR Liberia	☐ TN Tunisia
☒ CR Costa Rica	☐ LS Lesotho	☐ TR Turkey
☒ CU Cuba	☒ LT Lithuania	☒ TT Trinidad and Tobago
☒ CZ Czech Republic	☐ LU Luxembourg	
☐ DE Germany	☒ LV Latvia	☐ TZ United Republic of Tanzania
☐ DK Denmark	☒ MA Morocco	☒ UA Ukraine
☒ DM Dominica	☐ MD Republic of Moldova	☐ UG Uganda
☒ DZ Algeria		☒ US United States of America
☒ EC Ecuador	☒ MG Madagascar	
☒ EE Estonia	☒ MK The former Yugoslav Republic of Macedonia	☒ UZ Uzbekistan
☐ ES Spain		☒ VN Viet Nam
☐ FI Finland	☒ MN Mongolia	☒ YU Yugoslavia
☐ GB United Kingdom	☐ MW Malawi	☒ ZA South Africa
☒ GD Grenada	☒ MX Mexico	☐ ZM Zambia
☒ GE Georgia	☒ MZ Mozambique	☐ ZW Zimbabwe
☐ GH Ghana	☒ NO Norway	

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.)*

35

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 *(in which, or for which, the application was filed)*	Filing Date *(day/month/year)*	Application No.	Office of filing *(only for regional or international application)*
item (1) *EP (designating NL)*	*11-06-2001*	*01202215.8*	*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)* *11-06-2001* Number: *01202215.8*

Box No. VIII CHECK LIST

This international application contains the following number of sheets:

1. request:	*4*	sheets
2. description:	*31*	sheets
3. claims:	*3*	sheets
4. abstract:	*1*	sheets
5. drawings:		sheets
6. sequence listing:		sheets
Total :	39	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.M.G.F. 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:

This sheet is not part of and does not count as a sheet of the international application.

36

PCT

FEE CALCULATION SHEET

Annex to the Request

For receiving Office use only

International application No.

Date stamp of the receiving Office

Applicant's or agent's file reference: *2001.650 WO*

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 *39* sheets.

first 30 sheets ..... *EUR 444,=* [b_1]

9 remaining sheets × *EUR 10,=* additional amount = *EUR 90,=* [b_2]

Add amounts entered at b_1 and b_2 and enter total at B ..... *EUR 534,=* [B]

Designation Fees

The international application contains *63* 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 1014,=* [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 2089,=* TOTAL

[ ] The designation fee is not paid at this time.

MODE OF PAYMENT

- [X] 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*

- [X] is hereby authorized to charge the total fees indicated above to my deposit account.
- [X] 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 0012 (Deposit Account Number) *04/06/2002* (Date *(day/month/year)*) Signature *P.M.G.F. van Wezenbeek*

See Notes to the fee calculation sheet

37

INTERNATIONAL SEARCH REPORT

	tional Application No
	PCT/EP 02/06185

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D498/04 C07D515/04 A61K31/553 A61K31/554 A61P25/00

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

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, 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.
Y	WO 96 38414 A (CORTEX PHARMA INC) 5 December 1996 (1996-12-05) cited in the application claims 1,16; examples 5,6	1-10
Y	WO 97 36907 A (UNIV CALIFORNIA ;CORTEX PHARMA INC (US)) 9 October 1997 (1997-10-09) cited in the application claims 1,24; examples 4,5,8	1-10
Y	WO 99 33469 A (CORTEX PHARMA INC ;MARRS CHRISTOPHER (US); ROGERS GARY A (US)) 8 July 1999 (1999-07-08) claims 1,16,17	1-10

[X] Further documents are listed in the continuation of box C. [X] 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.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
29 July 2002	02/08/2002

Name and mailing address of the ISA	Authorized officer
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	Seymour, L

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATI NAL SEARCH REPORT

rnational application No.
PCT/EP 02/06185

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 10 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

PATENT COOPERATION TREATY

38
39

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

To:
P.M.G.F. van WEZENBEEK
Attn. Van Wezenbeek
P.O. Box 20
NL-5340 BH Oss
NETHERLANDS

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

Applicant's or agent's file reference 2001.650WO	Date of mailing (day/month/year) 02/08/2002 FOR FURTHER ACTION See paragraphs 1 and 4 below
International application No. PCT/EP 02/06185	International filing date (day/month/year) 05/06/2002
Applicant AKZO NOBEL N.V.	

1. [X] 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 90*bis*.1 and 90*bis*.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 Kerstin G^tz

Form PCT/ISA/220 (July 1998)

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. 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 latter to be published for the purpose 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 19(1)" (see below, under "Statement under Article 19(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.

PATENT COOPERATION TREATY

PCT

42

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
2001.650WO		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP 02/06185	05/06/2002	11/06/2001
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 4 sheets.

[X] 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 readble 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. [X] 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.

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

   BENZOXAZEPINE DERIVATIVES AND THEIR USE AS AMPA RECEPTOR STIMULATORS

5. With regard to the abstract,

   [X] 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.

   [X] None of the figures.

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 99 42456 A (GOULIAEV ALEX HAAHR ;NIELSEN ELSEBET OESTERGAARD (DK); LARSEN MOGE) 26 August 1999 (1999-08-26) cited in the application * compounds 127, 128 * claims 1,26,27	1-10
A	SCHULTZ A G ET AL: "ENANTIOSELECTIVE METHOD FOR REDUCTIVE ALKYLATION OF AROMATIC CARBOXYLIC ACID DERIVATIVES. EXAMINATION OF THE FACTORS THAT PROVIDE STEREOSELECTIVITY" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC, US, vol. 110, no. 23, 1988, pages 7828-7841, XP000918768 ISSN: 0002-7863 * compounds 1a - 1d, 6a, 6b *	1

1

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 02/06185

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D498/04 C07D515/04 A61K31/553 A61K31/554 A61P25/00

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

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, 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.
Y	WO 96 38414 A (CORTEX PHARMA INC) 5 December 1996 (1996-12-05) cited in the application claims 1,16; examples 5,6	1-10
Y	WO 97 36907 A (UNIV CALIFORNIA ;CORTEX PHARMA INC (US)) 9 October 1997 (1997-10-09) cited in the application claims 1,24; examples 4,5,8	1-10
Y	WO 99 33469 A (CORTEX PHARMA INC ;MARRS CHRISTOPHER (US); ROGERS GARY A (US)) 8 July 1999 (1999-07-08) claims 1,16,17	1-10

-/--

[X] Further documents are listed in the continuation of box C.

[X] 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.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
29 July 2002	02/08/2002

Name and mailing address of the ISA	Authorized officer
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	Seymour, L

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 02/06185

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 10 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 02/06185

45

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 9638414	A	05-12-1996	US	5650409 A	22-07-1997
			AU	708715 B2	12-08-1999
			AU	5929396 A	18-12-1996
			CA	2222976 A1	05-12-1996
			EP	0839134 A1	06-05-1998
			JP	2001503012 T	06-03-2001
			PL	323667 A1	14-04-1998
			WO	9638414 A1	05-12-1996
			US	5783587 A	21-07-1998
WO 9736907	A	09-10-1997	US	5736543 A	07-04-1998
			AU	708212 B2	29-07-1999
			AU	2427497 A	22-10-1997
			AU	4454399 A	21-10-1999
			CA	2249654 A1	09-10-1997
			EP	0891365 A1	20-01-1999
			JP	3170294 B2	28-05-2001
			JP	2000503664 T	28-03-2000
			NZ	331992 A	25-02-1999
			US	5962447 A	05-10-1999
			WO	9736907 A1	09-10-1997
WO 9933469	A	08-07-1999	US	5985871 A	16-11-1999
			AU	746971 B2	09-05-2002
			AU	1930599 A	19-07-1999
			BR	9814478 A	10-10-2000
			CA	2316356 A1	08-07-1999
			CN	1283114 T	07-02-2001
			EP	1054673 A1	29-11-2000
			HU	0102056 A2	28-11-2001
			JP	2001527045 T	25-12-2001
			NO	20003166 A	07-08-2000
			PL	341427 A1	09-04-2001
			TR	200001971 T2	22-01-2001
			WO	9933469 A1	08-07-1999
WO 9942456	A	26-08-1999	AU	2512399 A	06-09-1999
			CA	2320354 A1	26-08-1999
			CN	1293665 T	02-05-2001
			WO	9942456 A2	26-08-1999
			EE	200000468 A	15-04-2002
			EP	1071426 A2	31-01-2001
			HU	0101280 A2	28-10-2001
			JP	2002504481 T	12-02-2002
			NO	20004121 A	17-10-2000
			PL	342843 A1	16-07-2001
			SK	11892000 A3	12-02-2001
			TR	200002427 T2	22-01-2001
			ZA	9901301 A	13-09-1999

DERIVADOS DE BENZOXAZEPINA Y SU USO COMO ESTIMULADORES DEL RECEPTOR AMPA

La presente invención se relaciona con derivados de benzoxazepina, con composiciones farmacéuticas que comprenden los mismos y con el uso de estos derivados de benzoxazepina en el tratamiento de enfermedades neurológicas y siquiátricas.

En el sistema nervioso central de los mamíferos (CNS), la transmisión de pulsos nerviosos es controlada mediante la interacción entre un neurotransmisor, que es liberada por una neurona de envío, y un receptor de superficie sobre una neurona receptora, que origina la excitación de esta neurona receptora. El L-Glutamato es el neurotransmisor más abundante en el CNS. Este media el principal camino excitatorio en mamíferos y es denominado como un aminoácido excitatorio (EAA). Los aminoácidos excitatorios son de gran importancia fisiológica, juegan un papel en una variedad de procesos fisiológicos, tales como aprendizaje y memoria en el desarrollo de plasticidad sináptica, control motor, respiración, regulación cardiovascular y percepción sensorial.

Los receptores que responden al glutamato son llamados receptores de aminoácido excitatorio (receptores EAA). Estos receptores son clasificados en dos tipos generales: (1) receptores "ionotrópicos" que están directamente acoplados a la abertura de canales de catión en la membrana central de las neuronas, y (2) G-proteína ligada a receptores "metabotrópicos" que están acoplados a múltiples sistemas mensajeros secundarios que conducen a hidrólisis fosfoinositida mejorada, activación de fosfolipasa D, incrementa o disminuye la formación de c-AMP y cambia en la función de canal ión.

Los receptores ionotrópicos pueden ser farmacológicamente subdivididos en tres subtipos, que son definidos por las acciones de despolarización de los agonistas selectivos N-metil-D-aspartato (NMDA), ácido α-amino-3-hidroxi-5-metilisoxazol-4-propiónico (AMPA), y ácido cainico (KA).

La activación de los receptores AMPA sinápticos media una corriente postsináptica excitatoria rápida de independiente voltaje (~ 1 ms a respuesta pico) (el EPSC rápido), mientras la activación de los receptores NMDA sinápticos generan una corriente excitatoria lenta

dependiente de voltaje (~ 20 ms a respuesta pico). La distribución regional de los receptores AMPA en el cerebro sugiere que los receptores AMPA medie la transmisión sináptica en aquellas áreas probablemente responsables de la cognición y la memoria.

La activación de los receptores AMPA mediante agonistas se cree que conduce a un cambio conformacional en el receptor originando rápida abertura y cierre del canal ión. La extensión y duración de la activación del canal puede ser decrecida por una droga que actúa de esta forma como un modulador alostérico negativo (por ejemplo GYKl 52466), o puede ser mejorada por una droga, que actúa entonces como un modulador alostérico positivo.

Una clase estructural de moduladores positivos receptores AMPA derivados de aniracetam (por ejemplo CX 516) son las llamadas AMPAquinas. Los moduladores positivos del receptor AMPA pueden así unirse al receptor glutamato y, a la subsecuente unión de un agonista receptor, permitir un flujo de iones a través del receptor de duración incrementada.

50 YA

Los defectos en neuro transmisión glutamatérgica se pueden asociar con muchas enfermedades neurológicas y siquiátricas en humanos. El potencial terapéutico de los moduladores receptores AMPA positivos en el tratamiento de enfermedades neurológicas y siquiátricas se ha revisado por llamada, K.A. (*Exp. Opin. Invest. Drugs.* 2000, **9**, 765-777), por Lees, G.J. (*Drugs*, 2000, **59**, 33-78) y por Grove S. J. A. Et al.(*Exp. Opin. Ther. Patents*, 2000, **10**, 1539-1548).

Varias clases de compuestos que incrementa la función del receptor AMPA se han reconocido y fueron recientemente revisados por Grove S. J. A. Et al (supra). N-anisol-2-pirrolidinona (aniracetama; Roche) es considerado como un prototipo de AMPAquina (Ito, I, et al.,*J. Physiol.* 1990, **424**, 533-543), cercanamente seguido posteriormente por el descubrimiento de cercas sulfonamidas (ejemplificadas por ciclotiazida);Eli Lilli & Co) y moduladores AMPA (llamada, K. A. Y Rothman, s. M. , J. *Physiol.*, 1992 **458**, 385-407). Sobre la base de la estructura de aniracetam, los derivados de estos que tienen potencia y estabilidad mejorada se desarrollaron por Linch, G. S. Y Rogers, G. A. Como se describió en la Solicitud de Patente Internacional WO 94/02475 (The

51 BO

Regents of the University of California). Las AMPAquinas adicionales en la forma de benzoilpiperidinas y pirrolidinas fueron subsecuentemente descritas en WO 96/38414 (Rogers, G. A. Y Nilsson. L.; CORTEX Pharmaceuticals), seguido por los compuestos en donde la función amida fue conformacionalmente restringida en un sistema de anillo de benzoxazina, como se describió en la wo 97/36907 (Rogers, G. A. Y Linch. G., the Regents of the University of California; CORTEX Pharmaceutical), o en un sistema de anillo de acilbenzoxazina, como se describió en la WO 99/51240 (Rogers G. A. Y Johnstrom, P., The Regents of the University of California). Los derivados estructuralmente relacionados de benzoxazina y especialmente los 1,2,4-benzotiadiazina-1,2-dióxidos, estructuralmente derivados de ciclotiazida™ se han descrito en la WO 99/42456 (NEUROSEARCH A/S) como modeladores positivos del receptor AMPA.

Los moduladores receptores AMPA positivos tienen muchas aplicaciones potenciales en humanos. Por ejemplo, incrementar la resistencia de la sinapsis excitatoria podría compensar las perdidas de sinapsis o receptores asociados con envejecimiento y enfermedad cerebral (enfermedad de Alzaheimer por ejemplo). La actividad

52 87

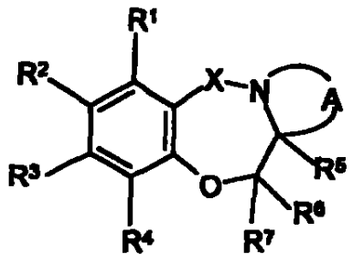
mediada por receptor AMPA mejorada podría originar más rápido procesamiento mediante circuitos multisinápticos encontrados en regiones más altas del cerebro y podría así producir un incremento en el motor perceptual y el desempeño intelectual. Las AMPAquinas han sido adicionalmente sugeridas por ser potencialmente útiles como mejoradores de la memoria, para mejorar el desempeño de sujetos con problemas sensoriales-motores y de sujetos afectados en tareas cognitivas dependientes de redes cerebrales que utilizan los sectores AMPA en le tratamiento de la depresión. Alcoholismo y esquizofrenia, y en la mejora de la recuperación de sujetos que sufren de trauma.

Se ha observado de otra parte que la activación del receptor AMPA sostenida en animales experimentales (por ejemplo, a altas dosis de algunos moderadores AMPA, especialmente aquellas que son potentes inhibidores de sensibilización receptora), puede originar ataques y potencialmente también otros efectos colaterales pro convulsionantes (Yamada, k. A. *Exp. Opin. Invest. Drugs*, 2000, **9**, 765-777). En vista del potencial de excitotocidad sobre la activación del receptor AMPA (particularmente mediante moduladores de la clase

53
52

tiadiazida), subsiste la necesidad del desarrollo de moduladores que tengan un índice terapéutico suficiente.

Para este fin la presente invención suministra derivados de benzoxazepina que tienen la fórmula general 1.



fórmula 1

En donde

X representa CO o SO_2;

R^1, R^2, R^3 Y R^4 son independientemente seleccionados de H, alquilo(C_{1-4}), alquiloxi(C_{1-4}), alquiloxi(C_{1-4}), alquilo(C_{1-4})), CF3, halógeno, nitro, ciano, NR^8R^9 NR^8COR^{10}, Y $CONR^8R^8$;

54 53

R^5, R^6, y R^7 son independientemente H o alquilo(C_{1-4}); R^8 Y R^9 son independientemente H o alquilo(C_{1-4});

R^8 y R^9 forman juntos con el átomo de nitrógeno al cual ellos están unidos un anillo heterocíclico saturado de 5 o 6 miembros, que opcionalmente contiene un heteroátomo adicional seleccionado de O, S o NR^{11};

R^{10} es alquilo(C_{1-4});

R^{11} es alquilo(C_{1-4});

A representa el residuo de un anillo heterocíclico saturado de 4-7 miembros, que opcionalmente contiene un átomo de oxigeno, siendo el anillo opcionalmente sustituido con 1-3 sustituyentes seleccionados de alquilo (C_{1-4}), alquiloxi(C_{1-4}), hidroxi, halógeno y oxo; o una sal farmacéuticamente aceptable de esta;

Con la condición de que

Los compuestos de fórmula 1 en donde X es CO; cada uno de R^1-R^7 es H, y A representa $(CH_2)_3$ o $(CH)_4$;

5554

El compuesto de fórmula 1 en donde X es CO; R^1 es H; R^2 es metilo; cada uno de R^3-R^7 es H; y A representa $(CH_2)_3$;

El compuesto de fórmula 1 donde X es CO; R^1 y R^2 son H; R^3 es metilo; cada uno de R^4-R^7 es H; y A representa $(CH_2)_3$;

El compuesto de fórmula 1 en donde X es CO; cada uno de R_1-R_3 es H; R_4 es metilo; cada uno de R^5-R^7 es H; y A representa $(CH_2)_3$; Y

El compuesto de fórmula 1 en donde X es CO; cada uno de R^1-R^4 es H; R^5 es metilo; R^6 y R^7 son H; y A representa $(CH_2)_3$; están excluidos.

Las benzoxazepinas para las cuales no se busca protección *per se* se relacionan con una descripción de Schultz, A. G. Et al (*J. Am, Chem. Soc.* 1988, 110, 7828-7841) donde en donde estos derivados de benzoxazepinona son descritos como intermedios sintéticos, sin ninguna actividad farmacológica.

5655

Las benzoxazepinas de la fórmula 1, incluyéndolas benzoxazepinonas de la técnica anterior descritas por Schultz et al. (supra), se han encontrado por ser moduladores receptores AMPA positivos que pueden ser útiles en el tratamiento de enfermedades neurológicas y siquiátricas donde el mejoramiento de las respuestas sinápticas mediadas por receptores AMPA se requiere.

El término alquilo(C_{1-4}) se utiliza en la definición de la fórmula 1 significa un grupo alquilo ramificado o no ramificado que tiene 1 a 4 átomos de carbono, como butilo, isobutilo, butilo terciario, propilo, isopropilo, etilo y metilo.

En el término alquiloxi (C_{1-4}) , alquilo(C_{1-4}) tiene el significado como se definió anteriormente.

El término alquiloxi(C_{1-4}) alquilo(C_{1-4}) significan un grupo alquilo (C_{1-4}) que es sustituido con un alquiloxi(C_{1-4}), teniendo ambos el significado como se definió anteriormente.

El término halógeno significa F, CLK, Br o I.

5x96

En la definición de la fórmula 1 R^8 y R^9 pueden formar juntos con el átomo de nitrógeno al cual ellos están unidos un anillo heterocíclico saturado de 5 o 6 miembros, que opcionalmente contiene un heteroátomo adicional seleccionado de O, S o NR^{11}. Ejemplos de tales anillos heterocíclicos sustituyentes son piperidino, pirrolidino, morfolino, N-metil-piperazino, N-etil-piperazino y similares.

En la definición de la fórmula 1 A representa el residuo de un anillo heterocíclico saturado de 4-7 miembros, opcionalmente que contiene un átomo de oxigeno, significando que A es un radical bivalente que contiene 2-5 átomos de carbono, tal como etileno, 1,3-propileno, 1,4-butileno,1,5-pentileno, un átomo de carbono el cual puede ser sustituido por oxigeno. Ejemplos de anillos heterocíclicos de 4-7 miembros formados mediante el residuo AA junto con el átomo de nitrógeno y carbono al cual a esta unido son azetidina, pirrolidina, piperidina, oxazolidina, isoxazolidina, morfolina, y azacicloheptano.

Son preferibles los derivados de benzoxazepina de fórmula 1 en donde X es CO, cuyos compuestos son benzoxazepinonas.

5647

Más preferidos son los derivados de benzoxazepina de la fórmula 1 en donde X es CO y donde R^5, R^6 y R^7 son H; y A representa $(CH_2)_3$.

Especialmente preferidos son los derivados de benzoxazepina de la fórmula 1, en donde X es CO, uno o más de R^1, R^2, R^3 Y R^4 es halógeno preferiblemente fluor o, y en donde R^5, R^6 y R^7 son H; y A representa $(CH_2)_3$.

Compuestos Particularmente preferidos de la invención son:

(R)-7-Fluor-2,3,11,11a-tetrahidro-1H,5H-pirrolo[2,1-c][1,4]benzoxazepina-5-ona;

(S)-7-Fluor-2,3,11,11a-tetrahidro-1H,5H-pirrolo[2,1-c][1,4]benzoxazepina-5-ona;

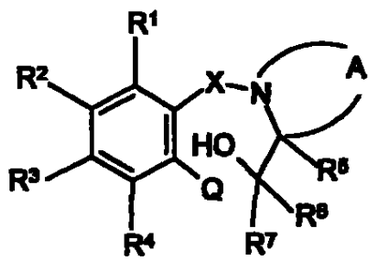
(S)-9-Fluor-2,3,11,11a-tetrahidro-1H,5H-pirrolo[2,1-c][1,4]benzoxazepina-5-ona;

(R)-9-Fluor-2,3,11,11a-tetrahidro-1H,5H-pirrolo[2,1-c][1,4]benzoxazepina-5-ona;

59 59

(S)-6-Fluor-2,3,11,11a-tetrahidro-1H,5H-pirrolo[2,1-c][1,4]benzoxazepina-5-ona;

Los derivados de benzoxazepina de la invención se pueden preparar mediante métodos conocidos en la técnica de la química orgánica en general. Más específicamente tales compuestos se pueden preparar utilizando procedimientos subrayados por A. G. Schultz et al(*J. Am. Chem. Soc.* 1988, 110, 7828-7841) o mediante modificación de aquellas rutas.



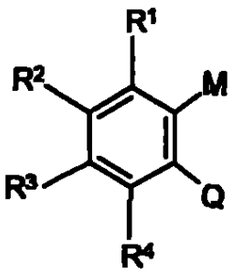
Fórmula II

Los derivados de benzoxazepina de la fórmula 1 pueden por ejemplo ser preparados mediante ciclización de

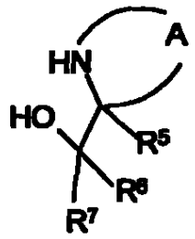
un compuesto de acuerdo a la fórmula II, en donde X, A y R^1-R^7 tienen el significado como se definió previamente, cualquier grupo funcional como un hidrógeno ácido estando protegido con un grupo protector adecuado, y en donde Q representa hidroxi, halógeno, o alquiloxi (C_{1-4})- después de lo cual cualquier grupo protector cuando está presente, se remueve. La reacción de ciclización para los compuestos donde Q es halógeno o alquiloxi (C_{1-4}) se puede llevar a cabo en la presencia de una base tal como hidruro de sodio o carbonato de cesio en un solvente tal como dimetilformamida a y una temperatura de 0-200° C, preferiblemente 25-150°C. Para los compuestos de fórmula II en donde Q es un grupo hidroxi, la ciclización se puede efectuar bajo las condiciones Mitsunobu (Mitsunobu, O., *Síntesis* 1981,1) utilizando trifenil fosfina y un dialquil azodicarboxilato, tal como diisopropil azodicarboxilato en un solvente tal como tetrahidrofurano.

Los grupos protectores adecuados para los grupos funcionales que deben ser temporalmente protegidos durante la síntesis, son conocidos en la técnica por ejemplo de Wults, P. G. M. Y Greene, T. W.: Protective

Groups in Organic Síntesis, tercera edición, Wiley, New York, 1999.



Fórmula III



Fórmula IV

Los compuestos de fórmula II se pueden preparar de la condensación de un compuesto de fórmula III en donde R^1-R^4 y Q tienen el significado como se definió previamente y NM representa un ácido carboxílico o un derivado activado de este, tal como un éster carboxílico o un haluro ácido carboxílico, preferiblemente un cloruro o un bromuro ,o M representa un haluro de sulfonilo, tal como fluor, cloro o bromo, con un compuesto de fórmula IV en donde R^5-R^7 y A tienen el significado como se definió previamente.

Cuando M representa un ácido carboxílico la reacción de condensación, es decir, una acilación se puede

62 9

efectuar con la ayuda de un reactivo acoplante, tal como por ejemplo carbonil diimidazol, diciclohexilcarbodiimida y similares, en un solvente tal como dimetilformamida o diclorometano.

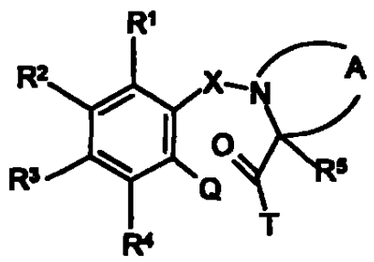
Cuando M representa un haluro de ácido carboxílico o un haluro de sulfonilo la condensación con el derivado de amina 4 se puede llevar a cabo en la presencia de una base, por ejemplo trietilamina, en un solvente tal como cloruro de metileno.

Cuando M representa un derivado de éster de ácido carboxílico una condensación directa con el derivado de amina de fórmula IV se puede llevar a cabo a una temperatura elevada, por ejemplo a aproximadamente 50 a 200°C. Esta Condensación se puede desarrollar utilizando un ácido Lewis, por ejemplo tricloruro de aluminio como se describió por D. R. Barn et al (*Biorg. Med. Chem. Lett.*, 1999, 9, 1329-34).

La preparación de los compuestos de fórmula I se pueden desarrollar utilizando los métodos descritos anteriormente AL emplear un procedimiento de dos etapas de un solo tipo significando que un compuesto de fórmula

62
63

II, que resulta de una reacción de condensación entre un compuesto de fórmula III con un compuesto de fórmula IV, no se aísla de la mezcla de reacción sino que se trata adicionalmente con una base para dar compuestos de fórmula I.



Fórmula V

Los compuestos de fórmula II también se pueden preparar de la reacción de un compuesto de fórmula V donde R^1 a R^5, X y A son como se definió anteriormente y T representa hidrógeno, alquilo $C_{(1-4)}$ o alquiloxi, con un reactivo de alquil metal $C_{(1-4)}$ por ejemplo reactivo de Gringard, en un solvente tal como tetrahidrofurano

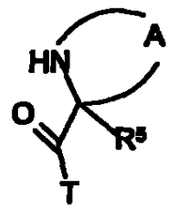
Un compuesto de fórmula II, donde R^5 representa un hidrógeno y R^7 representa un grupo alquilo $C_{(1-4)}$ puede ser

63
64

preparado de un compuesto de fórmula V donde T representa un grupo alquilo $C_{(1-4)}$ mediante una reducción, por ejemplo borohidrudo de sodio en un solvente tal como etanol.

Un compuesto de fórmula V donde X es CO y T representa un grupo alquilo se puede preparar de un compuesto de fórmula III donde M representa un cloruro de ácido carboxílico y un derivado de alcanolamina imina de un alquil glicolato como se describió por D.E. Thurston et al (*j. Chem. Soc., Chem. Commun., 1990, 874-876*).

Un compuesto de fórmula V se puede preparar al acoplar un compuesto de fórmula III en donde R^1-R^4, M y Q tienen el significado como se definió previamente con un compuesto de fórmula VI, en donde R^5, A y T tienen el significado como se definió previamente empleando los métodos descritos anteriormente para el acoplamiento de compuestos de fórmula II y IV



Fórmula VI

Los compuestos de fórmula III, IV y VI se pueden obtener de fuentes comerciales preparados por procedimientos de la literatura o modificaciones de procedimientos de la literatura conocidos por aquellas personas expertas en la técnica.

La persona experta apreciará de manera similar que varios compuestos de fórmula I se pueden obtener mediante las reacciones de conversión apropiadas de grupos funcionales que corresponden a ciertos de los sustituyentes R^1-R^4.

Por ejemplo, la reacción de un alcohol de alquilo $C_{(1-4)}$ con un compuesto de fórmula I, en donde X, A u R^5-R^7 son como se definió anteriormente, y en donde uno de R^1 a R^4 es un grupo saliente tal como, pero no limitado a,

fluor o cloro, en la precedencia de una base tal como hidruro de sodio da compuestos de fórmula donde uno de R^1 a R^4 es alquiloxi $C_{(1-4)}$.

Los compuestos de fórmula I donde uno o más de R^1 a R^4 son $CONR^8R^9$ se pueden preparar mediante conversión de un compuesto de fórmula I donde uno o más de R^1 a R^4 son bromo o yodo el éster de ácido carboxílico correspondiente utilizando un paladio (II) por ejemplo diclorobis (trifenilfosfina) paladio, reacción de carbonilación catalizada como se describió por A. Schoenberg et al (J. Org. Chem. 1974, 39, 3318). La saponificación del éster al ácido carboxílico utilizando por ejemplo hidróxido de sodio en tetrahidrofurano-agua, y acoplando el ácido carboxílico en una amina de fórmula NHR^8R^9 utilizando, por ejemplo carbonil diimidazol como agente acoplante, da compuestos de fórmula I donde uno o más de R^1 a R^4 son $CONR^8R^9$. El precursor de ácido carboxílico a los compuestos de fórmula I en donde uno o más de R^1 a R^4 son $CONR^8R^9$ se pueden preparar mediante oxidación de un compuesto de fórmula I donde uno o más de R^1 a R^4 es un grupo metilo utilizando un oxidante, por ejemplo un tri óxido de cromo. Los compuestos de fórmula I donde uno o más de R^1 a R^4 son $CONR^8R^9$ se pueden reparar

66
67

mediante un paladio (II) tal como diclorobis (trifenilfosfina) paladio, carbonilación catalizada de fórmula I donde uno o más de R^1 a R^4 son bromo o yodo en la presencia de una amina de fórmula NHR^8R^9 utilizando el método descrito por A. Schoenberg y R. F. Heck (J. Org. Chem. 1974, 39, 3327).

Un compuesto de fórmula I donde uno o más de R^1 a R^4 son CN se pueden preparar de un compuesto de fórmula I en donde uno o más de R^1 a R^4 es $CONH_2$ mediante deshidratación con un agente deshidratante por ejemplo oxicloruro de fósforo. Un compuesto de fórmula I donde uno o más de R^1 a R^4 son CN se puede preparar de un compuesto de fórmula I donde uno o más de R^1 a R^4 es bromo o yodo utilizando una reacción de cianación catalizada con paladio (O) como se describió por M. Alterman y A. Hallberg (J. Org. Chem. 200, 65, 7984).

Un compuesto de fórmula I donde uno o más de R^1 a R^4 son NR^8R^9 se pueden preparar de un compuesto de fórmula I donde uno o más de R^1 a R^4 es fluor o cloro mediante el desplazamiento del halógeno con una amina de la fórmula NHR^8R^9. Un compuesto de fórmula uno o más de R^1 a R^4 son

NR^8R^9 se pueden preparar de un compuesto de fórmula I donde uno o más de R^1 a R^4 es fluor o cloro mediante el desplazamiento del halógeno con una amina de la fórmula NHR^8R^9. Un compuesto de fórmula I donde uno o más de R^1 a R^4 son NR^8R^9 se pueden preparar de un compuesto de fórmula 1 donde uno o más de R^1 y R^4 es cloro, bromo o yodo mediante una reacción de aminación catalizada con paladio con una amina de la fórmula NHR^8R^9 como se describió por J. P. Wolfe et al (*J. Org. Chem.* 2000, **65**, 1158). Un compuesto de fórmula 1 donde uno o más de R^1 a R^4 son NR^8R^9 y uno de R^8 o R^9 es hidrógeno se puede preparar de un compuesto de fórmula 1 donde uno o más de R^1 a R^4 son NR^8R^9 y ambos R^8 y R^9 son H mediante alquilación del átomo de nitrógeno con un agente alquilatante de fórmula R^9Y donde Y es un grupo saliente tal como un sulfonato de alquilo o arilo, cloro, bromo o yodo. Un compuesto de fórmula uno donde uno o más de R^1 a R^4 son NR^8R^9 y ambos R^8 y R^9 son H se pueden preparar de un compuesto de fórmula 1 donde uno o más de R^1 a R^4 son nitro mediante una reducción por ejemplo de reducción catalizada de paladio con hidrógeno. Un compuesto de fórmula 1 donde uno o más de R^1 a R^4 son NR^8COR^{10} se pueden preparar de un compuesto de fórmula 1 donde uno o más de R^1 a R^4 son NHR^8 mediante tratamiento con un agente acilatante tal como cloruro

clorhidrido ácido $C_{(1-5)}$, por ejemplo anhídrido acético en un solvente, por ejemplo piridina.

El tratamiento de un compuesto de fórmula 1, donde A representa un residuo de un anillo heterociclico saturado de 4-7 miembros sustituido con grupos 1-3 hidroxi, con una base tal como hidruro de sodio, en un solvente, tal como tetrahidrofurano, con un agente alquilatante de fórmula $C_{(1-4)}$alquilY donde Y se definió como anteriormente da un compuesto de fórmula I donde A representa un residuo de un anillo heterocíclico saturado de 4-7 miembros opcionalmente sustituidos con grupos 1-3alquiloxi.

En un compuesto de fórmula I, donde A representa un residuo de un anillo heterocíclico saturado de 4-7 miembros sustituido con grupos 1-3 hidroxi, el o los grupos hidroxi se pueden sustituir mediante halógeno mediante el tratamiento con un reactivo halogenante tal como trifluoruro de (dietilamino) azufre (DAST) o con la combinación tetrahaluro de carbono-trifenil fosfina.

Similarmente, un compuesto de fórmula I donde A representa un residuo de un anillo heterocíclico saturado

de 4-7 miembros opcionalmente sustituido con dos grupos halógeno en el mismo átomo de carbono se pueden preparar del derivado oxo correspondiente mediante tratamiento con un agente halogenante tal como DAST.

La oxidación del compuesto de fórmula I, donde A representa un residuo de un anillo heterocíclico saturado de 4-7 miembros opcionalmente sustituido con grupos 1-3 hidroxi, con un agente oxidante tal como en la oxidación Swern como se describió con R. E. Ireland and D. W. Norbeck (*J. Org. Chem.* 1985, 50, 2198-2200), da compuestos de fórmula I donde A representa un residuo de un anillo heterocíclico saturado de 4-7 miembros opcionalmente sustituido con grupos 1-3 oxo.

Los derivados de benzoxazepina de la fórmula I sus sales contienen al menos un centro de quiralidad, y existe por lo tanto como esteroisómeros, incluyendo enantiómeros y cuando sea apropiado, diastereomeros. La presente invención incluye los esteroisómeros anteriormente mencionados dentro del alcance de cada uno de los enantiómeros individuales R y S de los compuestos de fórmula I sus sales, sustancialmente libres, es decir, asociadas a menos de 5%, preferiblemente menos de 2%, en

particular menos de 1% de otro enantiómero, y mezclas de tales enantiómeros en cualquiera proporciones incluyendo las mezclas racemicas que contienen sustancialmente las mismas cantidades de los dos enantiómeros.

Los métodos para la síntesis asimétrica por medio de los cuales se obtienen los esteroisomeros puros son bien conocidos en la técnica, por ejemplo, síntesis con inducción quiral o partida de intermedios quirales, en convenciones enzimáticas enantioselectivas, separación de esteroisómeros o en antiomeros utilizando cromatografía sobre el medio quiral. Tales métodos son por ejemplo descritos en Chirality in Industry (editada por A. N. Collins, G.N. Sheldrake and J. Crosby, 1992; John Wiley). Los métodos específicos aplicables para la preparación estereoselectiva de derivados de benzoxazepina de esta invención son aquellos descritos por Schultz, A. G. et al. (J. Am. Chem Soc. 1988, 110, 7828-7841).

Las sales farmacéuticamente aceptables se pueden obtener mediante tratamiento de una base libre de un compuesto de acuerdo con la fórmula I con un ácido mineral total como ácido clorhídrico, ácido bromhídrico, ácido fosfórico y ácido sulfúrico, a un ácido orgánico

tal como por ejemplo ácido ascórbico, ácido cítrico, ácido tartárico, ácido láctico, ácido maleico, ácido malonico, ácido fumárico, ácido glicolico, ácido succínico, ácido propiónico, ácido acético, ácido metanosulfónico y similares.

Los compuestos de la invención pueden existir en forma no solvatada así como también en forma solvatada con solventes farmaceuticamente aceptables tales como agua, etanol y similares. En general, las formas solvatadas son consideradas equivalentes a las formas no solvatadas para los propósitos de la invención.

La presente invención suministra además composiciones farmacéuticas que comprenden un derivado de benzoxazepina que tiene la fórmula general I, a una sal farmacéuticamente aceptable de esta, en mezcla con auxiliares farmacéuticamente aceptables y opcionalmente otros agentes terapéuticos. En término "aceptable" significa ser compatible con otros ingredientes de la composición y no deletreos a los receptores de esta. Las composiciones incluyen por ejemplo aquellas adecuadas para administración oral, sublingual, subcutánea,

intravenosa, intramuscular, local, o rectal, y similares, todas en formas de dosis unitarias para administración.

Para la administración oral, el ingrediente activo se puede presentar como unidades discretas, tales como tabletas, cápsulas, polvos, granulados, soluciones, suspensiones, y similares. Para administración parenteral, la composición farmacéutica de la invención puede estar presente en recipientes de dosis unitarias multidosis, por ejemplo, líquidos de inyección en cantidades predeterminadas, por ejemplo en frascos y ampollas selladas y también se pueden almacenar en condición seca congelada (liofilizada) requiriendo solo la adición de un portador líquido estéril, por ejemplo, agua, antes de uso.

Mezclada con tales auxiliares farmacéuticamente aceptables, por ejemplo, como se describió en la referencia estándar, Gennaro, A. R. et al., Remington: The Science and Practice of Pharmacy (20th Edición, Lippincott Williams & Wilkins, 2000, ver especialmente parte 5: Pharmaceutical Manufacturing), el agente activo se puede comprimir en unidades de dosis sólidas, tales como píldoras, tabletas, o ser procesada en cápsulas o

supositorios. Por medio de líquidos farmacéuticamente aceptables el agente activo se puede aplicar como una composición fluida, por ejemplo como una preparación de inyección, en la forma de una solución, suspensión, emulsión o un roseado, por ejemplo, un roseado nasal.

Para elaborar unidades de dosis sólida, el uso de aditivos convencionales tales como llenadores, colorantes, ligadores poliméricos y similares se contempla. En general cualquier aditivo farmacéuticamente aceptable que no interfiera con la función de los compuestos activos se puede utilizar. Los portadores adecuados con los cuales el agente activo de la invención se puede administrar como composiciones sólidas incluyen lactosa, almidón, derivados de celulosa y similares, o mezclas de estos, utilizadas en cantidades adecuadas. Para administración parenteral se pueden utilizar suspensiones acuosas, soluciones salinas isotónicas y soluciones inyectables estériles, que contienen agentes dispersantes farmacéuticamente aceptables y/o agentes humectantes tales como propilenglicol o butilen glicol. La invención además incluye una composición farmacéutica, como se describió anteriormente, en combinación con un material de empaque adecuado para dicha composición,

dicho material de empaque incluye instrucciones para uso de la composición para el uso como se describió anteriormente,.

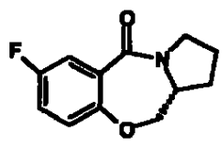
Las benzoxazepinas de la invención son estimuladores del receptor AMPA, como se puede determinar mediante un incremento en estado constante habitualmente inducido mediante aplicación de glutamato en un método de agarre de parche de celda completa convencional cuando la benzoxazepina de la invención esta presente (ver ejemplo 30 y tabla 1). Los compuestos se pueden utilizar en el tratamiento de enfermedades neurológicas y siquiátricas donde una mejora de las respuestas sinápticas mediadas por receptores AMPA se requiere, tal como desordenes neuro degenerativos, disfunción cognitiva o de memoria, desordenes de memoria y de aprendizaje, tal como puede resultar del envejecimiento, desordenes de atención, trauma, ataques, epilepsia, enfermedad de Alzheimer, depresión, esquizofrenia, desordenes sicóticos, ansiedad, disfunciones sexuales, autismo, o en desorden o enfermedad que resulta de agentes neuróticos o abuso de sustancias e intoxicación de alcohol.

Los compuestos de la invención se pueden administrar en humanos en una dosis de 0, 001-50 mg por kg de peso de cuerpo, preferiblemente en una dosis de 0, 1-20 mg por kg de peso de cuerpo.

La invención se ilustra mediante los siguientes ejemplos.

Ejemplo 1

(R)-7-Fluoro-2,3,11,11a-tetrahidro-1H, 5H-pirrolo [2,1-c][1, 4] benzoxazepina-5-uno



Una solución de ácidos 2,5-difluorobenzoico 81,0 g; 6,325 mmol) en dimetilformamida (5 ml) se agregó 1,1'-carbonildiimidazol (1,07 g; 6, 64 mmol) y la solución se agito a temperatura ambiente de cuarto durante 1 h, seguido por la adición de (R)-(-)-2-pirrolidinometanol (0,655 ml; 6,64 mmol). La reacción se agitó a temperatura ambiente de cuarto durante toda la noche luego de lo cual

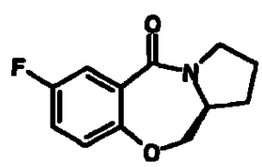
26
27

se agregó cuidadosamente hidruro de sodio al 60% del aceite mineral (0, 507 g; 12, 7 mmol) y la mezcla se calentó a 120°C durante 2 h. La reacción fue cautelosamente diluida con agua y extraída con acetato de etilo y la capa orgánica se lavó con agua y se secó (Na_2SO_4) y se evaporo para darle producto crudo. La trituración con éter y la filtración lograda logró el compuesto del título (0, 29 g)

P.f.: 85-86 °C; EIMS: m/z = 222.2 $[M+H]^+$

Ejemplo 2

(S)-7-Fluoro-2,3,11,11a-tetrahidro-1H, 5H-pirrolo [2,1-c][1, 4] benzoxazepina-5-ona



El compuesto del título se preparo se preparo siguiendo el método del ejemplo 1

Utilizando (S-(+)-2-pirrolidinometanol. P.f.:80-82 °C; EIMS: m/z = 222.2 $[M+H]^+$

Ejemplo 3

El procedimiento descrito bajo el ejemplo 1 fue el más utilizado para preparar los siguientes compuestos:

3A: (R)-7-Fluoro-2,3,11,11a-tetrahidro-1H, 5H-pirrolo [2,1-c][1, 4] benzoxazepina-5-una se obtuvo de ácido 2,3-diflorobenzoico y (R)-(-)-2-pirrolidinometanol. P.f.: 94-95 °C, EIMS: m/z = 222.1 $[M+H]^+$

3B: (S)-7-Fluoro-2,3,11,11a-tetrahidro-1H, 5H-pirrolo [2,1-c][1, 4] benzoxazepina-5-una se obtuvo de ácido 2,3-difluorobenzoico y (S)-(+)-2pirrolidinometanol. Mp.:92-93 °C; EIMS: m7z = 222.2 $[M+H]^+$

3C: (R)-8-Trifluorometil-2.3,11,11a-tetrahidro-1H, 5H-pirrolo [2,1-c][1,4] benzoxazepina-5-una se obtuvo de ácido 2-fluoro-trifluorometilbenzoico y (R)-(-)-2-pirrolidinometanol. P.f.: 92-94 °C; EIMS: m/z = 272.2 $[M+H]^+$

78
79

3D: (S)-8-Trifluorometil-2.3,11,11a-tetrahidro-1H, 5H-pirrolo [2,1-c][1,4] benzoxazepina-5-una se obtuvo de ácido 2-fluoro-trifluorometilbenzoico y (S)-(+)-2-pirrolidinometanol. P.f., 92-94 °C; EIMS: m/z = 272.1 $(M+H)^+$

3E: (R)-6-Fluoro 2, 3, 11, 11a-tetrahidro-1H, 5H-pirrolo [2,1-c][1,4]benzoxazepina-5-una se obtuvo de ácido 2,6-difluorobenzoico y (R)-(-)-2-pirrolidimometanol, p.f., 146-148 °C; EIMS: m/z = 222.2 $[M+H]^+$

3F (S)-8-cloro-2,3,11,11a-tetrahidro-1H, 5H-pirrolo[2,1-c][1,4]benzoxazepina-5-una se obtuvo de ácido 2, 4-diclororobenzoico y (S)-(+)-2-pirrolidenometanol. P.f., 1105-106 |C; EIMS: m/z = 238.2 $[M+H]^+$

3G: (S)-7-cloro-2,3,11,11a-tetrahidro-1H,5H-pirrolo[2,1][1,4]benzoxazepina-5-una se obtuvo de ácido 2,5-diclororobenzoico y (S)-(+)-2-pirrolidinometanol. P.f. 124-126 °C; EIMS: m/z = 238 $[M+H]^+$

3H: (±)-3-Fluoro-6,6a,7,8,9,10-hexahidro-12H-pirido[2,1-c][1,4]benzoxazepina-12-una se obtuvo de ácido 2,5-difluorobenzoico y 2-piperidinometanol y se aisló como una goma. EIMS: m/z = 236 $[M+H]^+$

3I: (R)-7-Bromo-2,3,11,11a-tetrahidro-1H, 5H-pirrolo[2,1-c][1,4]benzoxazepina-5-una se obtuvo de ácido 5-bromo-2-clorobenzoico y (R)-(-)-2-pirrolidinometanol. P.f. 115-116 |C; EIMS: m/z = 284 $[M+H]^+$

3J: (S)-7-Bromo-2,3,11,11a-tetrahidro-1H, 5H-pirrolo[2,1-c][1,4]benzoxazepina-5-una se obtuvo de ácido 5-bromo-2-clorobenzoico y (R)-(+)-2-pirrolidinometanol. P.f. 115-116 °C; EIMS: m/z = 284 $[M+H]^+$

3K: (R)-Nitro-2,3,11,11a-tetrahidro-1H-5H-pirrolo[2,1][1,4]benzoxazepina-5-una se obtuvo de ácido 5-nitro-2-clorobenzoico y (R)-(-)-2-pirrolidinometanol. P.f. 169-170 °C; EIMS: m/z = 249 $[M+H]^+$

3L: (S)-Nitro-2,3,11,11a-tetrahidro-1H-5H-pirrolo[2,1][1,4]benzoxazepina-5-una se obtuvo de ácido 5-nitro-2-clorobenzoico y (S)-(+)-2-pirrolidinometanol. P.f. 170-171 °C; EIMS: m/z = 249 $[M+H]^+$

Ejemplo 4

(R)-8-cloro-2,3,11,11a-tetrahidro-1H, 5H-pirrolo[2,1-c][1,4]benzoxazepina-5-ona-c][1,4]benzoxazepina-5-ona

A una solución de ácido 2,4-diclorobenzoico (1,21 g; 6,325 mmol)en dimetilformamida (5 ml) se agregó 1,1´-carbonildiimidazol ((1,07 g; 6,64 mmol) y la solución se agitó a temperatura ambiente durante un H antes de la adición de (R)-(-)-2-pirrolidinometanol (0,655 ml; 6,64 mmol). La reacción se agitó a temperatura ambiente de cuarto durante toda la noche luego el solvente se removió en vacío y el residuo se purificó mediante cromatografía sobre sílica (eluyendo con 5% de metanol en diclorometano) para dar la amida intermedia que no se caracterizó pero se tomó directamente en la siguiente etapa. A una solución de esta amida (0,6 g) en dimetil formamida se agregó carbonato de cesio (1,5 g). La mezcla se calentó a 150°C durante 2 h, luego se enfrío a temperatura ambiente de cuarto. La reacción se diluyó con agua y se extrajo con acetato de etilo. La capa orgánica se lavó con agua y se secó (Na_2SO_4). Evaporación del

81
82

solvente y el solvente se removió. El producto crudo se purificó mediante cromatografía sobre sílica (eluyendo con metanol 5% en diclorometano). El aceite claro resultante cristalizado en reposo y se titulo con heptano. Se logró filtración del compuesto del título (0,22 g). P.F., 92-94°C; EIMS: m/z = 238.1 $[M+H]^+$

Ejemplo 5.

El procedimiento descrito bajo el ejemplo 4 fue más utilizado para preparar :

(s)-8-fluoro-2,3.11,11a-tetrahidro-1H,5H-pirrolo[2,1-c][1,4]benzoxazepina-5-ona se obtuvo de ácido 2,4-difluorobenzoico y (S)-(+)-2-pirrolidinometanol. P.F.,75-76°C; EIMS: m/z = 222.2 $[M+H]^+$

Ejemplo 6

(±)-3-trifluorometil-6,6a,7,8,9,10,-hexahidro-12H-pirido[2,1-c][1,4]benzoxazepin-12-ona

82
83

A una solución de ácido 2-fluoro-4-(trifluorometil)-benzoico (1,31 g; 6,325 mmoles) en dimetilformamida (5 ml) se agregó 1,1'-carbonildiimidazol (1,08 g; 6,64 mmoles) y la solución fue agitada a temperatura ambiente durante una hora, luego de lo cual se agregó 2-piperidinemetanol (0,765 g; 6,64 mmoles). La reacción fue agitada a temperatura ambiente durante la noche y luego se agregó el carbonato de calcio (4,12 g) y la mezcla fue calentada a 120° C durante 4 h. se diluyó con agua el producto y el producto fue extraído en acetato de etilo y lavado con agua. La capa orgánica fue secada (Na_2SO_4) y la evaporación del solvente en vacío dio el producto crudo el cual se cristalizó a partir del 5% de éter en hexanos para dar el compuesto titulado (0,83 g). p.f.: 103 - 104° C; EIMS: m/z = 286 $[M+H]^+$

Ejemplo 7

El procedimiento descrito bajo el ejemplo **6** fue usado adicionalmente para preparar los siguientes compuestos:

83
84

7A: (±)-4-fluoro-6,6a,7,8,9,10-hexahidro-12H-pirido[2,1-c][11,4]benzoxazepina-12-ona fue obtenido a partir de ácido 2,3-difluorobenzoico y de 2-piperidinemetanol como una goma. EIMS: m/z = 235,8 $[M+H]^+$

7B: (±)-3-fluoro-6,6a,7,8,9,10-hexahidro-12H-pirido[2,1-c][11,4]benzoxazepina-12-ona fue obtenido a partir de ácido 2,4-difluorobenzoico y de 2-piperidinemetanol como una goma. EIMS: m/z = 236,2 $[M+H]^+$

7C: (±)-1-fluoro-6,6a,7,8,9,10-hexahidro-12H-pirido[2,1-c][11,4]benzoxazepina-12-ona fue obtenido a partir de ácido 2,6-difluorobenzoico y de 2-piperidinemetanol. p.f. 133-134° C; EIMS: m/z = 236,2 $[M+H]^+$

Ejemplo 8

(S)-9-cloro-2,3,11,11a-tetrahidro-1H,5H-pirrolo[2,1-c][1,4]benzoxazepina-5-ona

A una solución de cloruro de 3-cloro-2-fluorobenzoilo (2,2 g; 11,4 mmoles) en dimetilformamida

8X
85

(5 ml) se agregó trietilamina (1,7 ml; 11,7 mmoles) y (S)-(+)-2-pirrolidinemetanol (1,13 ml; 11,4 mmoles). La mezcla fue agitada durante una hora y luego se agregó carbonato de calcio (7,4 g; 22,7 mmoles) y la reacción fue calentada a 120° C durante 5 horas. la reacción fue enfriada a temperatura ambiente y luego diluida con agua y extraída con acetato de etilo. Los orgánicos fueron lavados con agua y secados (Na_2SO_4) y evaporados en vacío. El producto crudo fue purificado por cromatografía sobre sílice (eluyendo con 5% de metanol en diclorometano). Luego de la remoción del solvente la amida pura cristalizada y heptano/éter fue agregado y el compuesto titulado fue recolectado (0,26 g). p.f., 89-90° C; EIMS m/z = 238 $[M+H]^+$

Ejemplo 9

El procedimiento descrito bajo el ejemplo 8 fue usado adicionalmente para preparar los siguientes compuestos:

9A: (S)-6-fluoro-2,3,11,11a-tetrahidro-1H,5H-pirrolo[2,1-c][1,4]benzoxazepina-5-ona fue obtenido de cloruro de 2,6-difluorobenzoilo y (S)-(+)-2-

~~85~~ 86

pirrolidinemetanol. P.f., 149 - 150° C; EIMS m/z = 222,2 $[M+H]^+$

9B: (S)-6-Cloro-2,3,11,11a-tetrahidro-1H,5H-pirrolo[2,1-c][1,4]benzoxazepina-5-ona fue obtenido de cloruro de 2,6-difluorobenzoilo y (S)-(+)-2-pirrolidinemetanol. P.f., 113 - 115° C; EIMS m/z = 238,2 $[M+H]^+$

9C: (S)-6-trifluorometil-2,3,11,11a-tetrahidro-1H,5H-pirrolo[2,1-c][1,4]benzoxazepina-5-ona fue obtenido de cloruro de 2-fluoro-6-trifluorometilbenzoilo y (S)-(+)-2-pirrolidinemetanol. P.f., 175 - 176° C; EIMS m/z = 272,2 $[M+H]^+$

9D: (S)-7-trifluorometil-2,3,11,11a-tetrahidro-1H,5H-pirrolo[2,1-c][1,4]benzoxazepina-5-ona fue obtenido de cloruro de 2-fluoro-5-trifluorometilbenzoilo y (S)-(+)-2-pirrolidinemetanol. P.f., 120 - 121° C; EIMS m/z = 272,4 $[M+H]^+$

9E: (S)-8,9-difluorometil-2,3,11,11a-tetrahidro-1H,5H-pirrolo[2,1-c][1,4]benzoxazepina-5-ona fue obtenido de cloruro a partir de ácido 2,3,4-trifluorobenzoico y

86
87

(S)-(+)-2-pirrolidinemetanol. P.f., 142 - 143° C; EIMS m/z = 272,2 $[M+H]^+$

Ejemplo 10

(S)-2,3,11,11a-tetrahidro-1H,5H-pirrolo[2,1-c][5,1,4]benzotiaoxazepina-5-dióxido

A una solución de cloruro de 2-fluorobencenosulfonilo (1,7 g, 8,8 mmoles) en metilencloruro (50 ml) se agregó trietilamina (1,8 ml; 12,9 mmoles) y (S)-(+)-2-pirrolidinemetanol (1,07 ml; 10,7 mmoles). La mezcla fue agitada durante 7 horas y luego diluida con cloruro de metileno y lavada con ácido clorhídrico al 2M y la capa orgánica fue secada (Na_2SO_4). La evaporación del disolvente dio la sulfonamida cruda la cual fue retirada en 100 ml de dimetilformamida y 1,0 g de hidruro de sodio al 60% en aceite mineral que fue agregado. La mezcla fue agitada durante la noche y luego la evaporación del solvente y el trabajo acuoso seguido por la purificación por cromatografía sobre sílice (eluyendo con acetato de etilo) dio el compuesto titulado como una goma; ^1H RMN (400MHz; $CDCl_3$) δ 1,93 - 2,00 (m,

97
98

3H), 2,20-2,27 (m, 1H), 3,05-3,09 (m, 1H), 3,58,3,63 (m, 1H), 3,94 (dd, 1H), 4,18-4,21 (m, 1H), 4,76 (dd, 1H), 7,09 (dd, 1H), 7,19 (dd, 1H), 7,43 (dd, 1H); EIMS: m/z = 240 $[M+H]^+$

Ejemplo 11

(S)-8-metoxi-2,3,11,11a-tetrahidro-1H,5H-pirrolo[2,1-c][1,4]benzoxazepina-5-ona

Una solución de (S)-8-fluoro-2,3,11,11a-tetrahidro-1H,5H-pirrolo[2,1-c][1,4]-benzoxazepina-5-ona (0,5 g; 2,14 mmoles), preparado como se describió en el ejemplo **5A**, y metóxido de sodio (0,244 g; 4,52 mmoles) en dimetilformamida (2 ml) fue calentado a 110° C durante 3H. La reacción fue diluida con agua y extraída con acetato de etilo y la capa orgánica fue lavada con agua y luego secada (Na_2SO_4) y evaporada en vacío. El producto crudo fue purificado por cromatografía sobre sílice (eluyendo con metanol al 5% en diclorometano) para dar el producto titulado, p.f. 104 - 106° C; EIMS: m/z = 234 $[M+H]^+$

88
89

Ejemplo 12

Sal de hidrocloruro de (S)-8-(1-pirrolo)-2,3,11,11a-tetrahidro-1H,5H-pirrolo[2,1-c][1,4]benzoxazepina-5-ona

Una solución de (S)-8-fluoro-2,3,11,11a-tetrahidro-1H,5H-pirrolo[2,1-c][1,4]-benzoxazepina-5-ona (0,5 g; 2,14 mmoles), preparado como se describió en el ejemplo **5A**, en pirrolidina (1 ml) fue calentado bajo reflujo durante 4 h. la reacción fue diluida con agua y extraída con acetato de etilo y lavada con agua y luego secada (Na_2SO_4) y evaporada en vacío. El producto crudo fue purificado por cromatografía sobre sílice (eluyendo con metanol al 5% en diclorometano) y luego cristalizada a partir de diclorometano al 5% en éter. El producto crudo fue disuelto en diclorometano y convertido a sal de hidrocloruro con HCl en éter y luego el éter fue agregado para precipitar el producto titulado (0,18 g). P.f. 169 - 176° C; EIMS: m/z = 273 $[M+H]^+$

Ejemplo 13

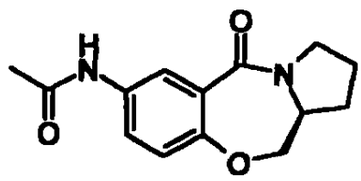
(S)-7-amino-2,3,11,11a-tetrahidro-1H,5H-pirrolo[2,1-c][1,4]benzoxazepina-5-ona

90

Una solución de (S)-7-nitro-2,3,11,11a-tetrahidro-1H,5H-pirrolo[2,1-c][1,4]-benzoxazepina-5-ona (7,4 g), preparado como se describió en el ejemplo 3L, en etanol (100 ml) y metanol (50 ml) fue hidrogenado sobre 10% de paladio en carbón activado bajo hidrógeno a una presión de 2 bar, hasta que la toma del hidrógeno cesó. La muestra fue filtrada parea remover el catalizador y evaporada hasta secado en vacío. El producto crudo fue pasado por una columna corta de sílice (eluyendo con 10% de metanol en diclorometano) para dar el producto título (6,1 g). EIMS: m/z = 219 $[M+H]^+$

Ejemplo 14

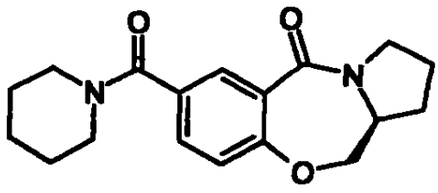
(S)-N-(2,3,11,11a-tetrahidro-5-oxo-1H,5H-pirrolo[2,1-c][1,4]-benzoxazepin-7-il) acetamida



Una solución del material del ejemplo 13 (2,29 mmoles) en anhídrido acético (0,237 ml, 2,5 mmoles) en piridina (5 ml) se le permitió permanecer a temperatura ambiente durante la noche. La reacción diluida con agua y extraída dentro de acetato de etilo, lavada con agua y luego secada (Na_2SO_4) y evaporada en vacío. El producto crudo fue cristalizadora partir de 5% de diclorometano en heptano para dar el producto título (140 mg). p.f. 185 - 187° C; EIMS: m/z = 261 $[M+H]^+$

Ejemplo 15

(S)-7-(piperidinocarbonil)-2,3,11,11a-tetrahidro-5-oxo-1H,5H-pirrolo[2,1-c][1,4]-benzoxazepin-5-ona



Una solución de (S)-7-Bromo-2,3,11,11ª-tetrahidro-1H,5H-pirrolo[2,1-c][1,4]-benzoxazepina-5-ona (0,56 g; 2 mmoles), preparado de acuerdo como se describió en el

ejemplo 3J, junto con piperidina (2 ml) y diclorobis(trifenilfosfina)paladio (II) (63 mg) fue calentado a 110° C bajo atmósfera de monóxido de carbono durante la noche. La evaporación, particionado el residuo entre agua y diclorometano y la evaporación de la capa orgánica se midió por purificación cromatográfica eluyendo con 5% de metanol en diclorometano y la cristalización a partir de acetato de etilo/éter de petróleo dio 400 mg del producto título. P.f. 140 - 140,5° C; EIMS: m/z = 315 $[M+H]^+$

Ejemplo 16

El procedimiento descrito bajo el ejemplo 15 usado adicionalmente para preparar los siguientes compuestos:

16A: (S)-7-(morfolinocarbonil)-2,3,11,11a-tetrahidro-1H,5H-pirrolo[2,1-c][1,4]-benzoxazepin-5-ona

El compuesto titulado fue obtenido usando morfolina en lugar de piperidina como reactivo. P.f. 158-161 °C; EIMS: m/z = 317$[M+H]^+$

92
93

16B: (S)-7-(N-etilpiperazinocarbonil)-2,3,11,11a-tetrahidro-1H,5H-pirrolo[2,1-c]-[1,4]benzoxazepina-5-ona sal de hidrocloruro de lo anterior

El compuesto titulo fue obtenido usando N-etilpiperazina en lugar de piperidina como el reactivo y aislado como una sal de hidrocloruro por cristalización a partir de acetona-eter. P.f.>200 °C; EIMS: m/z = 344 $[M+H]^+$

Ejemplo 17

17A: (S) -7-(aminocarbonil)-2,3,11,11ª-tetrahidro-1H,5H-pirrolo[2,1-c][1,4]benzoxazepina-5-ona

A una solución de (S)-7-Bromo-2,3,11,11a-tetrahidro-1H,5H-pirrolo[2,1-c]-[1,4]-benzoxazepina-5-ona (5 g; 17,76 mmoles), preparado como se describió en el ejemplo **3J**, en dimetilsulfoxido (80ml) se le agregó a acetato (225 mg; 1 mmol), 1,3-bis-(difenilfosfino)propano (413 mg; 1 mmol) trietilamina (5 ml; 36 mmoles) y metanol (4 ml). Después de agitar bajo argon hasta que todos los sólidos han sido disueltos la vasija de reacción fue purgada varias veces con monóxido de carbono y colocada

bajo atmósfera de monóxido de carbono (balón). La mezcla fue entonces calentada a 100° C y agitada durante la noche. Porciones adicionales de acetato de paladio (0,50 mmoles) y 1,3-bis-(difenilfosfino) propano (0,50 mmoles) fueron agregados y la mezcla fue agitada a 100° C durante 6 h. adicionales. Después de enfriar se agregó agua (200 ml) y la solución acuosa fue extraída con tres porciones de 75 ml de acetato de etilo. Los extractos combinados fueron secados (Na_2SO_4) y el disolvente evaporado bajo presión reducida. El aceite café resultante fue purificado por cromatografía de columna eluyendo con acetato de etilo. Una purificación adicional por recristalización a partir de dietil éter dio (S)-2,3,11,11a-tetra-hidro-1H, 5H-pirrolo[2,1-c][1,4]benzoxazepina-5-ona-7-carboxilato de metilo (3,13 g) como un sólido cristalino blanco.

A una solución de este éster de metilo (2,54 g; 9,73 mmoles) en metanol (40 ml) se agregó hidróxido de sodio 4M (12 ml). La mezcla fue calentada bajo reflujo durante 1,5h y luego se le permitió enfriarse a temperatura ambiente. El metanol fue evaporado bajo presión reducida y la solución acuosa fue acidificada con HCl acuoso al 1M. El precipitado resultante fue filtrado retirado y

secado bajo vacío para dar ácido (S)-2,3,11,11a-tetrahidro-1H,5H-pirrilo[2,1-c][1,4]benzoxazepina-5-ona-7-carboxilico (2,39 g) como un sólido muy blanco.

Una solución del anterior derivado de ácido carboxílico (2,38 g; 9,64 mmoles) en cloruro de tionilo (10 ml) fue calentado bajo reflujo durante 1,5 h. el cloruro de tionilo en exceso fue evaporado bajo presión reducida para dar cloruro de ácido (S)-2,3,11,11a-tetrahidro-1H,5H-pirrilo[2,1-c][1,4]benzoxazepina-5-ona-7-carboxilico (2,56 g) como un sólido amarillo pálido.

Una solución del cloruro ácido (1,02 g; 3,85 mmoles) en diclorometano (8 ml) fue agregado a una solución agitada de 38% de amoniaco acuoso (5 ml). Depuse de agitar durante 20 minutos el diclorometano fue removido bajo presión reducida. El precipitado blanco que se había formado fue recolectado por filtración y secado baja vacío para dar el compuesto titulado (886 mg) como un sólido blanco. P.f. 287-290° C; EIMS; m/z = 247,4 $[M+H]^+$

17B: (R)-7-(Aminocarbonil)-2,3,11,11a-tetrahidro-1H,5H-pirrilo[2,1-c][1,4]benzoxazepina-5-ona fue obtenido siguiendo el método del ejemplo **18A** partiendo del

95
96

material preparado en el ejemplo 3I. P.f. 290-295 °C EIMS: m/z = 247,2 $[M+H]^+$

Ejemplo 18

(R)-7-(Metilaminocarbonil)-2,3,11,11a-tetrahidro-1H,5H-pirrilo[2,1-c][1,4]benzoxazepina-5-ona

Una solución de cloruro de ácido (R)-2,3,11,11a-tetrahidro-1H,5H-pirrilo[2,1-c][1,4]benzoxazepina-5-ona-carboxílico (0,330 g; 1,24 mmoles), preparado como se describió en el ejemplo 17A, partiendo del material descrito en el ejemplo 3I, en diclorometano (3 ml) fue agregado gota a gota a una solución agitada al 10% de metilamina en tetrahidrofurano, la mezcla fue agitada a temperatura ambiente durante 1h. adicional y luego evaporada hasta secado bajo presión reducida. El residuo fue retirado en diclorometano (20 ml) y lavado con HCL al 0,5M (2 x 20 ml). La capa de diclorometano fue secada ($MgSO_4$) y el disolvente evaporado bajo presión reducida. La recristalización del producto crudo a partir de acetato de etilo/dietil éter dio el compuesto titulado (0,262 g) como un sólido blanco. P.f. 186-189 °C; EIMS: m/z = 261.0 $[M+H]^+$

96
97

Ejemplo 19

(R)-7-ciano-2,3,11,11a-tetrahidro-1H,5H-pirrilo[2,1-c][1,4]benzoxazepina-5-ona

A una solución agitada de el material preparado en el ejemplo **17B** (1,57 mmoles) en dimetilformamida (5 ml) bajo una atmósfera de nitrógeno se agregó oxicloruro fosforoso (731 µl; 7,85 mmoles). La mezcla fue agitada durante 0,5 h a 80 °C. Después de enfriar se agregó agua (20 ml) y luego de agitación un precipitado blanco se formó. El precipitado fue recolectado por filtración, lavado con agua y secado bajo vacío para dar el compuesto titulado (261 mg). P.f. 164-165 °C; EIMS: m/z = 229,0 $[M+H]^+$

Ejemplo 20

20A: (11R, 11aS)-11-etil-2,3,11,11a-tetrahidro-1H,5H-pirrolo[2,1-c][1,4]benzoxazepina-5-ona

A ácido 2-clorobenzoico (10 g; 63,9 mmoles) en dimetilformamida (100 ml) bajo nitrógeno se agregó

97
98

carbonildiimidazol (10,9 g; 67,1 mmoles) y la solución fue agitada durante 1 h a temperatura ambiente. (S)-(+)-2-pirrolidinemetanol (7,56 ml, 76,6 mmoles) se agregó y la mezcla se agitó a 40° C durante 18 horas. el disolvente fue removido bajo presión reducida y el producto crudo purificado por cromatografía sobre sílice (eluyendo con 50% a 75% de acetato de etilo en heptano) para proporcionar (S)-1-(2-clorobenzoil)-2-pirrolidinemetanol (10,2 g), el cual fue usado directamente en la siguiente etapa.

Tetrahidrofurano (24 ml) fue enfriado a -60° C con agitación y se agregó cloruro de oxalilo (1,15 ml, 13,2 mmoles). Luego se agregó gota a gota dimetilsulfóxido (0,98 ml, 13,8 mmoles). La mezcla fue agitada durante 20 minutos, luego una solución de 1-(2-clorobenzoil)-2-pirrolidinemetanol (3,0 g, 12,5 mmoles) en tetrahidrofurano (24 ml) se agregó gota a gota durante 15 minutos. Luego de 15 minutos adicionales, la mezcla fue tratada con trietilamina (7,0 ml, 50,1 mmoles). La mezcla fue calentada brevemente a 0° C antes de reenfriarse a -78° C. Bromuro de etilmagnesio (3,0 M endietiléter; 16,7 ml, 50,1 mmoles) se agregó gota a gota a la mezcla de reacción agitada vigorosamente. La reacción fue calentada

98
99

a -40° C durante 1 h, reenfriada a -78° C y luego tratada con cuidado con etanol (5 ml) seguido por una solución de cloruro de amonio saturada. La mezcla se le permitió calentarse a temperatura ambiente, y luego se extrajo con acetato de etilo (ca. 150 ml). La capa orgánica fue secada (Na_2SO_4) y concentrada para proporcionar (2S,αRS)-1-(2-clorobenzoilo)-α-etil-2-pirrolidinemetanol crudo como una mezcla de diastereoisómeros. El producto crudo fue disuelto en dimetilformamida (100 ml) bajo nitrógeno. Hidruro de sodio (60% en dispersión en aceite mineral, 1,0 g, 25,0 mmoles) fue agregado en proporciones. La reacción fue agitada temperatura ambiente durante 30 minutos y luego calentada a 120° C durante 5, después de lo cual la temperatura fue reducida a 80° C durante 16 h adicionales. La reacción se le permitió enfriarse a temperatura ambiente y luego se calmó con metanol (16 ml) y se agitó durante 10 minutos. Los disolventes fueron removidos bajo presión reducida. El residuo fue retirado en agua (50 ml) y extraído con diclorometano (2 x 50 ml) para proporcionar el producto como una mezcla cruda de distereoisómeros (proporción aproximada 30:70). La cromatografía de destello sobre sílice (eluyendo con 0% a 80% de acetato de etilo en heptano) proporcionó el

99
100

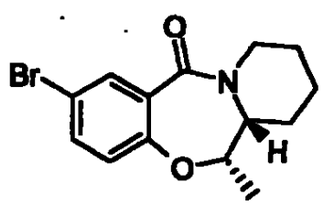
compuesto titulado (80 mg) como un aceite sin color; ^{1}H RMN (400MHz; $CDCl_3$) δ 4,24 (1H, dt, J 10,5, Hz, 11-H); EIMS: m/z = 232 $[M+H]^+$

20B: (11S), 11aS)-11<etil-2,3,11,11a-tetrahidro-1H,5H-pirrol[2,1-c][1,4]benzoxazepine-5-ona

Elusión adicional de la mezcla preparada en el Ejemplo 20A dio el compuesto titulado, el cual fue recristalizado a partir de acetato de etilo/heptano para proporcionar un producto cristalino blanco. p.f. 18 - 119° C; ^{1}H RMN (400MHz; $CDCl_3$) δ 4,04 (1H, td, J 0 9,8, 2,5Hz 11-H); EIMS: m/z = 323 $[M+H]^+$.

Ejemplo 21

21A: (6RS,6aSR)-2-Bromo-6-metil-6,6a,7,8,9,10-hexahidro-12H-pirido[2,1-c][1,4]-benzoxazepina-12-ona



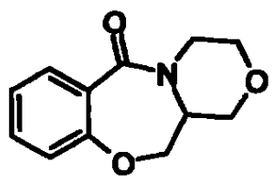
El compuesto titulado fue preparado siguiendo el métododel ejemplo **20A**, usando ácido 5-bromo-2-clorobenzoico, (RS)-2-piperidinemetanol y bromuro de metilmagnesio. P.f. 1105-1106° C; EIMS: m/z = 312 $[M+H]^+$

21B: (6RS,6aRS)-2-Bromo-6-metil-6,6a,7,8,9,10-hexahidro-12H-pirido[2,1-c][1,4]-benzoxazepina-12-ona

Este enantiómero fue obtenido con elusión adicional de la mezcla obtenida del ejemplo **21A** que dio el producto titulado, p.f. 105 - 107° C; EIMS: m/z = 312 $[M+H]^+$

Ejemplo 22

6,6a-dihidro-12H-dihidro-12H-morfolino[3,4-c][1,4]benzoxazepin-12-ona



Una solución de ácido morfolin-3-carboxílico (4,035 g; 30,8 mmoles) en metanol (250 ml) fue saturado con HCl gaseoso, y luego agitado durante una semana. El disolvente fue evaporado y el residuo fue retirado en agua y se hizo básica (pH ~ 10) con carbonato de hidrógeno de sodio y carbonato de sodio. La mezcla fue entonces extraída con diclorometano (7x), los extractos combinados secados (Na_2SO_4) y el disolvente evaporado para dar morfolin-3-carboxilato de etilo (746 mg). EIMS: m/z = 160,4 $[M+H]^+$. Este derivado de éster e hidruro de litio aluminio (1 M en THF, 9,4 ml, 9,4 mmoles) fue combinado cuidadosamente bajo atmósfera de nitrógeno luego de la adición fueron calentados hasta reflujo. Después de 5 h la reacción fue enfriada a temperatura ambiente y calmada cuidadosamente usando una adición de agua gota a gota con hielo de enfriamiento, y luego se filtró y se lavó con diclorometano. El disolvente fue evaporado para dar 3-(hidroximetil)morfolina (409 mg). EIMS: m/z = 118,2 $[M+H]^+$

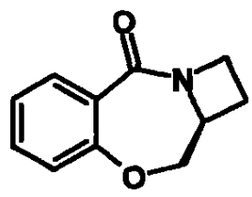
A una solución de 3-(hidroximetil)morfolina (345 mg; 2,95 mmoles) en diclorometano (10 ml) se agregó cuidadosamente cloruro de 2-fluorobenzoilo (0,35 ml; 2,95

102
103

mmoles) y trietilamina (0,62 ml; 4,42 mmoles) y la reacción fue agitada durante 0,5 h. el producto fue combinado con NaOH al 4 N (10 ml) para hidrolizar cualquier éster y la capa orgánica fue extraída (diclorometano, 3 x). Las capas orgánicas combinadas fueron secadas (Na_2SO_4) y el disolvente evaporado para dar un aceite, el cual fue purificado por cromatografía de columna de destello sobre sílice (gradiente de elusión diclorometano - metanol 1:0 a 9:1) para dar 4-(2-fluorobenzoil)-3-(hidroximetil)morfolina (1665 mg; 0,69 mmoles) EIMS: m/z = 240,2 $[M+H]^+$. Este producto el carbonato de cesio (0,544 g) fueron calentados a 120° C en dimetilformamida (10 ml) bajo nitrógeno durante 4 horas. el disolvente fue evaporado, y el residuo fue retirado en agua y extraído con diclorometano (3 x). Los extractos de diclorometano combinados fueron secados (Na_2SO_4) y el disolvente evaporado para dar un sólido crudo que fue purificado por cromatografía de columna de destellos sobre sílice eluyendo con éter para dar el compuesto titulado (77 mg). p.f. 1105-107° C. EIMS: m/z = 220,2 $[M+H]^+$.

4 ejemplo 23

(S)-1,2,10,10a-tetrahidroazetidinil[2,1-c][1,4]benzoxazepin-4-ona



N-metilmorfolina (1,35 ml, 12 mmoles) fue agregado a una solución agitada de ácido (S)-acetinida-2-carboxílico (1,08 g; 10 mmoles) y di-tert-butil-dicarbonato (3,03 g; 114 mmoles) en 1,4-dioxano: agua (1:1, 30 ml) enfriada a 0° C. El sistema se le permitió agitarse durante 18 h con permiso de la temperatura para elevarse lentamente a temperatura ambiente. Una solución de bicarbonato de sodio saturada (15 ml), enfriada 5° C fue agregada y el sistema fue lavado con acetato de etilo (3 x 75 ml). La fase acuosa fue entonces acidificada a un pH 3 por la adición de sulfato de potasio hidrógeno. La fase acuosa fue entonces extraída con acetato de etilo (3 x 100 ml) estas capas orgánicas fueron combinadas, secadas ($MgSO_4$), filtradas y el disolvente removido en vacío para dar el

producto ácido (S)-N-tert-butoxicarbonil-azetidina-2-carboxílico (2,15 g) como un aceite viscoso. EIMS: m/z = 201 $[M+H]^+$. El complejo de Borano-THF (solución al 1M, 35 ml, 35 mmol) fue agregado lentamente a una solución agitada del ácido carboxílico anterior en tetrahidrofurano seco enfriado a menos de 5° C bajo nitrógeno. La reacción se le permitió agitarse durante 18 h, con la temperatura elevándose lentamente hasta temperatura ambiente. El sulfato de hidrógeno de potasio acuoso al 10% (10 ml) fue entonces agregado gota a gota. Componentes volátiles fueron evaporados en vacío y la lechada remanente fue extraída con acetato de etilo (3 x 75 ml). La fase orgánica combinada fue secada ($MgSO_4$), filtrada y el disolvnete removidoen vacío para dar el producto (S)-N-tert-butoxicarbonil-2-hidroximetilazetidina como un aceite viscoso (11,48 g, 74%), m/z $[M+H]^+$ 210.

Ácido trifluoroacético (5 ml) en diclorometano (5 ml) fueron agregados a una solución agitada de (S)-N-tert-butoxicarbonil-azetidin-2-ilmetanol (1,17 g, 6,25 mmoles) en diclorometano (8 ml) enfriada ~ 5° C bajo nitrógeno. La reacción fue agitada durante 18 horas con

106

la temperatura subiendo lentamente hasta temperatura ambiente. El disolvente y el ácido en exceso fueron removidos en vacío para dar el producto sal de trifluoroacetato de (S)-2-hidroximetilacetidina como un aceite viscoso (1,26 g). se agregó trietilamina (0,61 ml, 4,38 mmoles) lentamente a una solución de 0,19 g de sal de trifluoroacetato de (S)-2-hidroximetilacetidina (0,94 mmoles) y cloruro de 2-fluorobenzoilo (0,16 ml, 1,30 mmoles) en diclorometano (8 ml) enfriado aproximadamente 5° C y bajo nitrógeno. La reacción agitada durante 18 h con la temperatura elevándose lentamente hasta temperatura ambiente. Se agregaron agua (15 ml) y diclorometano (20 ml) y las capas fueron separadas. La capa acuosa fue lavada con m{as diclorometano (20 ml) y capas orgánicas combinadas fueron secadas (MgSO4), mientras el disolvente removido es vacío. El residuo crudo fue purificado por cromatografía sobre gel de sílice usando acetato de etilo: éter de petróleo (40/60 1:1), como eluyente dando (S)-N-(2-fluorobenzoil)-2-hidroximetilacetidina (0,15 g; 0,72 mmoles) cxomo un agente viscosso, EIMS: m/z = 192 $[([M+H])-H_2O]^+$

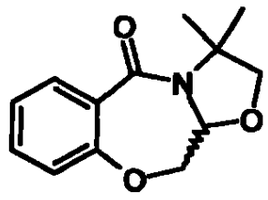
El producto crudo fue disuelto en dimetilformamida seca (5 ml) y carbonato de cesio anhidroso (0,28 g, 0,87

mmoles) fue agregado a la solución agitada. La temperatura fue incrementada hasta 110° C y la reacción fue agitada durante 18 h. después de enfriamiento, la dimetilformamida fue removida al vacío. El residuo fue entonces separado en agua (20 ml) y extraído con diclorometano (2 x 25 ml). Las capas orgánicas combinadas fueron secadas ($MgSO_4$), filtradas y el disolvente removido en vacío. El residuo crudo fue purificado por cromatografía sobre del de sílice usando acetato de etilo: éter de petróleo (40/60) 4:1 como eluyente dando el producto titulado (50 mg) como un sólido blanco. P.f. 148 - 149° C; ^1H RMN (400 MHz; $CDCl_3$) δ 2.11-2.17 (m, 2H), 2.54-2.58 (m, 2H), 4,07-4,16 (m, 1H), 4,19 (dd, 1H), 4,28 - 4,32 (m, 1H), 4,45 (dd, 1H), 4,65-4,79 (m, 1H), 6,97 (d, 1H), 7,05 (dd, 1H), 7,38 (ddd, 1H), 8,11 (dd, 1H); EIMS: m/z = 190 $[M+H]^+$

Ejemplo 24

2,11,11a,trihidro-3,3-dimetiloxazolidinil[2,1-c][111,4]-benzoxazepin-5-ona

105
108



2-amino-2-metil-1-propanol (9,54 ml, 0,10 mol) fue agregado a una solución agitada de glioxilato de etilo (50% de solución, en tolueno, 21 ml, 0, 10 moles) en diclorormetano (100 ml) en la presencia de tamices moleculares de 4 Å. La reacción fue agitada bajo nitrógeno durante 16 h después de los cual el sistema fue filtrado a través de Dicalite® y lavado con más diclorometano. La evaporación del disolvente pasivo dio (un éster de etilo de ácido (1,1-dimetil-2-hidroxi-etilimino)-acético (17,0 g) como un aceite (EIMS: m/z = 174 $[M+H]^+$. Cloruro de 2-fluorobenzoilo (0,60 ml, 5,0 mmoles)y luego piridina (0,96 ml, 12,0 mmoles) fueron agregados a una solución agitada del éster de etilo descrito anteriormente (0,87 g, 5,00 mmoles) en diclorometano (8 ml) enfriado a aproximadamente 5° C y bajo nitrógeno. Luego de 1,5 h se agregó agua (20 ml), las capas separadas y la fase acuosa fueron lavadas con más diclorometano (30 ml). La fase orgánica combinada fue

entonces lavada con ácido clorhídrico al 1 N (25 ml) antes de ser secada ($MgSO_4$), filtrada y el disolvente removidoen vacío. El residuo crudo fue purificado por cromatografía sobre sílice usando diclorometano como eluyente, para dar éster de etilo de ácido 3-(2-fluorobenzoil)-4,4-dimetil-oxazoliddina-2-carboxílico (0,64 g) como un aceite, EIMS: m/z = 296 $[M+H]^+$

borohidruro de litio en exceso fue agregado a una solución agitada del éster de etilo de ácido 3-(2-fluorobenzoil)-4,4-dimetil-oxazoliddina-2-carboxílico (0,47 g, 1,58 mmoles) en dietiléter seco (5 ml). Tolueno seco (8 ml) fue entonces agregado y el sistema fue calentado a 100° C. después de dos horas, el dietiléter fue destilado retirado como se describió por H. C. Brown et al (J. Org. Chem., 1982, 47(24) 4702). Después de 6 h de calentamiento, el sistema se le permitió enfriarse y entonces el tolueno fue removido en vacío. Ácido acuoso (HCl al 5 N: H_2O = 1:3 v/v; 8 ml) fue entonces agregado y el sistema fue agitado a temperatura ambiente durante 1 h. carbonato de potasio fue entonces agregado para saturar la solución acuosa la cual fue entonces extraída con dietiléter (2 x 25 ml). Las capas orgánicas combinadas fueron secadas ($MgSO_4$), filtrada y el

disolvente removido en vacío. El residuo crudo fue purificado por cromatografía sobre gel de sílice usando diclorometano:metanol 19:1 como eluyente. Este dio (±)-3-(2-fluorobenzoil)-4,4-dimetil-2-hidroximetil-oxazolidina (0,30 g) como un agente viscoso, EIMS: m/z = 254 $[M+H]^+$

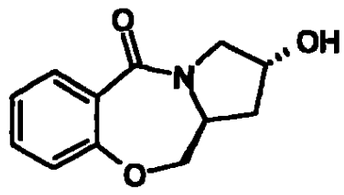
carbonato de cesio (0,60 g, 1,85 mmoles) fue agregado a una solución agitada de la oxazolidina descrita anteriormente (0,31 g, 1,23 mmoles en dimetilformamida seca (5 ml). La mezcla de reacción fue calentada a 130° C y agitada durante 18 h. después de enfriamiento, la dimetilformamida fue removida en vacío, el agua (10 ml) fue agregada al residuo el cual fue entoncesextraído condiclorometano (3 x 30 ml). Las capas orgánicas combinadas fueron secadas ($MgSO_4$), filtradas y el solvente removido en vacío. El residuo crudo fue purificado por cromatografía sobre gel de sílice usando éter de petróleo (40/60): acetato de etilo 4:1 v/v como eluyente para dar el producto titulado (0,23 g) como un sólido ceroso blanco.

p.f. 65,5° C; ^1H RMN (400MHz; $CDCl_3$) δ 1,59 (s, 3H), 1,64 (s, 3H), 3,76 (d, 1H), 3,90 (d, 1H), 4,02 (dd, 1H),

111

4,54 (dd, 1H), 5,18 (dd, 1H), 6,96 (d, 1H), 7,08 (ddd, 1H), 7,36 (ddd, 1H), 8,06 (dd, 1H); EIMS: m/z = 234 $[M+H]^+$

Ejemplo 25



(2R,11aS)-2-hidroxi,3,11,11a-tetrahidro-1H,5H-pirrolo[2,1-c][1,4]benzoxazepina-5-ona

A un lodo agitado de (3R,5,S)-3-hidroxi-5-hidroximetilpirrolidina (3,67 g; 23,9 mmoles) (M. W. Reed et al, J. Med. Chem., 1995, 38, 4587-4596) y diisopropiletilamina (9,3 ml; 52,58 mmoles) en diclorometano anhidro (30 ml bajo una atmósfera de nitrógeno se agregó gota a gota cloruro de 2-fluorobenzoilo (3,8 g; 23,9 mmoles) mientras se mantuvo la temperatura por debajo de 25° C por medio de un balón

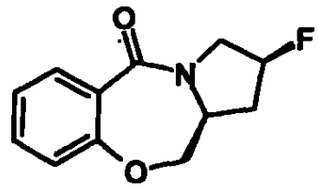
en hielo. La mezcla se le permitió agitarse a temperatura ambiente durante la noche y luego evaporada bajo presión reducida. La mezcla resultante fue retirada en acetato de etilo (100 ml), lavada con agua (2 x 50 ml) y secada (Na_2SO_4). El disolvente fue evaporado bajo presión reducida y el residuo purificado por cromatografía de destello eluyendo con 1:9 de metanol en diclorometano para dar la amina intermedia (5,2) como un aceite sin color, EIMS: m/z = 240,2 $[M+H]^+$. Esta amida (21,76 mmoles) fue suspendida en dimetilformamida (70 ml) y carbonato de cesio (8,5 g;; 26,1 mmoles) fue agregado y la suspensión fue agitada bajo una atmósfera de nitrógeno a 110° C durante 16 horas. la mezcla fue entonces evaporada hasta secado bajo presión reducida y el residuo fue retirado en 100 ml de acetato de etilo. La solución fue lavada con agua (80 ml) y la capa de agua entonces fue extraída con acetato de etilo adicional (100 ml). Los extractos orgánicos combinados fueron entonces lavados con salmuera (2 x 50 ml) y secados (Na_2SO_4). El disolvente fue evaporado bajo presión reducida y el residuo fue purificado adicionalmente por cromatografía de destello eluyendo 7% de MeOH en cloruro de metileno para dar el compuesto titulado (2,2 g) como un sólido cristalino

113

blanco. ^{1}H RMN (400MHz; $CDCl_3$) δ 2,75 a 2,87 (m, 1H), 2,02 (d, 1H), 2,2 a 2,30 (m, 1H), 3,857 (d, 2H), 4,03 a 4,07 (m, 1H), 4,24 (q, 1H), 4,48 (d, 1H), 4,55 (s, 1H), 6,97 (d, 1H), 7,06 (t, 1H), 7,36 (t, 1H), 8,109 (t, 1H); EIMS: m/z = 220,2 $[M+H]^+$

Ejemplo 26

(2S,11aS)-2-fluoro-2,3,11,11a-tetrahidro-1H,5H-pirrolo[2,1-c][1,4]benzoxazepina-5-ona

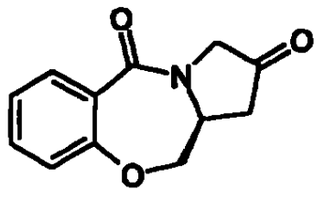


Una solución de material de preparada en el ejemplo 25 (200 mg; 0,91 mmoles) en acetato de etilo seco (10 ml) fue enfriado a -50° C y se agregó gota a gota trifluoruro de (dietilamino)azufre (191 mg; 1,19 mmoles). La solución resultante fue agitada a -50° C durante 1 h y se le permitió calentarse lentamente hasta temperatura ambiente durante un periodo de 3 h. La mezcla fue entonces vertida en una solución de $NaHCO_3$ acuosa saturada (50 ml) y se

agregó acetato de etilo adicional (50 ml). Después de un mezclado fuerte la capa orgánica fue separada, lavada secuencialmente con agua (50 ml) y salmuera (50 ml), y secada (Na_2SO_4). El disolvente fue evaporado bajo presión reducida y el residuo fue purificado por cromatografía de destellos para dar el compuesto titulado como un sólido cristalino amarillo pálido (60 mg). ^1H RMN (400MHz; $CDCl_3$) δ 2,13 a 2,48 (m, 2H), 3,79 (qd, 1H), 4,09 (t, 1H), 4,25 a 4,35 (m, 2H), 4,43 - 4,49 (m, 1H), 5,333 (d, 1H), 7,04 (d, 1H), 7,15 (t, 1H), 7,41 (dd, 1H), 7,88 (dd, 1H); EIMS: m/z = 222,2 $[M+H]^+$

Ejemplo 27

(S)-2-oxo-2,3,11,11a-tetrahidro-1H,5H-pirrolo[2,1-c][1,4]benzoxazepina-5-ona



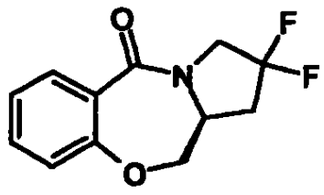
A una solución agitada de cloruro de benzalilo (0,52 ml; 5,94 mmoles) en diclorometano seco (15 ml) enfriado a

-78° C se agregó una solución de dimetilsulfóxido (0,81 ml, 11,42 mmoles) en diclorometano seco (2 ml). La agitación fue continuada durante 10 minutos seguido por la adición gota a gota de una solución del material (1 g) preparado en el ejemplo **25** (5,57 mmoles) en diclorometano seco (10 ml). La mezcla fue agitada durante unos 15 minutos adicionales y luego se agregó trietilamina (3,8 ml; 27,3 mmoles). Después de agitar a -78° C durante 10 minutos adicionales la mezcla se le permitió calentarse hasta 0° C antes de que se agregara acetato de etilo (50 ml) y agua (50 ml). Después de un mezclado fuerte la capa orgánica fue separada, lavada secuencialmente con HCl al 1 M (50 ml) y salmuera (50 ml), y secada (Na_2SO_4). El disolvente fue removido bajo presión reducida y el residuo fue purificado por cromatografía de destello eluyendo con MeOH al 3% en cloruro de metileno para dar el producto titulado (220 mg) que fue recristalizado una vez del mínimo de acetato de etilo caliente, ^1H RMN (400MHz; $CDCl_3$) δ 2,13 a 2,41 (dd, 1H), 2,87-2,93 (m, 1H), 4,15-4,33 (m, 3H), 4,45 a 4,49 (m, 2H), 7,06 (d, 1H), 7,18 (t, 1H), 7,44 (dd, 1H), 8,03 (dd, 1H); EIMS: m/z = 218,4 $[M+H]^+$

116

Ejemplo 28

(2S)-2,2-difluoro-2,3,11,11a-tetrahidro-1H,5H-pirrolo[2,1-c][1,4]benzoxazepina-5-ona



A una solución del material preparado en el ejemplo 27 en cloruro de metileno (5 ml) se agregó trifluoruro de dietilaminoazufre (254 mg; 1,5 mmoles) la reacción fue agitada durante dos días a temperatura ambiente luego calmada por la adición de hielo y lavada con agua (10 ml) y saturada con una solución de bicarbonato de sodio (10 ml) y secada (Na_2SO_4). La evaporación y purificación por cromatografía de destello eluyendo con 19:1 de cloruro de metileno- éter proporcionó el compuesto titulado como un sólido muy blanco (63 mg). p.f. 116-5-119,5° C; EIMS: m/z = 240,0 $[M+H]^+$

117

Ejemplo 29: Electrofisiología por Pinchamiento de Membrana de Célula Completa

A: Cultivo de células

Neuronas hipocAMPAles fueron preparadas a partir de ratas Sprague-Dawley embriónicas o de 1 a 3 días de nacidas que fueron decapitadas y las cabezas colocadas inmediatamente en hielo frío HBS (solución amortiguada HEPES: 130 mM de NaCl, 5,4 mM de KCl, 10 mM de HEPES, 1,0 mM de $MgCl_2$, 1,8 $CaCl_2$, 25 mM de glucosa ajustado a un pH de 7,4). El cerebro completo fue cortado y colocado en papel de filtro preesterilizado, sumergido en HBS y el cerebelo fue removido. El cerebro fue cortado en pedazos y una solución de enzima (0,5 mg/ml de proteasa X y 0,5 mg/0,5 mg/ml de proteasa en HBS) se agregó y subsecuentemente se elevó durante 40 minutos a temperatura ambiente para digerir antes de la trituración. Las células fueron resuspendidas y luego cortadas para dar una concentración final de 1,5 x 10^6 por ml. Las células fueron alicuotadas cubiertas de poli-D-lisina- y Matrigel® y dejadas en incubación a 37° C durante una a dos horas. Cuando la incubación fue completa, 1 ml del medio de crecimiento fue agregado a

117
118

cada pozo que contenía una cubierta de deslizamiento y las células fueron regresadas a la incubadora. Después de 3 a 5 días la citocina arabinocida inhibidora metótica (5 µm) fue agregada y las células regresaron a la incubadora hasta que se requirió.

B: Registro de Pinchamiento de Membrana

La configuración de célula completa de la técnica de pinchamiento de membrana (Hamill et al., Pflügers Arch. 1981, 39, 85-100) fue usada para medir las corrientes evocadas por glutamato de las neuronas hipocAMPAles postnatales retenidas en el cultivo durante 4 a 7 días. Una cubierta de deslizamiento de vidrio que contenía el cultivo fue transferida a la cámara de grabación (Warner Instrument Corp., Hamden, CT) montada sobre una etapa de un microscopio invertido (Nikon, Kingston, UK). La cámara de registro o grabación contenía 1 a 2 ml de solución extracelular (145 mM de NaCl, 5,4 mM de KCl, 10 mM de HEPES, 0,8 mM de $MgCl_2$, 1,8 $CaCl_2$, 10 mM de glucosa y 30 mM de sacarosa, ajustadas a un pH de 7,4 con NaOH al 1 M) y fue perfundida a una velocidad de 1 ml/min. Los registros fueron llevados a cabo a temperatura ambiente

118

119

(20 a 22° C) usando un amplificador Axopach 200B (Axon Instruments Ltd., Foster City, CA). La adquisición de datos y el análisis de ellos fue llevado a cabo usando un soporte lógico Signal (Cambridge Electronic Design Ltd., Cambridge, UK). Las pipetas fueron fabricadas de vidrio GC120F-10 (Harvard Apparatus, Edenbridge UK) usando un halador de electrodo modelo P-87 (Sutter Instruments Co., Novarto, CA). Los electrodos de pinchamiento tenían resistencias típicas entre 3 a 5 MΩ cuando fueron llenadas con solución intracelular (140 mM de gluconato de potasio, 20 mM de HEPES, 1,1 mM de EGTA, 5 mM de fosfocreatina, 3 mM de ATP, 0,3 mM de GTP, 0,1 mM de $CaCl_2$, 5 mM de $MgCl_2$, ajustados a un pH de 7,4 con KOH al 1 M).

Las células fueron pinchadas con voltaje a un potencial sostenido de 60 mV y glutamato (0,5 ml) fue aplicado usando un dispositivo de aplicación de droga de canal semi rápido 12 (DAD-12. Digitimer Ltd., Welwyn Garden City, UK). El glutamato agonista fue aplicado durante 1 segundo cada 30 s. La respuesta no se frenó durante el tiempo usando la configuración de célula completa. Entre las aplicaciones la salina fluyó para

clarificar cualquier volumen muerto en el sistema. Para cada aplicación corrientes estables fueron graficadas a partir de la diferencia en la línea base y la corriente de estado estable y promediados sobre 30 ms.

Dos soluciones del compuesto en la solución extracelular fueron levantadas, una con glutamato y otra sin glutamato. El protocolo fue: aplicación en 10 segundos del compuesto, aplicación de 1 segundo de compuesto + glutamato y luego 10 segundos lavado con salina, luego un espacio de 10 segundos. Cuando el compuesto no era soluble, se usó 0,5% de MSO como un codisolvente. Los resultados se presentan en la tabla 1 como incremento en porcentaje en la corriente de estado estable a 10 μm de concentración y el compuesto de la invención es la solución extracelular.

Ejemplo 30

Refuerzo diferencial de ratas bajas de respuesta, 72 segundos (DRL72)

120

121

Las ratas fueron preentrenadas en una cama operante estándar para llevar a cabo un procedimiento DRL 72 de acuerdo con Andrews et al (Andrews JS, Jansen JHM, Linders S, Princen A, Drinkenburg WHIM, Coenders CJH y Vossen (1994). Los efectos de la imipramina ymirtazapina en el comportamiento operante en las ratas. Drug Develoment Research, 32:58-66). La sesión de ensayos duró 60 minutos sin ningún límite en número de ensayos. Cada ensayo se inició con luz de estímulo sobre el nivel activo. Una respuesta sobre la palanca solo resulta en el suministro de una pepita si han pasado 72 segundos. Una respuesta sobre la palanca antes de 72 segundos ha caducado en el reposicionamiento del temporizador y no es premiado. El número de pepitas ganadas y el número de palancas presionadas se registra y es usado para calcular un registro de eficiencia. Los compuestos de ensayo son administrados vía intraperitoneal 30 minutos antes de iniciar la sesión de ensayos. Los antidepresivos incrementan el número de pepitas ganadas y disminuye el número de palancas presionadas (Andrews et al., 1994).

(S)-9-fluoro-2,3,11,11a-tetrahidro-1H,5H-pirrolo[2,1-c][1,4]benzoxazepina-5-ona (Ejemplo **3B**) exhibió un perfil similar antidepresivo.

122

Ejemplo 31

Inhibición de la hiperlocomoción inducida por amfetamina

Los ratones fueron inyectados sc con droga o con un control de vehiculo. 30 minutos después los ratones fueron inyectados son 1,5 mg/kg de sulfato de d-amfetamina o salina e inmediatamente se colocan en cajas locomotoras de infrarrojos en donde la actividad locomotora (duración larga de interrupciones del rayo de dos rayos adyacentes) y comportamiento estereotípico (interrupción corta de interrupciones de rayo repetitivas) fueron medidos durante un periodo de 60 minutos. El experimento fue analizado usando un ANOVA de tres vías con una sesión experimental, cajas locomotoras de infrarrojos y en tratamientos como factores, y en el caos de tratamiento, efectos significativos fueron seguidos usando un ensayo Tukey (HSD). (S)-2,3,11,11a-tetrahidro-1H,5H-pirrolo[2,1-c][1,4]benzoxazepina-5-ona y (R)-9-fluoro-2,3,11,11a-tetrahidro-1H,5H-pirrolo[2,1-c][1,4]benzoxazepina-5-ona (Ejemplo **3A**) mostraron

12R
123

actividad antisicótica similar a la que mostraron la hiperlocomoción inducida por anfetamina inhibida.

Tabla I

Compuesto	% de incremento en la corriente estable a 10 μM
(S)-2,3,11,11a-tetrahidro-1H,5H-pirrolo[2,1-c][1,4]benzoxazepina-5-ona*	53
(R)-2,3,11,11a-tetrahidro-1H,5H-pirrolo[2,1-c][1,4]benzoxazepina-5-ona	24
(R)-7-fluoro-2,3,11,11a-tetrahidro-1H,5H-pirrolo[2,1-c][1,4]benzoxazepina-5-ona (Ejemplo 1)	17
(S)-7-fluoro-2,3,11,11a-tetrahidro-1H,5H-pirrolo[2,1-c][1,4]benzoxazepina-5-ona (Ejemplo 2)	19
(R)-9-fluoro-2,3,11,11a-tetrahidro-1H,5H-pirrolo[2,1-c][1,4]benzoxazepina-5-ona (Ejemplo 3A)	23
(S)-9-fluoro-2,3,11,11a-tetrahidro-	20

123
124

1H,5H-pirrolo[2,1-c][1,4]benzoxazepina-5-ona (Ejemplo **3B**)	
(S)-2,3,11,11a-tetrahidro-1H,5H-pirrolo[2,1-c][1,4]benzoxazepina-5-dióxido (Ejemplo **10**)	7
(S)-8-metoxi-2,3,11,11a-tetrahidro-1H,5H-pirrolo[2,1-c][1,4]benzoxazepina-5-ona (Ejemplo **11**)	21
(S)-N-(2,3,11,11a-tetrahidro-1H,5H-pirrolo[2,1-c][1,4]benzoxazepin-7-il)acetamida (Ejemplo **14**)	49
(S)-7-(morfolinocarbonil)-2,3,11,11a-tetrahidro-1H,5H-pirrolo[2,1-c][1,4]benzoxazepina-5-ona (Ejemplo **16A**)	24
(S)-7-(aminocarbonil)-2,3,11,11a-tetrahidro-1H,5H-pirrolo[2,1-c][1,4]benzoxazepina-5-ona (Ejemplo **17A**)	28
(11R, 11aS)-11-etil-2,3,11,11ª-tetrahidro-1H,5H-pirrolo[2,1-c][1,4]benzoxazepina-5-ona (Ejemplo **20A**)	31
(11S, 11aS)-11-etil-2,3,11,11ª-tetrahidro-1H,5H-pirrolo[2,1-c][1,4]benzoxazepina-5-ona (Ejemplo **20B**)	28

124
125

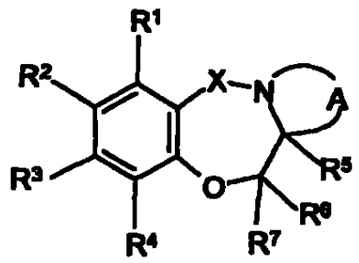
6,6a-dihidro-12H-dihidro-12H-morfolino[3,4-c][1,4]benzoxazepin-12-ona (Ejemplo **22**)	31
(S)-1,2,10,10a-tetrahidroazetidinil[2,1-c][1,4]benzoxazepin-4-ona (Ejemplo **23**)	16
2,11,11a-trihidro-3,3-dimetiloxazolidinil[2,1-c][1,4]benzoxazepina-5-ona (Ejemplo **24**)	18
(2R,11aS)-2-hidroxi,3,11,11a-tetrahidro-1H,5H-pirrolo[2,1-c][1,4]benzoxazepina-5-ona (Ejemplo **25**)	31
(2S,11aS)-2-fluoro-2,3,11,11a-tetrahidro-1H,5H-pirrolo[2,1-c][1,4]benzoxazepina-5-ona (Ejemplo **26**)	24
(2S,11aS)-2,2-difluoro-2,3,11,11a-tetrahidro-1H,5H-pirrolo[2,1-c][1,4]benzoxazepina-5-ona (Ejemplo **28**)	9

*: este compuesto fue preparado como se describió por Schultz, Agrobacterium. Et al (J. Am. Chem Soc. 1988, 110, 7828-7841) quien uso la nomenclatura: (3aS)-2,3,3a,4-tetrahidro-1H,1H-pirrolo[2,1-c]benzoxazepin-10-ona.

125
126

REIVINDICACIONES

1. Un derivado de benzoxazepina que tiene la fórmula general I



Fórmula I

en donde

X representa CO o SO_2;

R^1, R^2, R^3, y R^4 son independientemente seleccionados de H, alquilo con 1 a 4 carbonos, alquiloxi con 1 a 4 carbonos, alquiloxi con 1 a 4 carbonos, alquilo con 1 a carbonos, CF_3, halógeno, nitro, ciano, NR^8R^9, NR^8COR^{10}, y $CONR^8R^9$;

127

R^5, R^6 y R^7 son independientemente H o alquilo con 1 a 4 carbonos;.

R^8 y R^9 son independientemente H o alquilo con 1 a 4 carbonos; o R^8 y R^9 forman juntos con el átomo de nitrógeno al cual ellos se ligan un anillo heterocíclico saturado con 5 o 6 miembros, opcionalmente que contiene un heteroátomo adicional seleccionado de O, S o NR^{11};

R^{10} es alquilo con 1 a 4 carbonos;

R^{11} es alquilo con 1 a 4 átomos de carbono

A representa el residuo de un anillo heterocíclico saturado con 4 a 7 miembros, que contiene opcionalmente un átomo de oxígeno, el anillo es opcionalmente sustituido con uno a tres sustituyentes seleccionado de alquilo con 1 a 4 átomos de carbono, alquiloxi con 1 a 4 átomos de carbono, hidroxi, halógeno y oxo; o una sal farmacéuticamente aceptable de ellos;

Con la condición que

127
128

Los compuestos de fórmula I en donde X es CO; cada uno de R^1 a R^7 es H y A representa $(CH_2)_3$ O $(CH_2)_4$;

El compuesto de fórmula I en donde X es CO; R^1 es H; R^2 es metilo; cada uno de R^3 a R^7 es H; y A representa $(CH_2)_3$;

El compuesto de fórmula I en donde X es CO; R^1 y R^2 son H; R^3 es metilo; cada uno de R^4 a R^7 es H; y A representa $(CH_2)_3$;

El compuesto de fórmula I en donde X es CO; cada uno de R^1 a R^3 es H; R^4 es metilo; cada uno de R^5 a R^7 es H; y A representa $(CH_2)_3$; y

El compuesto de fórmula I en donde X es CO; cada uno de R^1 a R^4 es H; R^5 es metilo; R^6 y R^7 son H; y A representa $(CH_2)_3$; son excluidos.

2. El derivado de benzoxazepina de la reivindicación 1, en donde X es CO.

3. El derivado de benzoxazepina de la reivindicación 2, en donde R^5, R^6 y R^7 son H; y A representa $(CH_2)_3$.

128
129

4. El derivado de benzoxazepina de la reivindicación 3, en donde uno o más de R^1, R^2, R^3, y R^4 es halógeno.

5. Un derivado de benzoxazepina que se selecciona de:

(R)-7-fluoro-2,3,11,11a-tetrahidro-1H,5H-pirrolo[2,1-c][1,4]benzoxazepina-5-ona;

(S)-7-fluoro-2,3,11,11a-tetrahidro-1H,5H-pirrolo[2,1-c][1,4]benzoxazepina-5-ona;

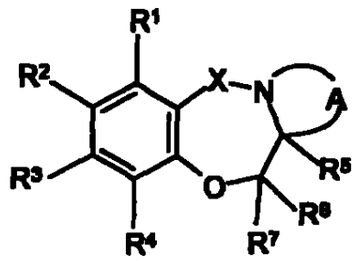
(S)-9-fluoro-2,3,11,11a-tetrahidro-1H,5H-pirrolo[2,1-c][1,4]benzoxazepina-5-ona;

(R)-9-fluoro-2,3,11,11a-tetrahidro-1H,5H-pirrolo[2,1-c][1,4]benzoxazepina-5-ona; y

(S)-6-fluoro-2,3,11,11a-tetrahidro-1H,5H-pirrolo[2,1-c][1,4]benzoxazepina-5-ona.

6. Un derivado de benzoxazepina que tiene la fórmula general

129
130



fórmula I

en donde

X representa CO o SO_2;

R^1, R^2, R^3, y R^4 son independientemente seleccionados de H, alquilo con 1 a 4 carbonos, alquiloxi con 1 a 4 carbonos, alquiloxi con 1 a 4 carbonos, alquilo con 1 a carbonos, CF_3, halógeno, nitro, ciano, NR^8R^9, NR^8COR^{10}, y $CONR^8R^9$;

R^5, R^6 y R^7 son independientemente H o alquilo con 1 a 4 carbonos;

R^8 y R^9 son independientemente H o alquilo con 1 a 4 carbonos; o R^8 y R^9 forman juntos con el átomo de

130
131

nitrógeno al cual ellos se ligan un anillo heterocíclico saturado con 5 o 6 miembros, opcionalmente que contiene un heteroátomo adicional seleccionado de O, S o NR^{11};

R^{10} es alquilo con 1 a 4 carbonos;

R^{11} es alquilo con 1 a 4 átomos de carbono

A representa el residuo de un anillo heterocíclico saturado con 4 a 7 miembros, que contiene opcionalmente un átomo de oxígeno, el anillo es opcionalmente sustituido con uno a tres sustituyentes seleccionado de alquilo con 1 a 4 átomos de carbono, alquiloxi con 1 a 4 átomos de carbono, hidroxi,, halógeno y oxo; para uso en terapia.

7. Una composición farmacéutica que comprende unos derivados de benzoxazepina de fórmula I según se definió en la reivindicación 4, junto con un portador farmacéuticamente aceptable de la misma.

131

132

8. El uso de un derivado de benzoxazepina de fórmula I según se definió en la reivindicación 4 en la preparación de un medicamento para el tratamiento de enfermedades neurológicas y desórdenes psiquiátricos que son responsables de la promoción de respuestas sinápticas mediadas por receptores AMPA en el sistema nervioso central.

9. El uso de acuerdo con la reivindicación 6, en donde la enfermedad o desorden se selecciona a partir de desórdenes neurogdegenerativos, con disfunción cognitiva o de memoria, desórdenes de aprendizaje y memoria como aquellos que resultan de la edad, desorden de atención, trauma, golpes, epilepsia, enfermedad de Alzheimer, depresión esquizofrenia, desórdenes sicóticos, ansiedad, disfunciones sexuales, autismo, y un desorden o enfermedad que resulta de agentes neuróticos o de abuso de sustancias y de intoxicación por alcohol.

10. Un método de tratamiento de una enfermedad neurológica o de un desfragmentación orden siquiátrico, dicha enfermedad o desorden responde a el mejoramiento de respuesta sinápticas mediadas por

receptores AMPA en el sistema nervioso central, dicho métoco comprende administrar una cantidad terapéuticamente efectiva de un derivado de benzoxazepina de acuerdo con la fórmula I de la reivindicación a.

133
134

DERIVADOS DE BENZOXAZEPINA Y SU USO COMO ESTIMULADORES DEL RECEPTOR AMPA

RESUMEN

La presente invención se relaciona con derivados de

Benzoxazepina que tienen la fórmula general 1, en donde X representa CO o SO_2; R^1, R^2, R^3, y R^4 son independientemente seleccionados de H, alquilo (C_{1-4}), alquiloxi(C_{1-4}), alquiloxi(C_{1-4})alquilo(C_{1-4}), halógeno, nitro, ciano, NR^8R^9, NR^8COR^{10} y $CONR^8R9$, R^5, y R^6 y R^7 son independientemente H o alquilo(C_{1-4}); R^8 y R^9 forman juntos con el átomo de nitrógeno al cual ellos están unidos un anillo heterocíclico saturado de 5 0 6 miembros, opcionalmente contiene un heteroátomo adicional seleccionado de O, SO NR^{11}; R^{10} es alquilo (C_{1-4}); R^{11} es alquilo($_{C1-4}$); A representa el residuo de un anillo heterocíclico saturado de 4 a 7 miembros, opcionalmente contiene un átomo de oxigeno, el anillo es opcionalmente sustituido con 1-3 sustituyentes seleccionados de alquilo(C_{1-4}), alquiloxi(C_{1-4}), hidroxi, halógeno, y oxo, y una sal

farmacéuticamente aceptable de esta. La invención también se relaciona con composiciones farmacéuticas que comprenden dichos derivados, y con el uso de estos de derivados de benzoxazepina en el tratamiento de enfermedades neurológicas y desordenes psiquiátricos que responden al mejoramiento de respuestas sinápticas mediadas por sectores AMPA en el sistema nervioso central.

12 FEB. 2003

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To:

P.M.G.F. van WEZENBEEK
P.O. Box 20
NL-5340 BH Oss
PAYS-BAS

NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	10/02/2003

Applicant's or agent's file reference	IMPORTANT NOTIFICATION
2001.650WO	

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP 02/ 06185	05/06/2002	11/06/2001

Applicant

AKZO NOBEL N.V. et al.

1. 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.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. 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 invention 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/	Authorized officer
European Patent Office D-80298 Munich Tel. (+49-89) 2399-0, Tx: 523656 epmu d Fax: (+49-89) 2399-4465	FERRO VASCONCELOS M Tel. (+49-89) 2399 2828

Form PCT/IPEA/416 (August 2002) P20473

PATENT COOPERATION TREATY

PCT

136

137

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	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
2001.650WO		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP 02/ 06185	05/06/2002	11/06/2001
International Patent Classification (IPC) or national classification and IPC		
C07D498/04		
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	Date of completion of this report
29/10/2002	05/02/2003
Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. (+49-89) 2399-0, Tx: 523656 epmu d Fax: (+49-89) 2399-4465	GELLIE B R Tel. (+49-89) 2399 2828

Form PCT/IPEA/409 (cover sheet) P20476 (October 2002)

I. Basis of the report

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

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The question of whether the claimed invention appears to be novel, to involve an inventive step, or to be industrially applicable has not been the subject of the international preliminary examination in respect of the claims which have not been searched (Article 17(2)(a) or (3) and Rule 66.1(e) PCT; see also international search report).

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

To the extent that the international preliminary examination has been carried out (see item III above), the following is pointed out:

In light of the documents cited in the international search report, it is considered that the invention as defined in at least some of the claims, which have been the subject of an international search report, does not appear to meet the criteria mentioned in Article 33(1) PCT, i.e. does not appear to be novel and/or to involve an inventive step (see international search report, in particular the documents cited X and/or Y and corresponding claim references).

Traducción

138

139

TRATADO DE COOPERACIÓN DE PATENTES

PCT

INFORME DE EXAMEN PRELIMINAR INTERNACI NAL

(Artículo 36 y Regla 70 del PCT)

(Informe racionalizado de acuerdo a la notificación hecha por el presidente de la EPO publicada en OJ11/2001)

Referencia del expediente del agente o solicitante	PARA ACTUACIONES ADICIONALES	Ver notificación de Transmisión del Reporte de Examen Preliminar (Formato PCT/IPEA416)
2001.650WO		
Solicitud Internacional No.	Fecha de presentación internacional (*día/mes/año*)	Fecha de prioridad (*día/mes/año*)
PCT/EP02/06185	5 de Junio de 2002	11 de Junio de 2001
Clasificación Internacional de Patentes (IPC) o clasificación nacional e IPC		
C07D 498/04		
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	Fecha de terminación de este reporte
29 de Octubre de 2002	5 de Febrero de 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 epmu d Fax: (+49-89) 2399-4465	Funcionario Autorizado GELLIE B R Teléfono No. (+49-89) 2399 28 28

Formato PCT/IPEA/409 (portada) (julio 1998)

I. Base del Informe

La base de este informe preliminar internacional es la solicitud como se presentó originalmente.

III. No establecimiento de opinión con respecto a la novedad, nivel inventivo y aplicabilidad industrial.

La pregunta de si la invención reivindicada parece tener novedad, nivel inventivo, o que sea aplicable industrialmente no ha sido examinada con respecto a las reivindicaciones a las cuales no se les ha realizado su búsqueda (Artículo 17(2)(a) o (3) y Regla 66.1 (e) PCT); ver también el Informe de búsqueda internacional).

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.

Hasta el punto donde se ha podido realizar este examen preliminar (ver arriba en el punto III), se puede señalar lo siguiente:

A la luz de los documentos citados en el informe de búsqueda internacional, se considera que la invención como se encuentra definida en algunas de las reivindicaciones, que han sido sujeto de búsqueda internacional, parece no cumplir con los criterios mencionados en el Artículo 33(1) del PCT, por ejemplo parece no ser novedosa y/o no alcanza el nivel inventivo (ver informe de búsqueda internacional, en particular los documentos citados como X y/o Y y corresponden a las referencias de las reivindicaciones).

FORMATO DE DIGITALIZACION
RELACION DE ANEXOS

Royal Technologies S.A.

141

Item		Expediente No 03107046	No de Folio
		No de unidades	√
1	CD		
2	DVD		
3	REVISTA		
4	LIBRO		
5	PERIODICO		
6	DISQUETES		
7	SOBRE DE MANILA		
8	SOBRE BLANCO TAMAÑO CARTA		
9	SOBRE BLANCO TAMAÑO OFICIO	1	
10	OTROS:		

Observaciones: Ficha Final

141 142

SUPERINDUSTRIA Y COMERCIO Folios: 141
Radicacion : 03107046 00000000
NIT : 800176089-2 Fecha (AMD): 2003-12-04 17:11:50
Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia: 2000 DIVISION DE NUEVAS CREACIONES

RECIBO OFICIAL DE CAJA : 03 - 85,319
FECHA : NOVIEMBRE 24 DE 2003

C O N S I G N A C I O N

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CAVELIER ABOGADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	17923914	24/11/2003	28,427,560.00

C O N C E P T O

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	400,000.00
		TOTAL : $	400,000.00

SON: CUATROCIENTOS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

Caln 1121.4-841-010-6

143

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

	USUARIO	RADICADOR
PATENTE DE INVENCIÓN ✓ 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: ANDREA POSSE

Fecha:

Folios 144, 145, 148
Extracto Publicado

446
144

Industria y Comercio
SUPERINTENDENCIA

2020
Bogotá, D.C.,

Doctor:
Emilio Ferrero
Apoderado
Akzo Nobel N.V.

Oficio N° 03360

ASUNTO:		
	Radicación N°	03 107046
	Solicitud internacional	PCT/EP2002/06185
	Fecha inicio fase nacional	11/01/2004
	Trámite	011
	Evento	379
	Actuación	430
	Folios	001

Como resultado del examen de forma, realizado con fundamento el el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

☐ La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante. (Art. 26-k) Decisión 486).

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

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

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones.

06 FEB. 2004

El anterior requerimiento fue notificado por fijación en lista de fecha_____.

202055