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REPÚBLICA DE COLOMBIA
DIVISIÓN DE PROPIEDAD INDUSTRIAL

PCT
PATENTE DE INVENCION



Industria y Comercio
SUPERINTENDENCIA

06-30123

TITULO: FORMA POLIMORFICA DE 3-FENILSULFONIL-8-PIPERAZIN-1-IL-QUINOLINA.

CIP: C07D215/40, A61U31/47, A61P25/00

SOLICITANTE: GLAXO GROUP LIMITED

DIRECCIÓN: Glaxo Wellcome House, Berkeley Avenue, gredford, Middlesex
UB6 ONN, Inglaterra

APODERADO: CARLOS R. OLARTE

BOGOTÁ, Marzo 27 de 2006

P2006000034

GW

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OLARTE RAISBECK



SUPERINDUSTRIA Y COMERCIO
Radicación : 06430123 00000000 Folios: 61
Fecha (UND): 2006-03-27 17:30:34
Trámite : 011 PCT-PATENT 370 FASE NACI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE PCT

ENTRADA EN FASE NACIONAL 26-04-2006

1	SOLICITUD DE:	
☒	Patente de Invención.	☐ Patente de Modelo de Utilidad.

☒	Capítulo I.	☐ Capítulo II.
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2 SOLICITANTE (71)	Nombre: <u>GLAXO GROUP LIMITED</u>	IDENTIFICACIÓN C.C. ☐ NIT ☐ C.E. ☐ Otro ☐ Cual _____ Número _____
	Dirección: <u>Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 ONN</u> Nacionalidad o Domicilio: <u>BRITANICA</u> Lugar de Constitución: <u>INGLATERRA</u> Teléfono: _____ Fax: _____ E-mail: _____	

3 REPRESENTANTE O APODERADO	Nombre: <u>CARLOS R. OLARTE</u>	IDENTIFICACIÓN C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Cual _____ Número <u>79.782.747 Btá</u> TP <u>74.295</u>
	Dirección: <u>World Trade Center Torre A, Calle 100 No. 8A-37 Piso 10</u> Teléfono: <u>601-7700</u> Fax: <u>601-7799</u> E-mail: <u>office@olarteraisbeck.com</u>	

4 INVENTOR (ES) (72)	Nombre: <u>ASA ELISABETH GLADWIN</u>
	Dirección: <u>Gunnels Wood Road, Stevenage, Hertfordshire, SG1 2NY,</u> Nacionalidad o Domicilio: <u>SUIZA</u>

5 PCT (86)	Solicitud Internacional No. <u>PCT/EP2004/010843</u>	Fecha <u>Septiembre 23, 2004</u>
	Publicación Internacional No. <u>WO 2005/040124</u>	Fecha <u>Mayo 6, 2005</u>

6 Título (54) <u>FORMA POLIMORFICA DE 3-FENILSULFONIL-8-PIPERAZIN-1-IL-QUINOLINA.</u>
--

7 Clasificación Internacional (51) <u>C07D 215/40, A61K 31/47, A61P 25/00.</u>

8 Prioridad SI ☒ N ☐	(33) País de Origen <u>GB</u>	(32) Fecha <u>Septiembre 26, 2003</u>	(31) Número de Solicitud <u>0322629.7</u>

9 Comprobante de pago No. <u>06-23.272</u>	Fecha <u>Marzo 23, 2006</u>
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10

ANEXOS

☒

Comprobante de pago de la tasa de presentación de la solicitud.

☐

Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.

☒

Poderes, si fuere el caso.

☒

Documento de cesión del inventor al solicitante o a su causante.

☐

Declaraciones.

☒

Copia de la solicitud Internacional. (Resumen, descripción, reivindicaciones, dibujos).

☒

Traducción de la solicitud Internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos).

☐

Copia del examen preliminar Internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA).

☐

Traducción del examen preliminar Internacional efectuado por la IPEA.

☐

De ser el caso, copia del contrato de acceso.

☐

De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.

☐

De ser el caso, certificado de depósito del material biológico.

☐

Arte final 12 x 12.

☐

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.

☐

De ser el caso, modificaciones efectuadas a la solicitud Internacional.

☒

Otros. Búsqueda Internacional

11

FIGURA CARACTERÍSTICA:

12

Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTE

FIRMA: 

C.C. 79.782.747 Btá T.P. 74.295

Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página.

73

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800174089-2

RECIBO OFICIAL DE CAJA : 06 - 23.272
FECHA : MARZO 23 DE 2006

SUPERINDUSTRIA Y COMERCIO
Radicacion : 06030123 00000000 Folios: 61
Fecha (HH): 2006-03-27 17:30:34
Tramite : 011 PCT-PATENT 278 FASE INCI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBEGR	CONSIGNACION	BANCO POPULAR	050-00110-6	51156208	23/03/2006	2,539,000.00

***** 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	463,000.00
	TOTAL :	\$ 463,000.00

SON: CUATROCIENTOS SESENTA Y TRES MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

9
4

Traducción oficial del Inglés por Marlén Neira Castro, resolución 2117 del Ministerio de Justicia de Colombia

**APOSTILLA EN PODER DE REPRESENTACIÓN DE
GLAXO GROUP LIMITED**

PODER DE REPRESENTACION

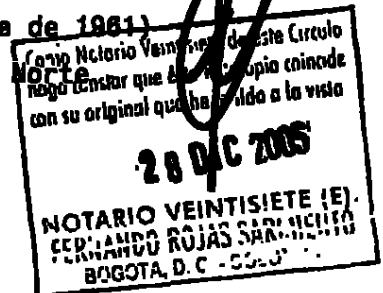
Bilingüe inglés- español otorgado en Brentford, Middlesex, Inglaterra el 13 de agosto de 2003 y firmado por Peter John Giddings, Apoderado y Funcionario autorizado.

Certificado de Notario De Pinna en español firmado por James Kerr Milligan

APOSTILLA

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

1. País: Reino Unido de Gran Bretaña e Irlanda del Norte
- Este documento Público
2. ha sido firmado por James Kerr Milligan
3. Quien ejerce funciones de Notario público
4. Lleva el sello del Notario público



CERTIFICADO

5. En Londres
6. El 14 agosto 2003
7. Por el Secretario de Estado Principal de su Majestad para Asuntos exteriores y de la Mancomunidad
8. No. G229474
9. Gran Sello de la Oficina de Asuntos exteriores y de la Mancomunidad
10. Firma legible de J. Garbrah- Por el Secretario de Estado

Si el documento se usa en un país que no pertenece a la Convención de la Haya del 5 de octubre de 1961 debe pasar por la sección consular de la Misión que representa el país.

Es traducción fiel del inglés, con copia archivo para confrontación. Bogotá 21 agosto-03.

Marlén Neira C

Marlén Neira C
MARLEN NEIRA CASTRO
Traductor e Intérprete Ofi.
Inglés - Español - Inglés
Resolución No. 2117 del 7 O.

Yo, el infrascrito **JAMES KERR MILLIGAN**, Notario Público de la Ciudad de Londres, Inglaterra, por la Autoridad Real debidamente admitido y juramentado,

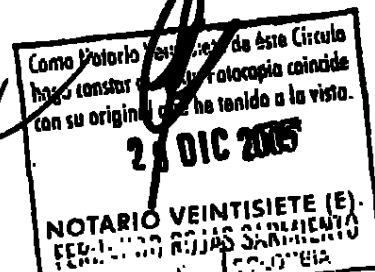
C E R T I F I C O:

QUE es auténtica la firma suscrita al pie del adjunto Poder, por ser del puño y letra del Señor Don **PETER JOHN GIDDINGS**, cuya identidad me consta, Apoderado de la Sociedad inglesa denominada "**GLAXO GROUP LIMITED**", Sociedad legalmente constituida y existente de acuerdo con las leyes de Inglaterra, e inscrita en la Oficina de Registro de Sociedades bajo el número **305979**, con domicilio social en **Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 ONN, Inglaterra;**

QUE el citado Señor Don **PETER JOHN GIDDINGS** está debidamente autorizado para firmar documentos de esta clase en nombre y representación de dicha Sociedad en virtud de un Poder otorgado por la referida Sociedad fechado 3 de julio de 2002.

Y QUE los objetos para los cuales se otorgó dicho Poder se encuentran dentro de los objetos o actividades de la citada Sociedad, de acuerdo con la Escritura Constitutiva y los Estatutos Sociales, los cuales he tenido a la vista.

Y PARA QUE CONSTE donde y como convenga y fuere necesario expido el presente Certificado que firmo y sello en dicha Ciudad de Londres, el día de hoy vece de agosto del año dos mil tres.



JAMES KERR MILLIGAN
Notario Público de Londres, Inglaterra



APOSTILLE
(Hague Convention of 5 October 1961 / Convention de La Haye du 5 octobre 1961)

UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND

1. Country: United Kingdom of Great Britain and Northern Ireland
Pays: Royaume-Uni de Grande-Bretagne et d'Irlande du Nord

This public document / Le présent acte public

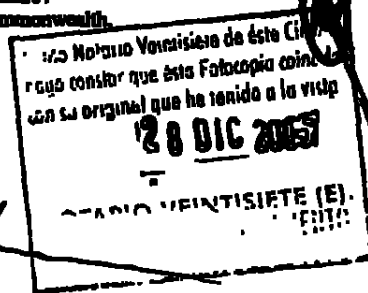
2. Has been signed by James Kerr Milligan
a été signé par
3. Acting in the capacity of Notary Public
agissant en qualité de
4. Bearer the seal/stamp of The Said Notary Public
est revêtu du sceau/timbre de

5. at London/A Londres
6. the/le 14 August 2003
7. by Her Majesty's Principal Secretary of State for Foreign and Commonwealth Affairs /
par le Secrétaire d'Etat Principal de Sa Majesté aux Affaires Etrangères et du Commonwealth

8. Number/sous No **G229474**

9. Stamp:
timbre:

10. Signature: J. Garibrah



For the Secretary of State / Pour le Secrétaire d'Etat

If this document is to be used in a country which is not party to the Hague Convention of 5 October 1961,
it should be presented to the consular section of the mission representing that country.

OLARTE RAISBECK

OLARTE RAISBECK & FRIERI, LTDA.
LEGAL & PROFESSIONAL SERVICES

WORLD TRADE CENTER - TORRE C
CALLE 100 No. 6A-55 Piso 10
BOGOTÁ, COLOMBIA
TELEPHONE: +57-1 638-8200
Fax: +57-1 638-8201

www.olarteraisbeck.com

Power of Attorney

The undersigned,

domiciled in

Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN, GB

by means of these presents hereby grants to **Carlos R. Olarte, J. Ian Ralsbeck and Ana María Frieri** full and sufficient Power of Attorney to file, prosecute, obtain, defend and enforce any and all of the company's Patents, Utility Models and Industrial Designs in the Republic of Colombia, to which end it empowers them to take all steps necessary before any administrative or judicial authority of any class for the objects stated, to file petitions, appeals, replicas and oppositions, pay taxes and annuities, request testimonies, receive documents and securities, abandon applications and collect refunds. Sufficient power is hereby granted to receive notifications on behalf of the Company, to confer powers on those who are to represent the company judicially and extrajudicially, to answer in court in the matter of all claims and demands that may be presented in connection with the objects stated, giving them likewise power to substitute these presents and revoke such substitutions.

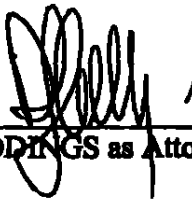
El suscrito,

Glaxo Group Limited

domiciliado en

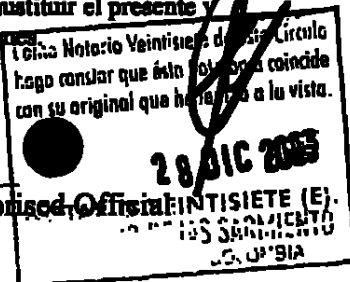
por medio del presente otorga a **Carlos R. Olarte, J. Ian Ralsbeck y Ana María Frieri** poder especial, amplio y suficiente para presentar, tramitar, obtener, defender y hacer respetar todas y cualquiera de Patentes, Modelos de Utilidad y Diseños Industriales de la compañía en la República de Colombia, a cuyo efecto los faculta para dar todos los pasos necesarios ante cualquier autoridad administrativa o judicial de cualquier jerarquía para cumplir con lo encomendado, elevar solicitudes, apelaciones, respuestas y oposiciones, pagar impuestos y anualidades, solicitar testimonios, recibir documentos y valores, desistir y percibir. Se concede poder bastante para recibir notificaciones a nombre de la compañía, otorgar poderes a quienes vayan a representar a la compañía judicial y extrajudicialmente, responder en juicio a todas las reclamaciones o demandas que por motivo de lo encomendado se presentaren, dándoles asimismo facultad para sustituir el presente y revocar dichas sustituciones.

Signature/Firma:


Peter John GIDDINGS as Attorney and Authorised Official

Date/Fecha: 13 August 2003

City/Country/Ciudad,País: Brentford, Middlesex, England



~~2~~
2

CESION

Yo,

Asa Elisabeth GLADWIN

Por medio de la presente cedo a

Glaxo Group Limited

Una compañía organizada bajo las leyes de la Gran Bretaña
domiciliada en

Glaxo Wellcome House, Berkeley Avenue, Greenford,
Middlesex, UB6 0NN, Gran Bretaña,

(en adelante el "Cesionario"), todos mis (nuestros)
derechos, título e interés sobre mi(nuestra) invención para
una nueva y útil mejora tal como describe en:

**FORMA POLIMORFICA DE 3-FENILSULFONIL-8-PIPERAZIN-1-IL-
QUINOLINA**

En lo que concierne a la República de Colombia.

Lugar y Fecha: Stevenage, 28 de febrero de 2006.

(Fdo) Asa Elisabeth GLADWIN

EN ESPAÑOL viene Certificación de la firma anterior por
parte de James Kerr Milligan, Notario Público de Londres,
Inglaterra

8

APOSTILLA

(Convención de la Haya del 5 de Octubre de 1961)

REINO UNIDO DE GRAN BRETAÑA E IRLANDA DEL NORTE

1. País: Reino Unido de Gran Bretaña e Irlanda del Norte

El presente documento público

2. Ha sido firmado por: **James Kerr Milligan**

3. Que actuó en su calidad de **Notario Público**

4. Lleva el sello del **mencionado Notario Público**

Se certifico

5. En **Londres**

6. El **10 de marzo de 2006**

7. Por parte del **Principal Secretario de Estado de su**
Majestad para Asuntos Extranjeros y de la
Mancomunidad.

8. Bajo el Número **G956755**

9. Lleva el Sello de la **Oficina de Asuntos Extranjeros y**
de la Mancomunidad de Londres.

10. Firmado por **N. Donkor**

Por el Secretario de Estado.

9

Y , el infrascrito, **James Kerr MILLIGAN**, Notario Público de la Ciudad de Londres, Inglaterra, por la Autoridad Real debidamente admitido y juramentado,

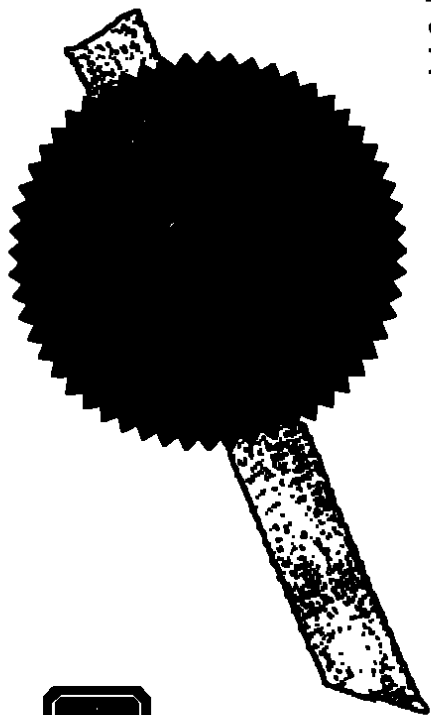
C E R T I F I C O:

QUE la Cesión que se adjunta fue firmada por la Señora Doña **Asa Elisabeth GLADWIN**, titular del carnet de conducir británico número **GLADW754266AE9VW 01** expedido el día 25 de noviembre de 2003.

Y PARA QUE CONSTE donde y como convenga y fuere necesario expido el presente Certificado que firmo y sello en dicha Ciudad de Londres, el día de hoy diez de marzo del año dos mil seis.



James Kerr MILLIGAN
Notario Público de Londres, Inglaterra



APOSTILLE
(Hague Convention of 5 October 1961 / Convention de La Haye du 5 octobre 1961)

UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND

1. Country: United Kingdom of Great Britain and Northern Ireland
Pays: Royaume-Uni de Grande-Bretagne et d'Irlande du Nord

This public document / Le présent acte public

2. Has been signed by James Kerr Milligan
a été signé par

3. Acting in the capacity of Notary Public
agissant en qualité de

4. Bears the seal/stamp of The Said Notary Public
est revêtu du sceau/timbre de

5. at London/à Londres
6. the/le 10 March 2006

7. by Her Majesty's Principal Secretary of State for Foreign and Commonwealth Affairs /
par le Secrétaire d'Etat Principal de Sa Majesté aux Affaires Etrangères et du Commonwealth.

8. Number/sous No **G956755**

9. Stamp:
timbre: 10. Signature: **N. Donker**



A handwritten signature in black ink, appearing to be 'N. Donker', written over a horizontal line.

For the Secretary of State / Pour le Secrétaire d'Etat

If this document is to be used in a country which is not party to the Hague Convention of 5 October 1961, it should be presented to the consular section of the mission representing that country. An apostille or legalization certificate only confirms that the signature, seal or stamp on the document is genuine. It does not mean that the contents of the document are correct or that the Foreign & Commonwealth Office approves of the contents.

ASSIGNMENT	CESION
Asa Elisabeth GLADWIN	
	por medio de la present cedo (cedemos) a
	una _____ organizada baja las leyes de
By means of this document assign to	domiciliada en
Glaxo Group Limited	
A company organized under the laws of Great Britain	(de ahora en adelante el CESIONARIO), todos mis (nuestros) derechos, titulo e interes sobre mi (nuestra) invencion tal como describe en:
Domiciled in Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex, UB6 0NN, Great Britain	
(hereinafter referred to as the ASSIGNEE). All my (our) rights, title and interest in and to my (our) invention for a new and useful improvement entitled and as fully set forth and described in:	En lo que concierne a la Republica de Colombia.
A POLYMORPHIC FORM OF 3-PHENYLSULFONYL-8-PIPERAZIN-1-YL-QUINOLINE	Place and date:
So far as the Republic of Colombia is concerned.	
Place and date: <i>Stevenage 28 feb 2006</i>	
 Asa Elisabeth GLADWIN	

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
6 May 2005 (06.05.2005)

PCT

(10) International Publication Number
WO 2005/040124 A1

(51) International Patent Classification:
A61K 31/47, A61P 25/00

SK, TR, OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

(21) International Application Number:
PCT/EP2004/010843

Declarations under Rule 4.17:

(22) International Filing Date:
23 September 2004 (23.09.2004)

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

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Date:
0323629.7 26 September 2003 (26.09.2003) GB

(71) Applicant (for all designated States except US): GLAXO GROUP LIMITED (GB/GB); Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).

(72) Inventor: and

(73) Inventor/Applicant (for US only): GLADWIN, Ann, Elizabeth (SE/GB); GlaxoSmithKline, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB).

(74) Agent: GIBSON, Mark; GlaxoSmithKline (CIP-CMY25.1), 980 Great West Road, Brentford Middlesex TW8 9GS (GB).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

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

of inventorship (Rule 4.17(iv)) for US only

Published:

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

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

WO 2005/040124 A1

(54) Title: A POLYMORPHIC FORM OF 3-PHENYLSULFONYL-8-PIPIRAZIN-1-YL-QUINOLIN-1-YL

(57) Abstract: This invention relates to a novel compound of 3-phenylsulfonyl-8-piprazin-1-yl-quinoline, to processes for its preparation, to compositions containing it and to its use in the treatment of CNS and other disorders.

K
12**A POLYMORPHIC FORM OF 3-PHENYLSULFONYL-8-PIPERAZIN-1-YL-QUINOLINE**

5 This invention relates to a novel compound having pharmacological activity, to processes for its preparation, to compositions containing it and to its use in the treatment of CNS and other disorders.

WO 2003/080580 (Glaxo Group Limited) describes the preparation of 3-phenylsulfonyl-8-piperazin-1-yl-quinoline (Example 16) in addition to two polymorphic forms of 3-phenylsulfonyl-8-piperazin-1-yl-quinoline (Form I; Example 51 and Form II; Example 52).
10 3-Phenylsulfonyl-8-piperazin-1-yl-quinoline is disclosed in WO 2003/080580 as having affinity for the 5-HT₂ receptor and is claimed to be useful in the treatment of CNS and other disorders.

15 It has now been found that 3-phenylsulfonyl-8-piperazin-1-yl-quinoline exists in a further polymorphic form which is primarily characterised in that it possesses a higher melting point than Forms I and II. This further polymorphic form of 3-phenylsulfonyl-8-piperazin-1-yl-quinoline is referred to as Form III.

20 Thus, according to a first aspect of the present invention, we provide 3-phenylsulfonyl-8-piperazin-1-yl-quinoline Form III.

Suitably, the present invention provides 3-phenylsulfonyl-8-piperazin-1-yl-quinoline, suitably as characterised by data provided by at least one of the following: infrared, Raman, X-ray powder diffraction or nuclear magnetic resonance and melting point data
25 as provided herein, including partial spectral data provided herein.

Thus, one aspect of the present invention provides a polymorphic form of 3-phenylsulfonyl-8-piperazin-1-yl-quinoline, characterised in that it provides:
30 (i) an infrared spectrum containing peaks at 724, 758, 777, 804, 818, 838, 858, 905, 918, 948, 1023, 1055, 1081, 1082, 1118, 1138, 1153, 1178, 1244, 1302, 1318, 1365, 1378, 1403, 1444, 1471, 1490, 1569, 1584, 1603 and 2819 cm⁻¹; and/or
(ii) a Raman spectrum containing peaks at 159, 184, 214, 241, 285, 304, 318, 429, 545, 558, 614, 706, 724, 803, 858, 1000, 1023, 1080, 1093, 1138, 1152, 1233, 1243, 1317, 1343, 1384, 1378, 1403, 1448, 1589, 1584, 1802, 3050 and 3073 cm⁻¹; and/or
35 (iii) an X-ray powder diffraction (XRPD) pattern which gives calculated lattice spacings at 10.29, 11.94, 17.47, 19.55, 19.84, and 20.33°; and/or
(iv) a melting point of 188°C.

40 In one preferred aspect, the polymorph of the present invention provides an infrared spectrum substantially in accordance with Figure 1.

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In one preferred aspect, the polymorph of the present invention provides a Raman spectrum substantially in accordance with Figure 2.

5 In one preferred aspect, the polymorph of the present invention provides an X-ray powder diffraction (XRPD) pattern which gives calculated lattice spacings at 10.29, 10.78, 11.84, 14.33, 14.81, 14.93, 16.02, 16.80, 17.47, 17.92, 19.13, 19.55, 19.84, 20.33, 21.18, 21.36, 23.33, 23.98, 24.44, 24.67, 25.51, 26.12, 27.13, 27.77, 28.08, 28.35, 29.23, 29.48, 30.06, 30.35, 31.27, 32.35, 32.68, 33.08, 33.77, 34.48, 35.18, 36.42, 37.34, 38.39 and 39.51°.

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In a more preferred aspect, the polymorph of the present invention provides an X-ray powder diffraction (XRPD) pattern substantially in accordance with Figure 3.

15 The present invention encompasses the polymorph isolated in pure form or when admixed with other materials, for example the known forms of 3-phenylsulfonyl-8-piperazin-1-yl-quinoline or any other material.

20 Thus, in one aspect there is provided the polymorph in isolated form. In a further aspect there is provided the polymorph in pure form. In yet a further aspect there is provided the polymorph in crystalline form. Most preferably, the polymorph is provided in pure form.

25 'Isolated in pure form' refers to 3-phenylsulfonyl-8-piperazin-1-yl-quinoline Form III present in an amount of preferably >75%, more preferably >80%, particularly >95%, especially >99% relative to other compounds or polymorphs of 3-phenylsulfonyl-8-piperazin-1-yl-quinoline which may be present in an isolated sample.

30 The compound of the present invention has affinity for the 5-HT₂ receptor and is believed to be of potential use in the treatment of certain CNS disorders such as anxiety, depression, epilepsy, obsessive compulsive disorders, migraine, cognitive memory disorders (e.g. Alzheimers disease, age related cognitive decline and mild cognitive impairment), Parkinsons Disease, ADHD (Attention Deficit Disorder/Hyperactivity Syndrome), sleep disorders (including disturbances of Circadian rhythm), feeding disorders such as anorexia and bulimia, panic attacks, withdrawal from drug abuse such
35 as cocaine, ethanol, nicotine and benzodiazepines, schizophrenia (in particular cognitive deficits of schizophrenia), stroke and also disorders associated with spinal trauma and/or head injury such as hydrocephalus. The compound of the invention is also expected to be of use in the treatment of certain GI (gastrointestinal) disorders such as IBS (Irritable Bowel Syndrome). The compound of the invention is also expected to be of
40 use in the treatment of obesity.

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Thus the invention also provides 3-phenylsulfonyl-8-piperazin-1-yl-quinoline (Form III), for use as a therapeutic substance, in particular in the treatment or prophylaxis of the above disorders. In particular the invention provides for 3-phenylsulfonyl-8-piperazin-1-yl-quinoline (Form III), for use in the treatment of depression, anxiety, Alzheimers disease, age related cognitive decline, ADHD, obesity, mild cognitive impairment, schizophrenia, cognitive deficits in schizophrenia and stroke.

The invention further provides a method of treatment or prophylaxis of the above disorders, in mammals including humans, which comprises administering to the sufferer a therapeutically effective amount of 3-phenylsulfonyl-8-piperazin-1-yl-quinoline (Form III).

In another aspect, the invention provides the use of 3-phenylsulfonyl-8-piperazin-1-yl-quinoline (Form III) in the manufacture of a medicament for use in the treatment or prophylaxis of the above disorders.

5-HT₂ antagonists have the potential to be capable of increasing basal and learning-induced polysyllated neuron cell frequency in brain regions such as the rat medial temporal lobe and associated hippocampus, as described in WO 2003/066056. Thus, according to a further aspect of the present invention, we provide a method of promoting neuronal growth within the central nervous system of a mammal which comprises the step of administering 3-phenylsulfonyl-8-piperazin-1-yl-quinoline (Form III).

In order to use the compound of the present invention in therapy, it will normally be formulated into a pharmaceutical composition in accordance with standard pharmaceutical practice. The present invention also provides a pharmaceutical composition, which comprises 3-phenylsulfonyl-8-piperazin-1-yl-quinoline (Form III), and a pharmaceutically acceptable carrier.

A pharmaceutical composition of the invention, which may be prepared by admixture, suitably at ambient temperature and atmospheric pressure, is usually adapted for oral, parenteral or rectal administration and, as such, may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable or infusible solutions or suspensions or suppositories. Orally administrable compositions are generally preferred.

Tablets and capsules for oral administration may be in unit dose form, and may contain conventional excipients, such as binding agents, fillers, tableting lubricants, disintegrants and acceptable wetting agents. The tablets may be coated according to methods well known in normal pharmaceutical practice.

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Oral liquid preparations may be in the form of, for example, aqueous or oily suspension, solutions, emulsions, syrups or elixirs, or may be in the form of a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and, if desired, conventional flavourings or colourants.

For parenteral administration, fluid unit dosage forms are prepared utilising a compound of the invention or pharmaceutically acceptable salt thereof and a sterile vehicle. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions, the compound can be dissolved for injection and filter sterilised before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilization cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspension in a sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The composition may contain from 0.1% to 99% by weight, preferably from 10 to 80% by weight, of the active material, depending on the method of administration.

The dose of the compound used in the treatment of the aforementioned disorders will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and other similar factors. However, as a general guide suitable unit doses may be 0.05 to 1000 mg, more suitably 0.05 to 200 mg, for example 20 to 40 mg; and such unit doses will preferably be administered once a day, although administration more than once a day may be required; and such therapy may extend for a number of weeks or months.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

The following Descriptions and Examples illustrates the preparation of the compound of the invention.

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Description 1

3-Iodo-8-nitroquinoline (D1)

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A stirred mixture of 8-nitroquinoline (100 g, 0.57 mol) in acetic acid (500 ml) was treated with *N*-iodosuccinimide (155 g, 0.69 mol) portionwise over 10 minutes, and warmed to 62 °C for 6 h. A further portion of *N*-iodosuccinimide (25 g, 0.14 mol) was introduced and the mixture stirred for a further 16 h before cooling to ambient temperature. The solvent was removed *in vacuo*, keeping the temperature below 35 °C. The residue was dissolved in dichloromethane (2 L) and washed successively with saturated aqueous sodium bicarbonate solution (2 x 1 L), 10% aqueous sodium thiosulphate solution (1 L), water (1 L), brine (100 ml), then the organic phase was dried over magnesium sulphate. The mixture was filtered and the solvent removed to give a yellow solid which was recrystallised from ethyl acetate to give the title compound (D1) (168 g, 97%) as a yellow solid;

δ_{H} (CDCl₃) 7.65 (1H, app.t), 7.94 (1H, dd), 8.07 (1H, dd), 8.66 (1H, d, *J* = 2 Hz), 9.19 (1H, d, *J* = 2 Hz);

Mass Spectrum : C₉H₆N₂ requires 300; found 301 (M⁺).

Description 2
8-Nitro-3-phenylsulfonylquinoline (D2)
3-Iodo-8-nitroquinoline (D1) (135 g, 0.45 mol), was suspended in dimethylformamide (2.4 L) in a 5 L 3-necked flask fitted with an overhead stirrer, under an argon atmosphere. This mixture was treated successively with anhydrous sodium phenylsulfinate (99.6 g 0.608 mol), and bis-(copper (I) triflate) benzene complex (170 g, 0.338 mol). The resulting slurry was heated to 65 °C for 18 h. The mixture was cooled, filtered and the solvent evaporated *in vacuo*. Acetone (2.5 L) was added to the residue and the solution filtered. The filtrate was evaporated *in vacuo*, a further 2.5 L of acetone added and the mixture filtered again. The solvent was evaporated *in vacuo* and the residue dissolved in chloroform (3 L) and washed with 10% aqueous ammonia (2 x 2 L), and the organic phase was dried over magnesium sulphate and the solvent evaporated *in vacuo*. The dark brown residue was purified using a Biotage flash-150 chromatography apparatus (5 kg silica gel) eluting with hexane and increasing proportions of ethyl acetate to give the title compound (D2) (81.5 g, 58%) as a yellow solid;

δ_{H} (d₆-DMSO) 7.67 (2H, t), 7.57 (1H, d, 7.96 (1H, t), 8.13 (2H, d), 8.51 (1H, d), 8.59 (1H, d), 9.42 (1H, d), 9.60 (1H, d);

Mass Spectrum : C₁₃H₁₀SO₄N₂ requires 314; found 315 (M⁺).

Description 3
8-Amino-3-phenylsulfonylquinoline (D3)
A slurry of 8-nitro-3-phenylsulfonylquinoline (D2) (46.7 g, 172 mmol), in tetrahydrofuran (750 ml) was added to a stirred solution of 30% titanium (III) chloride in aqueous HCl (470 ml) [Supplied by BDH] cooled in an ice bath, at such a rate that the temperature was maintained below 35 °C. Once the addition was completed, the solution was stirred for a further 10 minutes then water (1.5 L) was introduced and the mixture poured into a

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- 5 L beaker. The rapidly stirred solution was treated by portionwise addition of solid potassium carbonate in order to attain pH ~8.5. EDTA (250 g, 0.86 mol) was added and followed by further potassium carbonate to maintain pH ~8.5. The mixture was extracted with dichloromethane (3 x 1 L) and the combined organic phase passed through a silica plug (500 g) eluting with further dichloromethane (1 L) and 10% ethyl acetate in dichloromethane (1 L). The combined organic phases were evaporated and the residue subjected to purification using Biotage Flash-75 chromatography apparatus (2 kg silica gel), eluting with dichloromethane and increasing proportions of ether to give the title compound (D3) (34.5 g, 72%) as a pale brown solid;
- 5 δ_H (CDCl₃) 5.0 (2H, br s), 7.02 (1H, dd), 7.25 (1H, dd), 7.44 (1H, t), 7.50-7.59 (3H, m), 8.00-8.40 (2H, m), 8.70 (1H, s), 0.09 (1H, s);
- 10 Mass Spectrum : C₁₆H₁₂SO₂N₂ requires 284; found 285 (MH⁺).

Description 4

- 15 **8-Iodo-3-phenylsulfonylquinoline (D4)**
8-Amino-3-phenylsulfonylquinoline (D3) (31.6 g, 0.11 mol) was dissolved in trifluoroacetic acid (80 ml) and the mixture evaporated. The resulting brown oil was dissolved in acetonitrile (200 ml) and added dropwise to a stirred solution of *n*-butyl nitrite (8.1 ml) in acetonitrile (300 ml) maintained at a temperature of <5 °C. Once the
- 20 addition was completed, the mixture was stirred for five minutes then tetra-(*n*-butyl)ammonium iodide (82 g, 0.22 mol) added portionwise, keeping the temperature below 10 °C. The mixture was stirred for a further 20 minutes then concentrated *in vacuo*. The dark residue was subjected to flash-75 chromatography (2 kg silica gel), eluting with hexane and dichloromethane to give a brown solid. This was dissolved in
- 25 dichloromethane (500 ml) and washed with 10% aqueous sodium thiosulphate (2 x 300 ml), dried over magnesium sulphate and concentrated to an orange solid. This was triturated with methanol to give the title compound (D4) (25.2 g, 75%) as a light yellow solid;
- 30 δ_H (CDCl₃) 7.39 (1H, t), 7.53-7.63 (3H, m), 7.86 (1H, d), 8.04 (2H, dd), 8.50 (1H, dd), 8.79 (1H, d), 9.32 (1H, d);
- Mass Spectrum : C₁₆H₁₀NO₂Si requires 395; found 396 (MH⁺).

Description 5

- 3-Phenylsulfonyl-8-piperazin-1-yl-quinoline (D5)**
- 35 A 100 ml three necked flask was charged with Pd₂(dba)₃ (174 mg, 0.19 mmol, 0.03eq), 8-Iodo-3-phenylsulfonylquinoline (D4) (2.5g, 6.33 mmol), 1,1'-bis-diphenylphosphenerrocene (316 mg, 0.57 mmol), sodium *tert*butoxide (851 mg, 8.86 mmol, 1.4eq) and piperazine (2.72g, 31.6 mmol, 5eq). The flask was evacuated and filled with nitrogen 4 times then anhydrous 1,4-dioxane (17.5 ml, 7vol) was added. The
- 40 mixture was stirred and heated to 40°C for 16 ½ hrs.
- The dark solution was allowed to cool to room temperature, dichloromethane (12.5 ml) was added and the solution was washed with H₂O (12.5 ml). The aqueous wash was

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- extracted with dichloromethane and the combined organic layers were extracted with 5M HCl (2x12.5 ml). The combined aqueous layers were washed with (dichloromethane 2.5 ml) then transferred to a conical flask, dichloromethane (12.5 ml) was added and the flask was cooled in an ice/water bath. 10M Aqueous sodium hydroxide (13 ml) was added whilst stirring, the mixture was then stirred at room temperature until all the solids were dissolved. The lower organic layer was removed and the aqueous layer was extracted with dichloromethane (7.5 ml), the combined organic layers were concentrated under reduce pressure to ~5 ml, isooctane (2.5 ml) was added to the dark brown solution resulting in crystallisation, the mixture was stirred at room temp for 5 min then isooctane (22.5 ml) was added over 5 min. The mixture was aged at room temp for 1½ hrs before being cooled in an ice/water bath for 30 min, the mixture was filtered and the cake washed with isooctane (5 ml). The cake was dried under reduced pressure to give the title compound D5; yield 1.67g, 75%.
- δ_{H} (CDCl₃): 1.6 (1H, bs), 3.18 (4H, m), 3.34 (4H, m), 7.27 (1H, m), 7.49-7.80 (5H, m), 8.01 (2H, dd), 8.75, (1H, d), 9.21 (1H, d).

Example 1

Crystallisation of 3-phenylsulfonyl-8-piperazin-1-yl-quinoline (Form III)

- 3-Phenylsulfonyl-8-piperazin-1-yl-quinoline (D5) (5g) was dissolved in isopropanol (80ml) with warming to reflux. The resultant solution was then treated with charcoal (1.25g), filtered, then the solution was allowed to cool to ambient, crystallisation initiating at -80°C. The product was collected by filtration, washed with isopropanol (10ml); and dried *in vacuo* at 45°C to give the title compound, 3.1g, 62%. Melting point 188°C.

Example 2

Crystallisation of 3-phenylsulfonyl-8-piperazin-1-yl-quinoline (Form III)

(Alternative Procedure)

- 3-Phenylsulfonyl-8-piperazin-1-yl-quinoline (D5) (10g) was dissolved in ethanol (80ml) with warming to 70°C. The resultant solution was then treated with charcoal (1g), filtered, and the filter bed rinsed with ethanol (20ml). The combined filtrate was adjusted to 54°C, then cooled to 50°C over 15 minutes. The solution was seeded with 3-phenylsulfonyl-8-piperazin-1-yl-quinoline (Form III) (10mg), cooled to 35°C over 30 minutes, held for 1 hour, then cooled to 20°C over 30 minutes, and stirred for a further 1 hour 15 minutes. The product was collected by filtration, washed with cold ethanol, (2 x 10ml); and dried *in vacuo* at 40°C to give the title compound, 6.64g, 66.4%. Melting point 188°C.

Example 3

Crystallisation of 3-phenylsulfonyl-8-piperazin-1-yl-quinoline (Form III)

(Alternative Procedure)

- 3-Phenylsulfonyl-8-piperazin-1-yl-quinoline (D5) (10g) was dissolved in ethanol (80ml) with warming to 72°C. The resultant solution was then pumped through a Cuno R55SP

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- filter into a second vessel (pre-heated to 55°C) via a sinter funnel. The original flask and the Cuno filter were washed with ethanol (20ml). The combined filtrate was heated to 72°C to redissolve the material, then adjusted to 50°C. The solution was seeded with 3-phenylsulfonyl-8-piperazin-1-yl-quinoline (Form III) (10mg), cooled to 35°C over 30 minutes, held for 1 hour, then cooled to 20°C over 30 minutes, and stirred for a further 48 hours. The product was collected by filtration, washed with ethanol (20ml) and dried *in vacuo* at 50°C to give the title compound, 5.64g, 56.4%. Melting point 188°C.

Characterising data recorded for Example 1:

- The infrared spectrum of the solid product was recorded using a Nicolet Avatar 360 FT-IR spectrometer fitted with a universal ATR accessory. The FT-IR spectrum (Figure 1) shows bands at 724, 758, 777, 804, 818, 838, 856, 905, 918, 948, 1023, 1055, 1081, 1092, 1118, 1136, 1153, 1178, 1244, 1302, 1318, 1365, 1378, 1403, 1444, 1471, 1490, 1589, 1584, 1603 and 2819 cm⁻¹.

- FT-Raman spectra of samples in glass tubes were acquired using a ThermoNicolet 980 E.S.P. spectrometer. Excitation at 1064 nm was provided by a Nd:YVO₄ laser with a power of 400 mW at the sample position. 1200 scans were recorded at 4 cm⁻¹ resolution.

- The FT-Raman spectrum (Figure 2) shows bands at 159, 184, 214, 241, 285, 304, 318, 429, 545, 558, 614, 706, 724, 803, 856, 1000, 1023, 1080, 1083, 1136, 1152, 1233, 1243, 1317, 1343, 1364, 1378, 1403, 1446, 1589, 1584, 1602, 3050 and 3073 cm⁻¹.

- The X-Ray Powder Diffractogram pattern of the solid product (Figure 3) was recorded using the following acquisition conditions: Unground material was packed into top-filled Si cups. Powder patterns were obtained using a Bruker D8 Advance X-Ray powder diffractometer configured with a Cu anode (40 kV, 40 mA), variable divergence slit, primary and secondary Soller slits, and a position sensitive detector. Data were acquired over the range 2 - 40 degrees 2-theta using a step size of 0.0145 degrees 2-theta (1 s per step). Samples were rotated during data collection. Characteristic 2θ XRPD angles are 10.29, 10.76, 11.94, 14.33, 14.61, 14.93, 16.02, 16.80, 17.47, 17.92, 19.13, 19.55, 19.84, 20.33, 21.16, 21.36, 23.33, 23.66, 24.44, 24.67, 25.51, 26.12, 27.13, 27.77, 28.06, 28.35, 29.23, 29.46, 30.06, 30.35, 31.27, 32.35, 32.66, 33.06, 33.77, 34.49, 35.18, 36.42, 37.34, 38.39 and 39.51°.

- Brief Description of the Drawings

Figure 1 shows the Infrared spectrum obtained for 3-phenylsulfonyl-8-piperazin-1-yl-quinoline (Form III).

- Figure 2 shows the Raman spectrum obtained for 3-phenylsulfonyl-8-piperazin-1-yl-quinoline (Form III).

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Figure 3 shows the X-Ray Powder Diffractogram obtained for 3-phenylsulfonyl-8-piperazin-1-yl-quinoline (Form III).

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Claims:

1. A polymorphic form of 3-phenylsulfonyl-8-piperazin-1-yl-quinoline characterised in that it provides:
 - 5 (i) an infrared spectrum containing peaks at 724, 758, 777, 804, 818, 838, 858, 905, 918, 948, 1023, 1055, 1081, 1092, 1118, 1136, 1153, 1178, 1244, 1302, 1318, 1365, 1378, 1403, 1444, 1471, 1490, 1589, 1584, 1603 and 2819 cm^{-1} ; and/or
 - (ii) a Raman spectrum containing peaks at 159, 184, 214, 241, 285, 304, 318, 429, 545, 558, 614, 706, 724, 803, 856, 1000, 1023, 1080, 1093, 1136, 1152, 1233, 1243, 10 1317, 1343, 1384, 1378, 1403, 1446, 1589, 1584, 1602, 3050 and 3073 cm^{-1} ; and/or
 - (iii) an X-ray powder diffraction (XRPD) pattern which gives calculated lattice spacings at 10.29, 11.94, 17.47, 19.55, 19.84, and 20.33°; and/or
 - (iv) a melting point of 188°C.
- 15 2. A polymorph according to claim 1 which provides an infrared spectrum substantially in accordance with Figure 1.
3. A polymorph according to claim 1 or claim 2 which provides a Raman spectrum substantially in accordance with Figure 2.
- 20 4. A polymorph according to any one of claims 1 to 3 which provides an X-ray powder diffraction (XRPD) pattern which gives calculated lattice spacings at 10.29, 10.76, 11.94, 14.33, 14.61, 14.93, 16.02, 16.80, 17.47, 17.92, 19.13, 19.55, 19.84, 20.33, 21.16, 21.36, 23.33, 23.96, 24.44, 24.67, 25.51, 26.12, 27.13, 27.77, 28.06, 25 28.35, 29.23, 29.46, 30.06, 30.35, 31.27, 32.35, 32.66, 33.08, 33.77, 34.49, 35.18, 36.42, 37.34, 38.39 and 39.51°.
5. A polymorph according to any one of claims 1 to 4 which provides an X-ray powder diffraction (XRPD) pattern substantially in accordance with Figure 3.
- 30 6. A polymorph according to any one of claims 1 to 5, in isolated form.
7. A polymorph according to any one of claims 1 to 5, in pure form.
- 35 8. A polymorph according to any one of claims 1 to 5, in crystalline form.
9. A pharmaceutical composition which comprises a polymorph according to any one of claims 1 to 8 and a pharmaceutically acceptable carrier or excipient.
- 40 10. A polymorph according to any one of claims 1 to 8 for use in therapy.

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11. A polymorph according to any one of claims 1 to 8 for use in the treatment of depression, anxiety, Alzheimers disease, age related cognitive decline, ADHD, obesity, mild cognitive impairment, schizophrenia, cognitive deficits in schizophrenia and stroke.
- 5 12. The use of a polymorph according to any one of claims 1 to 8 in the manufacture of a medicament for the treatment or prophylaxis of depression, anxiety, Alzheimers disease, age related cognitive decline, ADHD, obesity, mild cognitive impairment, schizophrenia, cognitive deficits in schizophrenia and stroke.
- 10 13. A pharmaceutical composition comprising a polymorph according to any one of claims 1 to 8 for use in the treatment of depression, anxiety, Alzheimers disease, age related cognitive decline, ADHD, obesity, mild cognitive impairment, schizophrenia, cognitive deficits in schizophrenia and stroke.
- 15 14. A method of treating depression, anxiety, Alzheimers disease, age related cognitive decline, ADHD, obesity, mild cognitive impairment, schizophrenia, cognitive deficits in schizophrenia and stroke which comprises administering a safe and therapeutically effective amount to a patient in need thereof of a polymorph according to any one of claims 1 to 8.
- 20 15. A method of promoting neuronal growth within the central nervous system of a mammal which comprises the step of administering a polymorph according to any one of claims 1 to 8.
- 25 16. Use of a polymorph according to any one of claims 1 to 8 in the manufacture of a medicament for promoting neuronal growth within the central nervous system of a mammal
- 30 17. A pharmaceutical composition comprising a polymorph according to any one of claims 1 to 8 for use in promoting neuronal growth within the central nervous system of a mammal.

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Figure 1 Infrared spectrum of 3-phenylsulfonyl-8-piperazin-1-yl-quinoline (Form III)

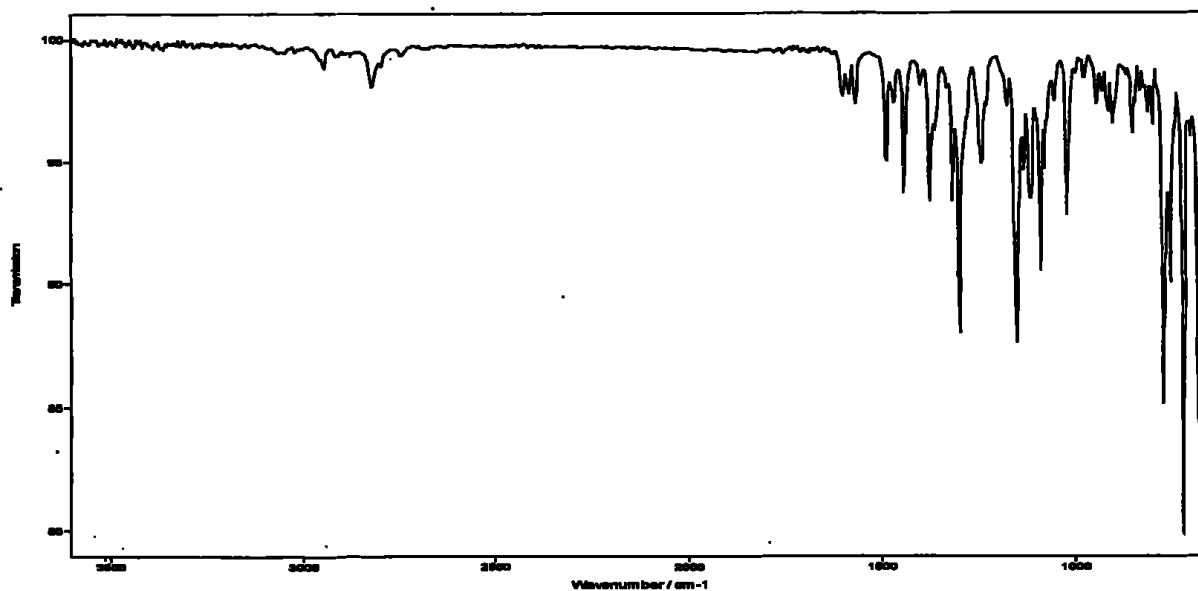
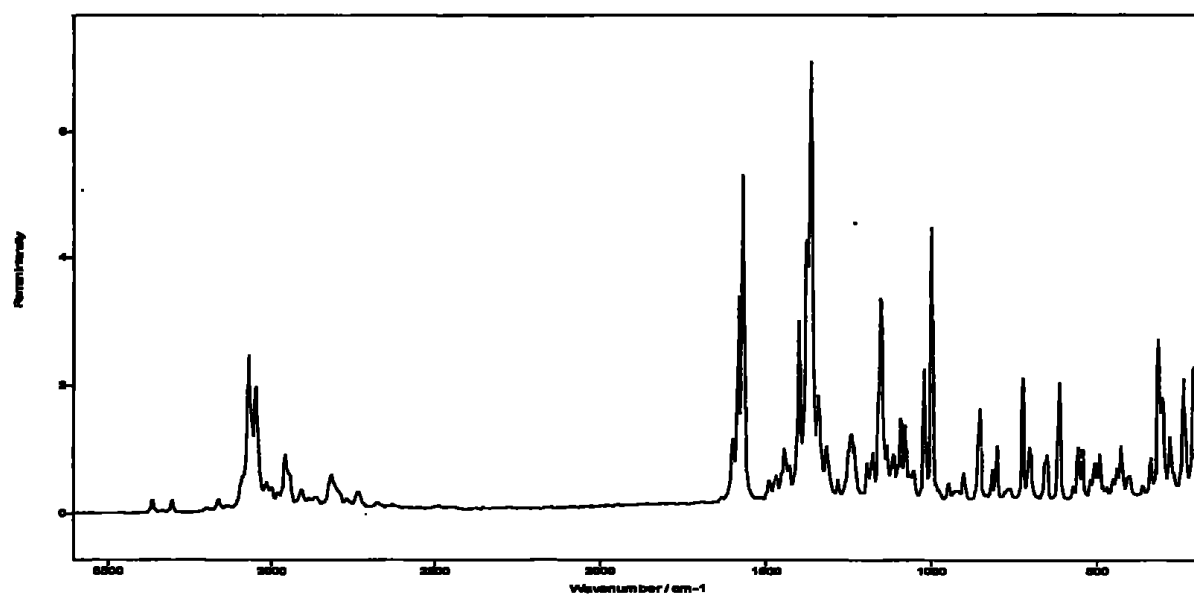
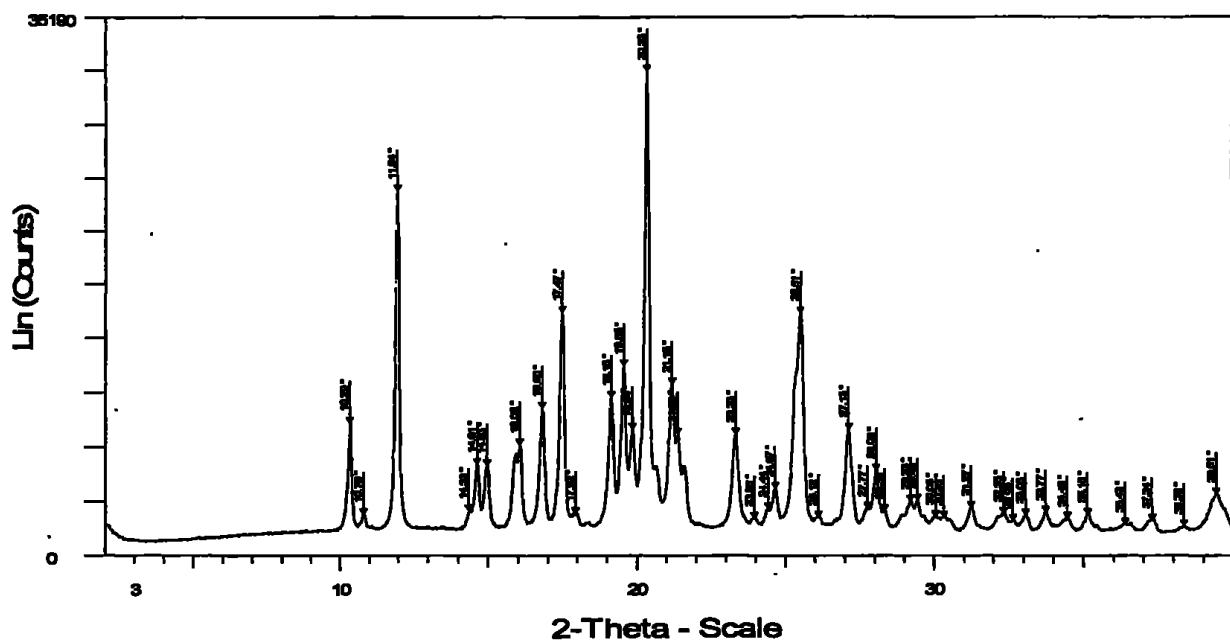


Figure 2 Raman spectrum of 3-phenylsulfonyl-8-piperazin-1-yl-quinoline (Form III)



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Figure 3 X-Ray Powder Diffractogram of 3-phenylsulfonyl-8-piperazin-1-yl-quinoline (Form III)



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INTERNATIONAL SEARCH REPORT

International Application No.
PCT/EP2004/010843

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D215/40 A61K31/47 A61P25/00

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

B. FILES SEARCHED

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

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

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

EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, A	WO 03/080580 A (GLAXO GROUP LIMITED; AHMED, MAHMOOD; JOHNSON, CHRISTOPHER, NORBERT; JO) 2 October 2003 (2003-10-02) cited in the application examples 16,51,52	1-17

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

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may have doubts on priority claims or which is cited to establish the publication date of another claim or other special reasons (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 considered with one or more other such documents, such combination being obvious to a person skilled in the art.
- *U* document counterpart of the same patent family

Date of the actual completion of the international search

1 March 2005

Date of mailing of the international search report

14/03/2005

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2004/010843

Box I Observations where certain claims were found unsearchable (Continuation of Item 2 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. ☒ Claims Nos.: 14, 15
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 14 and 15 are 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 compounds.
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 8.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 3 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/EP2004/010843

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FORMA POLIMORFICA DE 3-FENILSULFONIL-8-PIPERAZIN-1-IL-
QUINOLINA

MEMORIA DESCRIPTIVA

5

Esta invención se refiere a un compuesto novedoso que tiene actividad farmacológica, a procedimientos para su preparación, a composiciones que lo contienen y a su uso en el tratamiento de CNS y otros trastornos.

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WO 2003/080580 (Glaxo Group Limited) describe la preparación de 3-fenilsulfonil-8-piperazin-1-il-quinolina (ejemplo 16) además de dos formas polimórficas de 3-fenilsulfonil-8-piperazin-1-il-quinolina (forma I; ejemplo 51 y forma II; ejemplo 52). 3-Fenilsulfonil-8-piperazin-1-il-quinolina se describe en WO 2003/080580 teniendo afinidad para el receptor 5-HT₂ y se reclama por ser útil en el tratamiento de CNS y otros trastornos.

15

Se ha encontrado ahora que 3-fenilsulfonil-8-piperazin-1-il-quinolina existe en una forma polimórfica adicional que se caracteriza principalmente porque posee un alto punto de fusión en comparación con las formas I y II. Además esta forma polimórfica adicional de 3-fenilsulfonil-8-
20 piperazin-1-il-quinolina se menciona como la forma III.

20

De este modo, de acuerdo con un primer aspecto de la presente invención, se proporciona 3-fenilsulfonil-8-piperazin-1-il-quinolina forma III.

De manera adecuada, la presente invención proporciona 3-fenilsulfonil-8-piperazin-1-il-quinolina, de manera adecuada como se caracteriza por datos proporcionados por al menos uno de los siguientes: infrarrojo, Raman, difracción de polvo de rayos X o resonancia magnética nuclear y datos de punto de fusión se proporcionan en la presente, incluyendo
5 datos espectrales parciales proporcionados en la presente.

De este modo, un aspecto de la presente invención proporciona una forma polimórfica de 3-fenilsulfonil-8-piperazin-1-il-quinolina, caracterizada porque proporciona:

10 i) un espectro infrarrojo que contiene picos en 724, 758, 777, 804, 818, 838, 856, 905, 918, 948, 1023, 1055, 1081, 1092, 1118, 1136, 1153, 1178, 1244, 1302, 1318, 1365, 1378, 1403, 1444, 1471, 1490, 1569, 1584, 1603 y 2819 cm^{-1} ; y/o

ii) un espectro Raman que contiene picos en 159, 184, 214, 241, 285, 304, 318, 429, 545, 558, 614, 706, 724, 803, 856, 1000, 1023, 1080, 1093, 1138, 1152, 1233, 1243, 1317, 1343, 1364, 1378, 1403, 1446, 1569, 1584, 1602, 3050 y 3073 cm^{-1} , y/o

iii) un patrón de difracción de polvo de rayos X (XRPD) que da separaciones calculadas de retículo en 10.29, 11.94, 17.47, 19.55, 19.84 y
20 20.33°; y/o

iv) un punto de fusión de 188°C.

En un aspecto preferido, el polimorfo de la presente invención proporciona un espectro infrarrojo sustancialmente de conformidad con la figura 1.

En un aspecto preferido, el polimorfo de la presente invención
5 proporciona un espectro Raman sustancialmente de conformidad con la figura 2.

En un aspecto preferido, el polimorfo de la presente invención proporciona un patrón de difracción de polvo de rayos X (XRPD) que da separaciones calculadas de retículo en 10.29, 10.76, 11.94, 14.33, 14.61,
10 14.93, 16.02, 16.80, 17.47, 17.92, 19.13, 19.55, 19.84, 20.33, 21.16, 21.36, 23.33, 23.96, 24.44, 24.67, 25.51, 26.12, 27.13, 27.77, 28.06, 28.35, 29.23, 29.46, 30.06, 30.35, 31.27, 32.35, 32.66, 33.08, 33.77, 34.49, 35.18, 36.42, 37.34, 38.39 y 39.51°.

En un aspecto más preferido, el polimorfo de la presente
15 invención proporciona un patrón de difracción de polvo de rayos X (XRPD) sustancialmente de conformidad con la figura 3.

La presente invención abarca el polimorfo aislado en forma pura o cuando se mezcla con otros materiales, por ejemplo las formas conocidas de 3-fenilsulfonil-8-piperazin-1-il-quinolina o cualquier otro material.

20 De este modo, en un aspecto se proporciona el polimorfo en forma aislada. En un aspecto adicional se proporciona el polimorfo en forma pura. En aún otro aspecto adicional se proporciona el polimorfo en forma cristalina. Más preferiblemente, el polimorfo se proporciona en forma pura.

"Aislado en forma pura" se refiere a 3-fenilsulfonil-8-piperazin-1-il-quinolina forma III presente en una cantidad de preferiblemente >75%, más preferiblemente >90%, particularmente >95%, especialmente >99% con relación a otros compuestos o polimorfos de 3-fenilsulfonil-8-piperazin-1-il-quinolina que pueden estar presentes en una muestra aislada.

El compuesto de la presente invención tiene afinidad para el receptor 5-HT₆ y se cree que es de uso potencial en el tratamiento de ciertos trastornos del CNS tal como ansiedad, depresión, epilepsia, trastornos obsesivos compulsivos, migraña, trastornos cognoscitivos de la memoria (por ejemplo, enfermedad de Alzheimer, disminución cognoscitiva relacionada con la edad) enfermedad de Parkinson, ADHD (trastorno del déficit de la atención/síndrome de hiperactividad) trastornos del sueño (incluyendo alteraciones del ritmo circadiano), trastornos de la alimentación tal como anorexia y bulimia, ataques de pánico, abstinencia de abuso de fármacos, tal como cocaína, etanol, nicotina y benzodiazepinas, esquizofrenia (en particular déficits cognoscitivos de esquizofrenia), apoplejía y también trastornos relacionados con trauma espinal y/o lesión de la cabeza tal como hidrocefalia. También se espera que el compuesto de la invención se utilice en el tratamiento de ciertos trastornos GI (gastrointestinales) tal como IBS (síndrome del intestino irritable). También se espera que el compuesto de la invención se utilice en el tratamiento de obesidad.

De este modo, la invención proporciona también 3-fenilsulfonil-8-piperazin-1-il-quinolina (forma III), para utilizarse como una sustancia

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terapéutica, en particular en el tratamiento o profilaxis de los trastornos anteriores. En particular, la invención proporciona 3-fenilsulfonil-8-piperazin-1-il-quinolina (forma III), para utilizarse en el tratamiento de depresión, ansiedad, enfermedad de Alzheimer, disminución cognoscitiva relacionada con la edad, ADHD, obesidad, deterioro cognoscitivo moderado, esquizofrenia, déficits cognoscitivos en esquizofrenia y apoplejía.

La invención además proporciona un método de tratamiento o profilaxis de los trastornos anteriores, en mamíferos, incluyendo humanos, que comprende administrar al doliente una cantidad terapéuticamente efectiva de 3-fenilsulfonil-8-piperazin-1-il-quinolina (forma III).

En otro aspecto, la invención proporciona el uso de 3-fenilsulfonil-8-piperazin-1-il-quinolina (forma III) en la fabricación de un medicamento para utilizarse en el tratamiento o profilaxis de los trastornos anteriores.

Los antagonistas de 5-HT₆ tienen el potencial de ser capaces de incrementar la frecuencia celular neuronal polisiliada inducida por el aprendizaje y basal en regiones del cerebro tal como el lóbulo temporal medio de ratas e hipocampo relacionado, como se describe en WO 2003/066056. De este modo, de acuerdo con un aspecto adicional de la presente invención, se proporciona un método para promover el crecimiento neuronal dentro del sistema nervioso central de un mamífero que comprende el paso de administrar 3-fenilsulfonil-8-piperazin-1-il-quinolina (forma III).

Con el fin de utilizar el compuesto de la presente invención en terapia, éste se formulará normalmente en una composición farmacéutica de conformidad con la práctica farmacéutica estándar. La presente invención también proporciona una composición farmacéutica, que comprende 3-
5 fenilsulfonil-8-piperazin-1-il-quinolina (forma III) y un portador farmacéuticamente aceptable.

Una composición farmacéutica de la invención, que puede prepararse al mezclar, de manera adecuada a temperatura ambiente y presión atmosférica, generalmente se adapta para administración oral, parenteral o
10 rectal, y como tal, puede estar en forma de tabletas, cápsulas, preparaciones líquidas orales, polvos, gránulos, trociscos, polvos que se reconstituyen, soluciones inyectables o que se pueden verter o suspensiones o supositorios. Las composiciones oralmente administrables generalmente se prefieren.

Las tabletas y cápsulas para administración oral pueden
15 encontrarse en una forma de dosis unitaria, y pueden contener excipientes convencionales, tales como agentes aglutinantes, llenadores, lubricantes en tabletas, desintegrantes y agentes humectantes aceptables. Las tabletas pueden revestirse de conformidad con métodos bien conocidos en la práctica normal farmacéutica.

20 Las preparaciones líquidas orales pueden encontrarse en forma de, por ejemplo, suspensión acuosa u oleosa, soluciones, emulsiones, jarabe o elixires, y pueden estar en forma de un producto seco para reconstitución con agua u otro vehículo adecuado antes de utilizarse. Dichas preparaciones

líquidas pueden contener aditivos convencionales tales como agentes de suspensión, agentes emulsificantes, vehículos no acuosos (que pueden incluir aceites comestibles), conservadores, y, si se desea, saborizantes o colorantes convencionales.

- 5 Para administración parenteral, las formas de dosificación unitarias fluidas se preparan utilizando un compuesto de la invención o una sal farmacéuticamente aceptable del mismo y un vehículo estéril. El compuesto, dependiendo del vehículo y concentración utilizada, puede ser suspendido o disuelto en el vehículo. En soluciones de preparación, el compuesto puede
- 10 disolverse para inyección y esterilizarse con filtro antes de llenarse en un recipiente adecuado o ampolla y sellarse. De manera útil, los adyuvantes, tales como anestésicos locales, conservadores y agentes reguladores de pH se disuelven en el vehículo. Para mejorar la estabilidad, la composición puede congelarse después de llenarse en el recipiente y el agua removerse bajo
- 15 vacío. Las suspensiones parenterales se preparan en una manera sustancialmente igual, salvo que el compuesto se suspende en el vehículo en lugar de disolverse, y la esterilización no puede lograrse mediante filtración. El compuesto puede esterilizarse mediante exposición a óxido de etileno antes de la suspensión en un vehículo estéril. De manera útil, un agente tensioactivo
- 20 o agente de humectación se incluye en la composición para facilitar la distribución uniforme del compuesto.

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La composición puede contener de 0.1% a 99% en peso, preferiblemente de 10 a 60% en peso, del material activo, dependiendo del método de administración.

La dosis del compuesto utilizada en el tratamiento de los trastornos antes mencionados, variará en la forma usual con la seriedad de los trastornos, el peso del doliente, y otros factores similares. Sin embargo, como una guía general, las dosis unitarias adecuadas pueden ser 0.05 a 1000 mg, de manera más adecuada 0.05 a 200 mg, por ejemplo 20 a 40 mg; y dichas dosis unitarias preferiblemente se administrarán una vez al día, aunque la administración más de una vez al día puede requerirse; y dicha terapia puede extenderse un número de semanas o meses.

Todas las publicaciones, incluyendo más no limitándose a patentes y solicitudes de patente, citadas en esta especificación se incorporan en la presente por referencia como si cada publicación individual se indicará específicamente e individualmente para incorporarse por referencia en la presente como se establece totalmente.

Las siguientes descripciones y ejemplos ilustran la preparación del compuesto de la invención.

DESCRIPCION 1**3-Yodo-8-nitroquinolina (D1)**

Una mezcla agitada de 8-nitroquinolina (100 g, 0.57 moles) en
5 ácido acético (500 ml) se trató con *N*-yodosuccinimida (155 g, 0.69 moles) en
porciones durante 10 minutos, y se calentó a 62°C durante 6 horas. Una
porción adicional de *N*-yodosuccinimida (25 g, 0.14 moles) se introdujo y la
mezcla se agitó durante 16 horas adicionales antes de enfriar a temperatura
ambiente. El solvente se removió *in vacuo*, manteniendo la temperatura por
10 debajo de 35°C. El residuo se disolvió en diclorometano (2 L) y se lavó
sucesivamente con solución de bicarbonato de sodio acuosa saturada (2 x 1
L), solución del tiosulfato de sodio acuosa al 10% (1 L), agua (1 L), salmuera
(100 ml), posteriormente la fase orgánica se secó sobre sulfato de magnesio.
La mezcla se filtró y el solvente se removió para dar un sólido amarillo que se
15 recristalizó a partir de acetato de etilo para dar el compuesto del título (D1)
(168 g, 97%) como un sólido amarillo;

δ_H (CDCl₃) 7.65 (1H, ap.t), 7.9 (1H, dd), 8.07 (1H, dd), 8.66 (1H,
d, $j = 2\text{Hz}$), 9.19 (1H, d, $J = 2\text{Hz}$);

Espectro de masa: C₉H₅IN₂ requiere 300;

20 Encontrado 301 (MH⁺).

DESCRIPCION 2**8-Nitro-3-fenilsulfonilquinolina (D2)**

3-Yodo-8-nitroquinolina (D1) (135 g, 0.45 moles) se suspendió
5 en dimetilformamida (2.4 L) en un matraz de 3 cuellos de 5 L adaptado con un
agitador superior, bajo una atmósfera de argón. Esta mezcla se trató
sucesivamente con fenilsulfonato de sodio anhidro (99.6 g, 0.608 moles) y
complejo de bis-(triflato de cobre (I)) benceno (170 g, 0.338 moles). La
suspensión resultante se calentó a 65°C durante 18 horas. La mezcla se
10 enfrió, se filtró y el solvente se evaporó *in vacuo*. Se agregó acetona (2.5 L) al
residuo y la solución se filtró. El filtrado se evaporó *in vacuo*, se agregaron
adicionalmente 2.5 L de acetona y la mezcla se filtró de nueva cuenta. El
solvente se evaporó *in vacuo* y el residuo se disolvió en cloroformo (3 L) y se
lavó con amoníaco acuoso al 10% (2 x 2 L) y la fase orgánica se secó sobre
15 sulfato de magnesio y el solvente se evaporó *in vacuo*. El residuo café oscuro
se purificó utilizando un aparato de cromatografía instantánea Biotage-150 (5
kg de gel de sílice) eluyendo con hexano e incrementando las proporciones de
acetato de etilo para dar el compuesto del título (D2) (81.5 g, 58%) como un
sólido amarillo;

20 δ_H (d6-DMSO) 7.67 (2H, t), 7.57 (1H, d), 7.96 (1H, t), 8.13 (2H, d),
8.51 (1H, d), 8.59 (1H, d), 9.42 (1H, d), 9.50 (1H, d);

Espectro de masa: $C_{15}H_{10}SO_4N_2$ requiere 314;

Encontrado 315 (MH^+).

DESCRIPCION 3**8-Amino-3-fenilsulfonilquinolina (D3)**

Una suspensión de 8-nitro-3-fenilsulfonilquinolina (D2) (46.7 g, 172 mmoles), en tetrahidrofurano (750 ml) se agregó a una solución agitada de cloruro de titanio (III) al 30% en HCl acuoso (470 ml) [suministrado por BDH] y se enfrió en un baño con hielo, a tal velocidad que la temperatura se mantuvo por debajo de 35°C. Una vez que se completó la adición, la solución se agitó durante 10 minutos adicionales, posteriormente se introdujo agua (1.5 L) y la mezcla se vertió en un vaso de precipitado de 5 L. La solución rápidamente agitada se trató mediante la adición en porciones de carbonato de potasio sólido con el fin de lograr pH ~ 8.5. EDTA (250 g, 0.86 moles) se agregó y fue seguido por carbonato de potasio adicional para mantener pH ~ 8.5. La mezcla se extrajo con diclorometano (3 x 1 L) y la fase orgánica combinada se pasó a través de un tapón de sílice (500 g) eluyendo con diclorometano adicional (1 L) y acetato de etilo al 10% en diclorometano (1 L). Las fases orgánicas combinadas se evaporaron y el residuo se sometió a purificación utilizando un aparato de cromatografía instantánea Biotage-75 (2 kg de gel de sílice), eluyendo con diclorometano e incrementando las proporciones de éter para dar el compuesto del título (D3) (34.5 g, 72%) como un sólido café pálido;

δ_H (CDCl₃) 5.0 (2H, br s), 7.02 (1H, dd), 7.25 (1H, dd), 7.44 (1H, t), 7.50-7.59 (3H, m), 8.00-8.40 (2H, m), 8.70 (1H, s), 0.09 (1H, s);

Espectro de masa: $C_{15}H_{12}SO_2N_2$ requiere 284;

Encontrado 285 (MH^+).

DESCRIPCION 4

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8-Yodo-3-fenilsulfonilquinolina (D4)

Se disolvió en ácido trifluoroacético (60 ml), 8-amino-3-fenilsulfonilquinolina (D3) (3.16 g, 0.11 moles) y la mezcla se evaporó. El aceite café resultante se disolvió en acetonitrilo (200 ml) y se agregó gota a gota a una solución agitada de nitrito de *n*-butilo (6.1 ml) y acetonitrilo (300 ml) mantenida a una temperatura de $<5^{\circ}C$. Una vez que se completó la adición, la mezcla se agitó durante cinco minutos posteriormente se agregó en porciones yoduro de tetra-(*n*-butil) amonio (82 g, 0.22 moles), manteniendo la temperatura por debajo de $10^{\circ}C$. La mezcla se agitó durante 20 minutos adicionales, posteriormente se concentró *in vacuo*. El residuo oscuro se sometió a cromatografía instantánea-75 (2 kg de gel de sílice), eluyendo con hexano y diclorometano para dar un sólido café. Este se disolvió en diclorometano (500 ml) y se lavó con tiosulfato de sodio acuoso al $10^{\circ}C$ (2 x 300 ml), se secó sobre sulfato de magnesio y se concentró a un sólido anaranjado. Este se trituró con metanol para dar el compuesto del título (D4) (25.2 g, 75%) con un sólido amarillo claro;

δ_H ($CDCl_3$) 7.39 (1H, t), 7.53-7.63 (3H, m), 7.96 (1H, d), 8.04 (2H, dd), 8.50 (1H, dd), 8.79 (1H, d), 9.32 (1H, d);

Espectro de masa: $C_{18}H_{10}NO_2Si$, requiere 395;

Encontrado 396 (MH^+).

DESCRIPCION 5

5 3-Fenilsulfonil-8-piperazin-1-il-quinolina (D5)

Un matraz de tres cuellos de 100 ml se cargó con $Pd_2(dba)_3$ (174 mg, 0.19 mmoles, 0.03eq), 8-yodo-3-fenilsulfonilquinolina (D4) (2.5 g, 6.33 mmoles), 1,1'-bis-difenilfosfenoferrroceno (316 mg, 0.57 mmoles), terbutóxido de sodio (851 mg, 8.86 mmoles, 1.4 eq) y piperazina (2.72 g, 31.6 mmoles, 5 eq). El matraz se evacuó y se llenó con nitrógeno 4 veces posteriormente se agregó 1,4-dioxano anhidro (17.5 ml, 7 vol). La mezcla se agitó y se calentó a 40°C durante 16½ horas.

La solución oscura se dejó enfriar a temperatura ambiente, se agregó diclorometano (12.5 ml) y la solución se lavó con H_2O (12.5 ml). El lavado acuoso se extrajo con diclorometano y las capas orgánicas combinadas se extrajeron con HCl 5M (2 x 12.5 ml). Las capas acuosas combinadas se lavaron con (diclorometano 2.5 ml) se transfirieron posteriormente a un matraz cónico, se agregó diclorometano (12.5 ml) y el matraz se enfrió en un baño con hielo/agua. Hidróxido de sodio acuoso 10M (13 ml) se agregó mientras se agitaba, la mezcla posteriormente se agitó a temperatura ambiente hasta que todos los sólidos se disolvieron. La capa orgánica inferior se removió y la capa acuosa se extrajo con diclorometano

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(7.5 ml), las capas orgánicas combinadas se concentraron bajo presión reducida a ~5 ml. Isooctano (2.5 ml) se agregó a la solución café oscura que resultó en cristalización, la mezcla se agitó a temperatura ambiente durante 5 minutos y posteriormente se agregó isooctano (22.5 ml) durante 5 minutos. La
5 mezcla se añejó a temperatura ambiente durante 1 ½ hrs antes de enfriarse en un baño con hielo/agua durante 30 min, la mezcla se filtró y la torta se lavó con isooctano (5 ml). La torta se secó bajo presión reducida para dar el compuesto del título D5;

Rendimiento 1.67 g, 75%.

10 δ_H (CDCl₃): 1.6 (1H, bs), 3.18 (4H, m), 3.34 (4H, m), 7.27 (1H, m), 7.49-7.60 (5H, m), 8.01 (2H, dd), 8.75 (1H, d), 9.21 (1H, d).

EJEMPLO 1

Cristalización de 3-fenilsulfonil-8-piperazin-1-il-quinolina (forma III)

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3-fenilsulfonil-8-piperazin-1-il-quinolina (D5) (5 g) se disolvió en isopropanol (60 ml) con calentamiento a reflujo. La solución resultante entonces se trató con carbón vegetal (1.25 g), se filtró, posteriormente la solución se enfrió a temperatura ambiente, la cristalización iniciando a ~60°C.
20 El producto se recolectó mediante filtración, se lavó con isopropanol (10 ml) y se secó *in vacuo* a 45°C para dar el compuesto del título, 3.1 g, 62%.

Punto de fusión 188°C.

EJEMPL 2**Cristalización de 3-fenilsulfonil-8-piperazin-1-il-quinolina (forma III)****(Procedimiento alternativo)**

- 5 3-fenilsulfonil-8-piperazin-1-il-quinolina (D5) (10 g) se disolvió en etanol (80 ml) con calentamiento a 70°C. La solución resultante entonces se trató con carbón vegetal (1 g), se filtró, y el lecho filtrante se enjuagó con etanol (20 ml). El filtrado combinado se ajustó a 54°C, posteriormente se enfrió a 50°C durante 15 minutos. La solución maduró con 3-fenilsulfonil-8-
- 10 piperazin-1-il-quinolina (forma III) (10 mg), se enfrió a 35°C durante 30 minutos, se mantuvo durante 1 hora, posteriormente se enfrió a 20°C durante 30 minutos, y se agitó durante 1 hora con 15 minutos adicional. El producto se recolectó mediante filtración, se lavó con etanol frío (2x10 ml) y se secó *in vacuo* a 40°C para dar el compuesto del título, 6.64g, 66.4%.
- 15 Punto de fusión 188°C.

EJEMPLO 3**Cristalización de 3-fenilsulfonil-8-piperazin-1-il-quinolina (forma III)****(Procedimiento alternativo)**

20

3-fenilsulfonil-8-piperazin-1-il-quinolina (D5) (10 g) se disolvió en etanol (80 ml) con calentamiento a 72°C. La solución resultante entonces se bombeó a través de un filtro Cuno R55SP en un segundo recipiente

(precalentado a 55°C) por medio de un embudote sinterización. El matraz original y el filtro Cuno se lavaron con etanol (20 ml). El filtrado combinado se calentó a 72°C para volver a disolver el material, posteriormente se ajustó a 50°C. La solución se maduró con 3-fenilsulfonil-8-piperazin-1-il-quinolina (forma III) (10 mg), se enfrió a 35°C durante 30 minutos, se mantuvo durante 1 hora, posteriormente se enfrió a 20°C durante 30 minutos y se agitó durante 48 horas adicionales. El producto se recolectó mediante filtración, se lavó con etanol (20 ml;) y se secó *in vacuo* a 50°C para dar el compuesto del título, 5.64g, 56.4%.

10 Punto de fusión 188°C.

Datos de caracterización registrados por el ejemplo 1:

El espectro infrarrojo del producto sólido se registró utilizando un espectrómetro Nicolet Avatar 360 FT-IR ajustado con un accesorio ATR universal. El espectro FR-IR (figura 1) muestra bandas en: 724, 758, 777, 804, 818, 838, 856, 905, 918, 948, 1023, 1055, 1081, 1092, 1118, 1136, 1153, 1178, 1244, 1302, 1318, 1365, 1378, 1403, 1444, 1471, 1490, 1569, 1584, 1603 y 2819 cm⁻¹.

El espectro FR-Raman de las muestras en los tubos de vidrio se adquirieron utilizando un espectrómetro ThermNicolet 960 E.S.P. La excitación a 1064 nm se proporcionó mediante un láser Nd:YVO₄ con una potencia de 400 mW en la posición de muestra. Se registraron 1200 exploraciones a la resolución 4 cm⁻¹.

El espectro FT-Raman (figura 2) mostró bandas en 159, 184, 214, 241, 285, 304, 318, 429, 545, 558, 614, 706, 724, 803, 856, 1000, 1023, 1080, 1093, 1136, 1152, 1233, 1243, 1317, 1343, 1364, 1378, 1403, 1446, 1569, 1584, 1602, 3050 y 3073 cm^{-1} .

5 El patrón de difractograma de potencia de rayos X del producto sólido (figura 3) se registró utilizando las siguientes condiciones de adquisición: el material sin conexión a tierra se empaquetó en copas de Si llenadas hasta el tope. Los patrones de polvo se obtuvieron utilizando un difractómetro de polvo de rayos X Bruker D8 Advanced configurado con un
10 ánodo de Cu (40 kV, 40 mA), una ranura de divergencia variable, ranuras Soller primarias y secundarias, y un detector sensible a la posición. Los datos se adquirieron sobre una escala de 2-40 grados 2-teta utilizando un tamaño de paso de 0.0145 grados 2-teta (1 s por paso). Las muestras se hicieron girar durante la recolección de datos. Los ángulos 2 θ XRPD característicos son
15 10.29, 10.76, 11.94, 14.33, 14.61, 14.93, 16.02, 16.80, 14.47, 17.92, 19.13, 19.55, 19.84, 20.33, 21.16, 21.36, 23.33, 23.96, 24.44, 24.67, 25.51, 26.12, 27.13, 27.77, 28.06, 28.35, 29.23, 29.46, 30.06, 30.35, 31.27, 32.35, 32.66, 33.08, 33.77, 34.49, 35.18, 36.42, 37.84, 38.39 y 39.51°.

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BREVE DESCRIPCION DE LOS DIBUJOS

La figura 1 muestra el espectro infrarrojo obtenido para 3-fenilsulfonil-8-piperazin-1-il-quinolina (forma III).

La figura 2 muestra el espectro Raman obtenido para 3-fenilsulfonil-8-piperazin-1-il-quinolina (forma III).

La figura 3 muestra el difractograma de polvo de rayos X que se obtiene para 3-fenilsulfonil-8-piperazin-1-il-quinolina (forma III).

NOVEDAD DE LA INVENCION**REIVINDICACIONES**

5 1.- Una forma polimórfica de 3-fenilsulfonil-8-piperizin-1-il-
quilonina caracterizada porque proporciona: i) un espectro infrarrojo que con
tiene picos en 724, 758, 777, 804, 818, 838, 856, 905, 918, 948, 1023, 1055,
1081, 1092, 1118, 1136, 1153, 1178, 1244, 1302, 1318, 1365, 1378, 1403,
1444, 1471, 1490, 1569, 1584, 1603 y 2819 cm^{-1} ; y/o ii) un experto Raman
10 que contiene picos en 159, 184, 214, 285, 304, 318, 429, 545, 558, 614, 706,
724, 803, 586, 1000, 1023, 1080, 1093, 1136, 1152, 1233, 1243, 1317, 1343,
1364, 1378, 1403, 1446, 1569, 1584, 1602, 3050 y 3073 cm^{-1} ; y/o iii) un patrón
de difracción en polvo de rayos X (XRPD) que da separaciones de retículo
calculado en 10.29, 11.94, 17.47, 19.55, 19.84, y 20.33°; y/o iv) un punto de
15 fusión de 188°C.

2.- El polimorfo de conformidad con la reivindicación 1
caracterizado además porque proporciona un espectro infrarrojo
sustancialmente de conformidad con la figura 1.

3.- El polimorfo de conformidad con la reivindicación 1 o 2,
20 caracterizado además porque proporciona un espectro de Raman
sustancialmente de conformidad con la figura 2.

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4.- El polimorfo de conformidad con cualquiera de las reivindicaciones 1 a 3, que proporciona un patrón de difracción en polvo de rayos X (XRPD) que da separaciones de retículo calculados en 10.29, 10.76, 11.94, 14.33, 14.61, 14.93, 16.02, 16.80, 17.47, 17.92, 19.13, 19.55, 19.84, 20.33, 21.16, 21.36, 23.33, 23.96, 24.44, 24.67, 25.51, 26.12, 27.13, 27.77, 28.06, 28.35, 29.23, 29.46, 30.06, 30.35, 31.27, 32.35, 32.66, 33.08, 33.77, 34.49, 35.18, 36.42, 37.34, 38.39 y 38.51°.

5.- El polimorfo de conformidad con cualquiera de las reivindicaciones 1 a 4, caracterizado además porque proporciona un patrón de difracción en polvo de rayos X (XRPD) sustancialmente de conformidad con la figura 3.

6.- El polimorfo de conformidad con cualquiera de las reivindicaciones 1 a 5, caracterizado además porque está en forma aislada

7.- El polimorfo de conformidad con cualquiera de las reivindicaciones 1 a 5, caracterizado además porque está en forma pura.

8.- El polimorfo de conformidad con cualquiera de las reivindicaciones 1 a 5, caracterizado además porque está en forma cristalina.

9.- Una composición farmacéutica que comprende un polimorfo de conformidad con cualquiera de las reivindicaciones 1 a 8, y un portador o excipiente farmacéuticamente aceptable.

10.- El polimorfo de conformidad con cualquiera de las reivindicaciones 1 a 8, para utilizarse en terapia.

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11.- El polimorfo de conformidad con cualquiera de las reivindicaciones 1 a 8, para utilizarse en el tratamiento de depresión, ansiedad, enfermedad de Alzheimers, enfermedad cognoscitiva relacionada con la edad, ADHD, obesidad, impedimento cognoscitivo ligero, esquizofrenia, déficit cognoscitivos en esquizofrenia y ataques.

12.- El uso de un polimorfo como se reclama en cualquiera de las reivindicaciones 1 a 8 en la fabricación de un medicamento para el tratamiento o profilaxis de depresión, ansiedad, enfermedad de Alzheimers, enfermedad cognoscitiva relacionada con la edad, ADHD obesidad, impedimento cognoscitivo ligero, esquizofrenia, déficit cognoscitivo en esquizofrenia y ataques.

13.- Una composición farmacéutica que comprende un polimorfo de conformidad con cualquiera de las reivindicaciones 1 a 8 para utilizarse en el tratamiento de depresión, ansiedad, enfermedad de Alzheimers, enfermedad cognoscitiva relacionada con la edad, ADHD obesidad, impedimento cognoscitivo ligero, esquizofrenia, déficit cognoscitivos en esquizofrenia y ataque.

14.- Un método para tratar depresión, ansiedad, enfermedad de Alzheimer, disminución cognoscitiva relacionada con la edad, ADHD, obesidad, deterioro cognoscitivo moderado, esquizofrenia, déficits cognoscitivos en esquizofrenia y apoplejía, que comprende administrar una cantidad terapéuticamente efectiva y segura a un paciente en necesidad del

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mismo de un polimorfo de conformidad con cualquiera de las reivindicaciones 1 a 8.

15.- Un método para promover el crecimiento neuronal dentro del sistema nervioso central de un mamífero que comprende el paso de
5 administrar un polimorfo de conformidad con cualquiera de las reivindicaciones 1 a 8.

16.- Uso de un polimorfo como el que se reclama en cualquiera de las reivindicaciones 1 a 8 en la fabricación de un medicamento para promover crecimiento neuronal dentro del sistema nervioso central de un
10 mamífero.

17.- Una composición farmacéutica que comprende un polimorfo de conformidad con cualquiera de las reivindicaciones 1 a 8 para utilizarse en la promoción de crecimiento neuronal dentro del sistema nervioso central de un mamífero.

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51**RESUMEN DE LA INVENCION**

Esta invención se refiere a un compuesto novedoso de -
fenilsulfonil-8-piperazin-1-il-quinolina, a procedimientos para su preparación, a
5 composiciones que lo contienen y a su uso en el tratamiento de CNS y otros
trastornos.

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PM/dvb*kra*ecj*gcg*

P06-269F

PATENT COOPERATION TREATY

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From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference see form PCT/ISA/220		FOR FURTHER ACTION See paragraph 2 below	
International application No. PCT/EP2004/010843	International filing date (day/month/year) 23.09.2004	Priority date (day/month/year) 26.09.2003	
International Patent Classification (IPC) or both national classification and IPC C07D215A0, A61K31A7, A61P25/00			
Applicant GLAXO GROUP LIMITED			

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☐ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:  European Patent Office D-80289 Munich Tel: +49 89 2369 - 0 Fax: 523656 epc@epo d Fax: +49 89 2369 - 4465	Authorized Officer Bakboord, J Telephone No. +49 89 2369-2165 
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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/EP2004/010843

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Box No. I Basis of the opinion

1. With regard to the language, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☐ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☐ in written format
 - ☐ in computer readable form
 - c. time of filing/furnishing:
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in computer readable form.
 - ☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

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Box No. III Non-establishment of opinion with regard to novelty, inventive step and Industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application,
☒ claims Nos. 14, 15

because:

- ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):
- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☒ no international search report has been established for the whole application or for said claims Nos. 14, 15
- ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:
- the written form ☐ has not been furnished
☐ does not comply with the standard
- the computer readable form ☐ has not been furnished
☐ does not comply with the standard
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.
- ☐ See separate sheet for further details

Box No. VI Certain documents cited

1. Certain published documents (Rules 43bis.1 and 70.10)
and/or
2. Non-written disclosures (Rules 43bis.1 and 70.9)
see form 210

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

Claims 14 and 15 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

V Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

V.1 The present invention relates to a novel polymorphic form of 3-phenylsulfonyl-8-piperazin-1-yl quinoline.

V.2 Reference is made to the following document:

D1: WO 03/080580 A (GLAXO GROUP LIMITED; AHMED, MAHMOOD;
JOHNSON, CHRISTOPHER, NORBERT; JO) 2 October 2003 (2003-10-02)
Document D1 was published after the priority date. In the presumption that the priority is valid this document is not regarded as prior art.

V.3 Novelty

It is noted that document D1 discloses the preparation of 3-phenylsulfonyl-8-piperazin-1-yl-quinoline and two polymorphic forms form I and form II.

A polymorphic form III of 3-phenylsulfonyl-8-piperazin-1-yl-quinoline is disclosed in none of the documents. Claims 1-8 therefore fulfill the requirements of Art 33(2) PCT.

Claims 9, 13 and 17 describe a pharmaceutical composition comprising a polymorph of claim 1 and are novel by consequence.

Claims 10 and 11 describe the use of the polymorph of claim 1 in therapy and are novel by consequence.

Claims 12 and 16 describe the use of a polymorph of claim 1 in the manufacture

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of a medicament and are novel by consequence.

Claims 14 and 15 describe a method of treating comprising administering a polymorph of claim 1 and are novel by consequence.

V.4 Inventive step

The problem to be solved by the present application may be regarded as how to provide a further polymorph of 3-phenylsulfonyl-8-piperazin-1-yl-quinoline, which has a higher melting point than the known polymorphs. From the examples it can be seen that the polymorph of the present application has a melting point of 188 °C (cf. the melting points of the known polymorphs are 158 °C and 164 °C respectively). As the polymorph of the present application has not been made obvious by the prior art the solution of the applicant may be regarded as involving an inventive step (Art 33(3) PCT).

V.5 Industrial applicability

For the assessment of the present claims 14 and 15 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference MXG-PB60517	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. PCT/EP2004/010843	International filing date (day/month/year) 23/09/2004	(Earliest) Priority Date (day/month/year) 26/09/2003
Applicant GLAXO GROUP LIMITED		

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 5 sheets.

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

1. Basis of the report

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

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

b. ☐ With regard to any nucleotide and/or amino acid sequences disclosed in the international application, see Box No. I.

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

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

4. With regard to the title,

☐ the text is approved as submitted by the applicant.

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

A POLYMORPHIC FORM OF 3-PHENYLSULFONYL -8-PIPERAZIN-1-YL-QUINOLINE

5. With regard to the abstract,

☐ the text is approved as submitted by the applicant.

☒ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the drawings,

a. the figure of the drawings to be published with the abstract is Figure No. _____

☐ as suggested by the applicant.

☐ as selected by this Authority, because the applicant failed to suggest a figure.

☐ as selected by this Authority, because this figure better characterizes the invention.

b. ☒ none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP2004/010843

Box No. IV Text of the abstract (Continuation of item 5 of the first sheet)

This invention relates to a novel polymorph of 3-phenylsulfonyl -8-piperazin-1-yl-quinoline
to processes for its preparation, to compositions containing it and to its use in the
treatment of CNS and other disorders.

INTERNATIONAL SEARCH REPORT

International Application No.
PCT/EP2004/010843

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D215/40 A61K31/47 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 A61K

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

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

EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, A	WO 03/080580 A (GLAXO GROUP LIMITED; AHMED, MAHMOOD; JOHNSON, CHRISTOPHER, NORBERT; JO) 2 October 2003 (2003-10-02) cited in the application examples 16,51,52	1-17

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

* Special categories of cited documents:

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

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

Date of the actual completion of the international search

1 March 2005

Date of mailing of the international search report

14/03/2005

Name and mailing address of the ISA

European Patent Office, P.O. Box 5816 Patentstrasse 2
NL - 3200 HV Rijswijk
Tel: (+31-70) 340-3040, Tx: 31 051 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Bakboord, J

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2004/010843

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Box II Observations where certain claims were found unsearchable (Continuation of item 2 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. ☒ Claims Nos.: 14, 15
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 14 and 15 are 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 compounds.
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 8.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 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/EP2004/010843

61. 51

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 03080580	A	02-10-2003	AU 2003219103 A1 08-10-2003
		BR 0308696 A	25-01-2005
		CA 2479786 A1	02-10-2003
		WO 03080580 A2	02-10-2003
		EP 1497266 A2	19-01-2005

Industria y Comercio
SUPERINTENDENCIA

62
SUPERINTENDENCIA Y COMERCIO
Radacion 06430123 00000000 Folios 61
Fecha (AMB): 2006-03-27 17:30 34
Tramite : 011 PCT-PATENT 376 FASE NACI 411 PRESENTAC
Dependencia 2020 DIVISION DE NUEVAS CREACIONES

Delegatura de Propiedad Industrial
División de Nuevas Creaciones

**REQUISITOS NECESARIOS PARA PRESENTACIÓN Y AGILIZACIÓN DEL
TRAMITE**

PCT

PATENTE DE INVENCION ()	MODELO DE UTILIDAD ()	USUARIO ()	RADICADOR ()
Indicación de que se solicita la concesión de una patente	()	()	(X)
Datos de identificación del solicitante o de la persona que se presenta la solicitud	()	()	(X)
Descripción de la invención	()	()	(X)
Dibujos de ser estos pertinentes	()	()	(X)
-Comprobante de Pago de las tasas establecidas	()	()	(X)
COMPLETA ()	INCOMPLETA ()	()	()

DISEÑO INDUSTRIAL ()

Indicación de que se solicita el registro de Diseño Industrial	()	()
Datos de identificación del solicitante o de la persona que se 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 se solicita el registro de Diseño Industrial.	()	()
Datos de identificación del solicitante o de la persona que se presenta la solicitud	()	()
-Representación gráfica del Esquema Trazado	()	()
-Comprobante de Pago de las tasas establecidas	()	()
COMPLETA ()	INCOMPLETA ()	()

Firma Responsable

Fecha

REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Folio 63

2020
Bogotá D.C.,

Doctor(a)
OLARTE GARCIA CARLOS REINALDO
Apoderado(a) y/o Representante de
GLAXO GROUP LIMITED

REFERENCIA	Radicación No.	06 30123
	Solicitud internacional	EP2004/010843
	Fecha inicio fase nacional	26/04/2006
	Trámite	11
	Evento	378
	Actuación	416
	Oficio No.	926
	Folios	1

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

Cúmplase
Dado en Bogotá DC,

21 JUL 2006

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

jramos