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**Castillo Grau & Asociados**

Radicación : 00049344 00000003 Folios: 2  
Fecha (A/D): 2002-11-07 16:32:13  
Trámite : 002 PATENTES D I REGISTRO/ 538 PETICION  
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

gt

**Señor Jefe**  
**DIVISION DE NUEVAS CREACIONES**  
**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO**  
**Bogotá, D.C.**

**Re: Expediente No. 00 49.344**  
**Solicitud de Patente a nombre de**  
**SMITHKLINE BEECHAM p.l.c.**  
**Código 02 - 01 - 538**

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En relación con la solicitud contenida en el Expediente de la referencia y, en particular, con la publicación del extracto de la misma en la Gaceta de la Propiedad Industrial No. 520 de Septiembre 27, 2002, por medio del presente escrito muy respetuosamente me permito solicitarle se sirva proceder a efectuar el **EXAMEN DE PATENTABILIDAD** de la solicitud aquí contenida.

Como consecuencia de esta solicitud, acompaño el comprobante de pago de la tasa correspondiente a la misma, Recibo No. 74.317/02 —

De Usted atentamente,

**GERMAN CASTILLO GRAU**  
**T.P. No. 2978 del C.S.J.**

86 93

# Industria y Comercio

SUPERINTENDENCIA

NIT : 800176087-2

Radicacion : 00049344 00000003

Folios: 2

Fecha (AMD): 2002-11-07 16:32:13

Tracite : 002 PATENTES D 1 REGISTRO/ 538 PETICION

Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

RECIBO OFICIAL DE CAJA : 02 - 74,317  
FECHA : NOVIEMBRE 7 DE 2002

\*\*\*\*\* CONSIGNACION \*\*\*\*\*

| DEPOSITANTE               | TIPO PAGO    | BANCO         | CUENTA      | No. PAGO | FECHA PAGO | Vr. PAGO     |
|---------------------------|--------------|---------------|-------------|----------|------------|--------------|
| CASTILLO GRAU Y ASOCIADOS | CONSIGNACION | BANCO POPULAR | 050-00110-6 | 6635317  | 06/11/2002 | 3,350,200.00 |

\*\*\*\*\* CONCEPTO \*\*\*\*\*

| CAN | DENTISTICO  | CONCEPTO                             | TOTAL CONCEPTO |
|-----|-------------|--------------------------------------|----------------|
| 1   | 50005-01-01 | SOLICITUDES                          |                |
|     |             | B5 EXAMEN DE PATENTABILIDAD DE INVEN | 318,000.00     |
|     |             | TOTAL :                              | \$ 318,000.00  |

SON: TRESCIENTOS DIEZ Y OCHO MIL PESOS

RESPONSABLE : 

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. \_\_\_\_\_

Carrera 13 No. 27-00 Pisos 5, 7 y 10  
Conmutador 382 0840  
Fax 350 5220  
E-mail: info@sic.gov.co  
www.sic.gov.co  
Bogotá, D.C., Colombia

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DIVISION DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. **00-49344**

EL EXTRACTO DE LA PRESENTE SOLICITUD DE **PATENTE DE INVENCION** FUE PUBLICADO EN  
LA GACETA DE PROPIEDAD INDUSTRIAL No **520**, DE FECHA **27 DE SEPTIEMBRE DE 2002**, EL  
TERMINO HABIL SEÑALADO POR LA LEY EXPIRA EL **26 DE DICIEMBRE DE 2002**.

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI \_\_\_\_\_

NO   X

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

2020/  
Bogotá, D.C.,

**Doctor**  
**Germán Castillo Grau**  
Apoderado

Oficio N° 8385

|                   |                   |                 |
|-------------------|-------------------|-----------------|
| <b>REFERENCIA</b> | <b>Radicación</b> | <b>00 49344</b> |
|                   | <b>Trámite</b>    | <b>002</b>      |
|                   | <b>Evento</b>     | <b>001</b>      |
|                   | <b>Actuación</b>  | <b>430</b>      |
|                   | <b>Folios</b>     | <b>020</b>      |

Como resultado del examen de patentabilidad de la solicitud de patente de invención N° 00 49344, realizado según el artículo 45 de la decisión 486 de la comisión de la Comunidad Andina, se notifica:

**Documentos estudiados:**

- . Descripción: folios 5-28
- . Ejemplos: folios 28-39
- . Capítulo reivindicatorio estudiado: folios 40-46
- . Se reivindica prioridad, presentada en Gran Bretaña el 02.07.99, bajo los números 9915589

**Objeto de la invención**

Según las reivindicaciones 1 a 11 de la presente solicitud, se refiere a compuestos de fórmula (I), cuyos sustituyentes se revelan en la descripción, así como sus sales farmacéuticamente aceptables. Tales compuestos poseen actividad anticonvulsivante y son útiles en el tratamiento de una variedad de desórdenes.

Clasificación internacional de patentes A 61 K 31/47

**Claridad de la solicitud**

El art. 30 de la Decisión 486 contempla que *“Las reivindicaciones definirán la materia que se desea proteger mediante la patente. Deben ser claras y concisas y estar enteramente sustentadas por la descripción”*

Teniendo en cuenta lo anterior, las expresiones “arilo”, “heteroarilo monocíclico o bicíclico” son vagas e indefinidas y hace poco clara la materia que se desea proteger

Se le pide al solicitante hacer las aclaraciones y correcciones del caso.

**Excepciones a la patentabilidad**

El art. 20d de la decisión 486 establece que *“No serán patentables los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnóstico aplicados a los seres humanos o a animales”*

Teniendo en cuenta lo anterior, el contenido de la reivindicación 10, que trata de “Un método de tratamiento...”, no es patentable.

El artículo 14 de la decisión 486 de la comisión de la comunidad andina establece que: *“Los países miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial”*

El contenido de la reivindicación 11 que trata de “Uso de un compuesto de fórmula (I)...”, no es patentable, debido a que la legislación vigente no contempla los usos como objeto de patente.

**Determinación del estado de la técnica:**

Consultadas las fuentes de información con que cuenta este despacho, se encontraron los siguientes documentos, anteriores a la fecha de prioridad de la presente solicitud - 02.07.99-, relacionados con la materia de la presente solicitud:

| Nº | Documento  | Título                                                                  | Fecha de Publicación |
|----|------------|-------------------------------------------------------------------------|----------------------|
| 1  | WO 9931068 | “Derivados de isoquinolina sustituida y su uso como anticonvulsivantes” | 24.06.99             |
| 2  | WO 9921836 | “Derivados de isoquinolina sustituida y su uso como anticonvulsivantes” | 06.05.99             |
| 3  | WO 9841508 | “Derivados de isoquinolina sustituida y su uso como anticonvulsivantes” | 24.09.98             |
| 4  | WO 9841507 | “Derivados de isoquinolilbenzamidias como anticonvulsivantes”           | 24.09.98             |
| 5  | WO 9748683 | “Derivados de banzamidia sustituidos y su uso como antuconvulsivantes”  | 24.12.97             |

### Evaluación de los requisitos de patentabilidad:

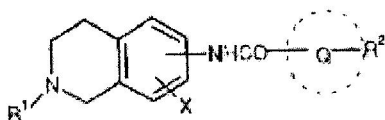
El artículo 14 de la decisión 486 de la comisión de la comunidad andina establece que: *"Los países miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial"*

En cumplimiento del artículo 14 de la decisión 486 de la comisión de la comunidad andina, se procedió a evaluar los requisitos de novedad, nivel inventivo y aplicación industrial con el fin de establecer la patentabilidad de la invención reivindicada en la solicitud en estudio.

### Evaluación de la NOVEDAD

El art. 16 de la decisión 486 contempla que *"Una invención se considerará nueva cuando no está comprendida en el estado de la técnica"*

La publicación WO 9841508 se relaciona con compuestos de fórmula (I):



Cuyos sustituyentes se revelan en la descripción, tales compuestos tienen actividad anticonvulsivante.

Comparando elemento por elemento, muchos de los compuestos de la presente solicitud son iguales a los de la anterioridad citada cuando Y es H; X es halógeno, alcoxi C1-C6, alquilo C1-C6; R<sup>1</sup> es H; R<sup>2</sup> es H o hasta 3 o más sustituyentes y pueden afectar la novedad de la presente solicitud.

### Evaluación del NIVEL INVENTIVO

El artículo 18 de la decisión 486 dispone *"Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la Materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica"*

Las publicaciones WO 9931068, WO 9921836, WO 9841508, WO 9841507 y WO 9748683 describen derivados de isoquinolina que tienen actividad anticonvulsivante

Teniendo en cuenta el objeto de la solicitud, el cual es proporcionar derivados de isoquinolina que tienen actividad anticonvulsivante, se observa que es una derivación del estado de la técnica, ya que los documentos citados revelan compuestos similares estructuralmente que tienen el mismo efecto farmacológico

Un técnico con sus conocimientos y combinando dos de los documentos citados, fabricaría los compuestos que se pretenden proteger.

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Finalmente no se demuestra un efecto mejorado o sorprendente de los compuestos de la presente solicitud con relación a los revelados en el estado de la técnica.

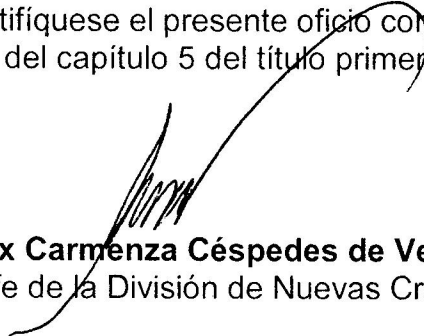
Lo anterior hace que el documento citado pueda afectar el nivel inventivo de la presente solicitud.

En conclusión los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

| Nº | Documento  | Reivindicaciones afectadas | Requisito que afecta |
|----|------------|----------------------------|----------------------|
| 1  | WO 9931068 | 1-9                        | Nivel inventivo      |
| 2  | WO 9921836 | 1-9                        | Nivel Inventivo      |
| 3  | WO 9841508 | 1-9                        | Novedad              |
|    |            | 1-9                        | Nivel Inventivo      |
| 4  | WO 9841507 | 1-9                        | Nivel Inventivo      |
|    |            |                            |                      |
| 5  | WO 9748683 | 1-9                        | Nivel Inventivo      |
|    |            |                            |                      |

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

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

  
**Álix Carmenza Céspedes de Vergel**  
Jefe de la División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha 15 SET. 2005

|                                 |                                     |
|---------------------------------|-------------------------------------|
| CONCEPTO TÉCNICO<br>Número 1328 | EXAMINADOR TÉCNICO<br>Código 202024 |
|---------------------------------|-------------------------------------|

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International Bureau

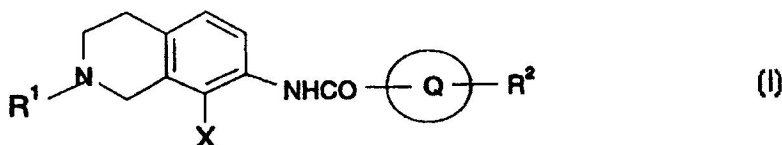


INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                           |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------|
| (51) International Patent Classification <sup>6</sup> :<br><b>C07D 217/02, 217/04, 217/06, 409/12, A61K 31/47</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |  | A1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | (11) International Publication Number: <b>WO 99/31068</b><br>(43) International Publication Date: 24 June 1999 (24.06.99) |
| (21) International Application Number: PCT/GB98/03785<br>(22) International Filing Date: 16 December 1998 (16.12.98)<br>(30) Priority Data: 9726695.1 17 December 1997 (17.12.97) GB<br>(71) Applicant (for all designated States except US): SMITHKLINE BEECHAM PLC [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB).<br>(72) Inventors; and<br>(75) Inventors/Applicants (for US only): COULTON, Steven [GB/GB]; SmithKline Beecham Pharmaceuticals, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB). PORTER, Roderick, Alan [GB/GB]; SmithKline Beecham Pharmaceuticals, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB).<br>(74) Agent: WEST, Vivien; SmithKline Beecham, Two New Horizons Court, Brentford, Middlesex TW8 9EP (GB). |  | (81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, 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, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).<br><br>Published<br>With international search report. |                                                                                                                           |

(54) Title: SUBSTITUTED ISOQUINOLINE DERIVATIVES AND THEIR USE AS ANTICONVULSANTS

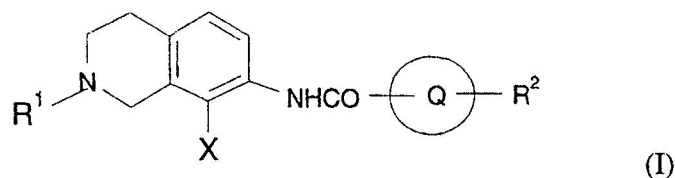


(57) Abstract

Compounds of formula (I) or pharmaceutically acceptable salts or solvates thereof, where Q is a monocyclic or bicyclic aryl or heteroaryl ring, R<sup>1</sup> is hydrogen, C<sub>1-6</sub>alkyl (optionally substituted by hydroxy or C<sub>1-4</sub>alkoxy), C<sub>1-6</sub>alkenyl, C<sub>1-6</sub>alkynyl, C<sub>1-6</sub>alkylCO-, formyl, CF<sub>3</sub>CO- or C<sub>1-6</sub>alkylSO<sub>2</sub>-, R<sup>2</sup> is hydrogen or up to three substituents selected from halogen, NO<sub>2</sub>, CN, N<sub>3</sub>, CF<sub>3</sub>O-, CF<sub>3</sub>S-, CF<sub>3</sub>CO-, trifluoromethyldiaziriny, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkenyl, C<sub>1-6</sub>alkynyl, C<sub>1-6</sub>perfluoroalkyl, C<sub>3-6</sub>cycloalkyl, C<sub>3-6</sub>cycloalkyl-C<sub>1-4</sub>alkyl-, C<sub>1-6</sub>alkylO-, C<sub>1-6</sub>alkylCO-, C<sub>3-6</sub>cycloalkylO-, C<sub>3-6</sub>cycloalkylCO-, C<sub>3-6</sub>cycloalkyl-C<sub>1-4</sub>alkylO-, C<sub>3-6</sub>cycloalkyl-C<sub>1-4</sub>alkylCO-, phenyl, phenoxy, benzyloxy, benzoyl, phenyl-C<sub>1-4</sub>alkyl-, C<sub>1-6</sub>alkylS-, C<sub>1-6</sub>alkylSO<sub>2</sub>-, (C<sub>1-4</sub>alkyl)<sub>2</sub>NSO<sub>2</sub>-, (C<sub>1-4</sub>alkyl)NHSO<sub>2</sub>-, (C<sub>1-4</sub>alkyl)<sub>2</sub>NCO-, (C<sub>1-4</sub>alkyl)NHCO, CONH<sub>2</sub>, CF<sub>3</sub>SO<sub>2</sub>, C<sub>1-6</sub>alkenyl, C<sub>1-6</sub>alkynyl or C<sub>1-6</sub>hydroxyalkyl; or -NR<sup>3</sup>R<sup>4</sup> where R<sup>3</sup> is hydrogen or C<sub>1-4</sub>alkyl, and R<sup>4</sup> is hydrogen, C<sub>1-4</sub>alkyl, formyl, -CO<sub>2</sub>C<sub>1-4</sub>alkyl or -COC<sub>1-4</sub>alkyl; or two R<sup>2</sup> groups together form a carbocyclic ring that is saturated or unsaturated and unsubstituted or substituted by -OH or =O; and X is halogen, C<sub>1-6</sub>alkoxy, C<sub>1-6</sub>alkyl, C<sub>2-6</sub>alkenyl optionally substituted by phenyl; are useful in the treatment and/or prophylaxis of anxiety, mania, depression, panic disorders and/or aggression, disorders associated with a subarachnoid haemorrhage or neural shock, the effects associated with withdrawal from substances of abuse such as cocaine, nicotine, alcohol and benzodiazepines, disorders treatable and/or preventable with anti-convulsive agents, such as epilepsy including post-traumatic epilepsy, Parkinson's disease, psychosis, migraine, cerebral ischaemia, Alzheimer's disease and other degenerative diseases such as Huntington's chorea, schizophrenia, obsessive compulsive disorders (OCD), neurological deficits associated with AIDS, sleep disorders (including circadian rhythm disorders, insomnia and narcolepsy), tics (e.g. Gilles de la Tourette's syndrome), traumatic brain injury, tinnitus, neuralgia, especially trigeminal neuralgia, neuropathic pain, dental pain, cancer pain, inappropriate neuronal activity resulting in neurodysesthesias in diseases such as diabetes, multiple sclerosis (MS) and motor neurone disease, ataxias, muscular rigidity (spasticity), temporomandibular joint dysfunction, or amyotrophic lateral sclerosis (ALS).

## CLAIMS

1. A compound of formula (I) or pharmaceutically acceptable salt or solvate thereof:



where Q is a monocyclic or bicyclic aryl or heteroaryl ring,

- 10  $R^1$  is hydrogen,  $C_{1-6}$  alkyl (optionally substituted by hydroxy or  $C_{1-4}$ alkoxy),  $C_{1-6}$ alkenyl,  $C_{1-6}$ alkynyl,  $C_{1-6}$ alkylCO-, formyl,  $CF_3$ CO- or  $C_{1-6}$ alkylSO<sub>2</sub>-,
- 15  $R^2$  is hydrogen or up to three substituents selected from halogen, NO<sub>2</sub>, CN, N<sub>3</sub>,  $CF_3$ O-,  $CF_3$ S-,  $CF_3$ CO-, trifluoromethyldiaziriny,  $C_{1-6}$ alkyl,  $C_{1-6}$ alkenyl,  $C_{1-6}$ alkynyl,  $C_{1-6}$ perfluoroalkyl,  $C_{3-6}$ cycloalkyl,  $C_{3-6}$ cycloalkyl- $C_{1-4}$ alkyl-,  $C_{1-6}$ alkylO-,  $C_{1-6}$ alkylCO-,  $C_{3-6}$ cycloalkylO-,  $C_{3-6}$ cycloalkylCO-,  $C_{3-6}$ cycloalkyl- $C_{1-4}$ alkylO-,  $C_{3-6}$ cycloalkyl- $C_{1-4}$ alkylCO-, phenyl, phenoxy, benzyloxy, benzoyl, phenyl- $C_{1-4}$ alkyl-,  $C_{1-6}$ alkylS-,  $C_{1-6}$ alkylSO<sub>2</sub>-,  $(C_{1-4}$ alkyl)<sub>2</sub>NSO<sub>2</sub>-,
- 20  $(C_{1-4}$ alkyl)NHSO<sub>2</sub>-,  $(C_{1-4}$ alkyl)<sub>2</sub>NCO-,  $(C_{1-4}$ alkyl)NHCO, CONH<sub>2</sub>,  $CF_3$ SO<sub>2</sub>,  $C_{1-6}$ alkenyl,  $C_{1-6}$ alkynyl or  $C_{1-6}$ hydroxyalkyl; or -NR<sup>3</sup>R<sup>4</sup> where R<sup>3</sup> is hydrogen or  $C_{1-4}$  alkyl, and R<sup>4</sup> is hydrogen,  $C_{1-4}$ alkyl, formyl, -CO<sub>2</sub> $C_{1-4}$ alkyl or -COC $C_{1-4}$ alkyl; or two R<sup>2</sup> groups together form a carbocyclic ring that is saturated or
- 25 unsaturated and unsubstituted or substituted by -OH or =O; and
- X is halogen,  $C_{1-6}$  alkoxy,  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl optionally substituted by phenyl.

- 30 2. A compound according to claim 1 of formula (IA)

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HO

or  $-NR^5R^6$  where  $R^5$  is hydrogen or  $C_{1-4}$  alkyl, and  $R^6$  is hydrogen,  $C_{1-4}$  alkyl, formyl,  $-CO_2C_{1-4}$  alkyl or  $-COC_{1-4}$  alkyl; or two  $R^2$  groups together form a carbocyclic ring that is saturated or unsaturated and unsubstituted or substituted by  $-OH$  or  $=O$ ; and

5 the two  $R^3$  groups and the two  $R^4$  groups are each independently hydrogen or  $C_{1-6}$  alkyl or the two  $R^3$  groups and/or the two  $R^4$  groups together form a  $C_{3-6}$  spiroalkyl group provided that at least one  $R^3$  and  $R^4$  group is not hydrogen.

10 The compounds of this invention are typically isoquinolinyl-carboxamides, especially (tetrahydroisoquinolin-7-yl)carboxamides. The carboxamide moiety may be a benzamide. When two  $R^2$  groups form a carbocyclic ring, this is typically a 5-7 membered ring, and the carboxamide moiety may be a naphthalene carboxamide or an indane or indanone carboxamide.

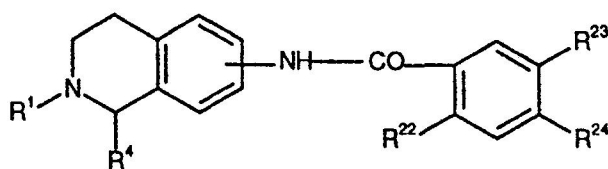
15 In the formula (I), alkyl groups, including alkyl groups that are part of other moieties, such as alkoxy or acyl, may be straight chain or branched. Phenyl groups, including phenyl groups that are part of other moieties, in  $R^2$  may optionally be substituted with one or more independently selected halogen or  $C_{1-6}$  alkyl,  $C_{1-6}$  alkoxy or  $C_{1-6}$  alkylcarbonyl.

20 Suitable  $C_{3-6}$  cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl. Suitable halo substituents include fluoro, chloro, iodo and bromo.

It should be appreciated that compounds of the present invention possess chiral centres and as such may exist in different enantiomeric forms, the present invention extends to

25 each enantiomeric form and mixtures thereof including diastereoisomers and racemates.

One suitable group of compounds of this invention are of formula (IA)



30

(IA)

where

$R^1$  is hydrogen,  $C_{1-6}$  alkyl (optionally substituted by hydroxy or  $C_{1-4}$  alkoxy),  $C_{1-6}$  alkenyl,  $C_{1-6}$  alkynyl, formyl,  $C_{1-6}$  alkylCO,  $C_{1-6}$  alkylSO<sub>2</sub>, or CF<sub>3</sub>CO-;

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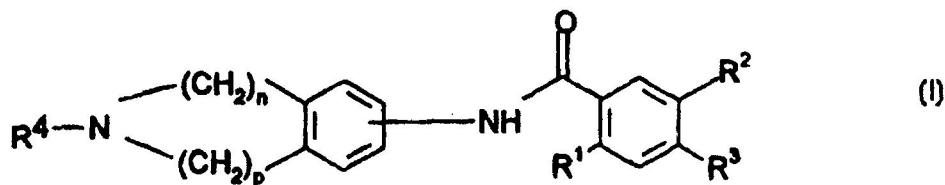
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|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------|
| (51) International Patent Classification <sup>6</sup> :<br>C07D 217/04, 217/02, 209/44, 223/16,<br>A61K 31/47, 31/40, 31/495, C07D 401/12                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |  | A1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | (11) International Publication Number: <b>WO 97/48683</b><br>(43) International Publication Date: 24 December 1997 (24.12.97) |
| (21) International Application Number: PCT/EP97/03131<br>(22) International Filing Date: 13 June 1997 (13.06.97)<br>(30) Priority Data:<br>9612608.1 17 June 1996 (17.06.96) GB<br>9615352.3 22 July 1996 (22.07.96) GB<br>9711013.4 28 May 1997 (28.05.97) GB<br>(71) Applicant (for all designated States except US): SMITHKLINE BEECHAM PLC [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB).<br>(72) Inventors; and<br>(75) Inventors/Applicants (for US only): HARLING, John, David [GB/GB]; SmithKline Beecham Pharmaceuticals, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB). ORLEK, Barry, Sidney [GB/GB]; SmithKline Beecham Pharmaceuticals, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB). THOMPSON, Mervyn [GB/GB]; SmithKline Beecham Pharmaceuticals, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB). |  | (74) Agent: LAWTON, Peter, Philip; SmithKline Beecham plc, Corporate Intellectual Property, Two New Horizons Court, Brentford, Middlesex TW8 9EP (GB).<br>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). |                                                                                                                               |

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(54) Title: SUBSTITUTED BENZAMIDE DERIVATIVES AND THEIR USE AS ANTICONVULSANTS



(57) Abstract

The invention relates to substituted benzamido-heterocyclic compounds of general formula (I) having an alkoxy substituent at the C2 position of the benzamido group and various substituents at positions C4 and C5, being optionally substituted on the N atom of the heterocyclic system, and where the unsaturated ring of the heterocyclic system is a 5, 6, 7 or 8-membered ring. Also to the use of these compounds as anticonvulsants in certain medical conditions, and to processes for making them.

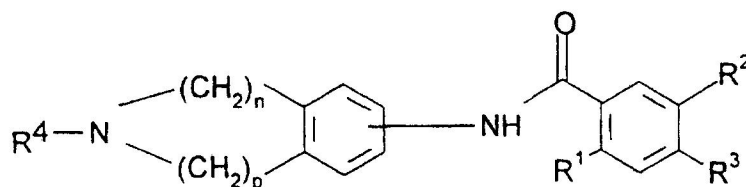
## SUBSTITUTED BENZAMIDE DERIVATIVES AND THEIR USE AS ANTICONVULSANTS

This invention relates to novel compounds, to processes for preparing them, and to their use as therapeutic agents.

5 US-A-4022900 (Marion), FR-A-2004748 (Marion) and DE-A-2101691 (Marion) disclose benzamido-tetrahydroisoquinolines having anti-hypertensive and vasodilator properties, including the compound 5-(2,4,5-trimethoxy-benzamido)-2-methyl-1,2,3,4-tetrahydroisoquinoline, which can also be expressed as 2,4,5-trimethoxy-N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)benzamide.

10 It has now been surprisingly found that benzamide compounds of formula (I) below possess anti-convulsant activity and are therefore believed to be useful in the treatment and/or prevention of anxiety, mania, depression, panic disorders and/or aggression, disorders associated with a subarachnoid haemorrhage or neural shock, the effects associated with withdrawal from substances of abuse such as cocaine, nicotine, alcohol and  
15 benzodiazepines, disorders treatable and/or preventable with anti-convulsive agents, such as epilepsy including post-traumatic epilepsy, Parkinson's disease, psychosis, migraine, cerebral ischaemia, Alzheimer's disease and other degenerative diseases such as Huntingdon's chorea, schizophrenia, obsessive compulsive disorders (OCD), neurological deficits associated with AIDS, sleep disorders (including circadian rhythm disorders,  
20 insomnia & narcolepsy), tics (e.g. Gilles de la Tourette's syndrome), traumatic brain injury, tinnitus, neuralgia, especially trigeminal neuralgia, neuropathic pain, dental pain, cancer pain, inappropriate neuronal activity resulting in neurodysesthesias in diseases such as diabetes, MS and motor neurone disease, ataxias, muscular rigidity (spasticity), temporomandibular joint dysfunction, and amyotrophic lateral sclerosis (ALS).

25 Accordingly, the present invention provides a compound of formula (I) or pharmaceutically acceptable salt thereof:



30

(I)

where n and p are independently integers from 1 to 4 and (n+p) is from 2 to 5;  
R<sup>1</sup> is C<sub>1-6</sub>alkylo-;

106  
H3

$R^2$  is hydrogen, halogen, CN,  $N_3$ , trifluoromethyldiaziriny,  $CF_3$ ,  $CF_3O-$ ,  $CF_3S-$ ,  $CF_3CO-$ ,  $C_{1-6}alkyl$ ,  $C_{3-6}cycloalkyl$ ,  $C_{3-6}cycloalkyl-C_{1-4}alkyl-$ ,  $C_{1-6}alkylo-$ ,  $C_{1-6}alkylCO-$ ,  $C_{3-6}cycloalkylCO-$ ,  $C_{3-6}cycloalkyl-C_{1-4}alkylCO-$ , phenyl, phenoxy, benzyloxy, benzoyl, phenyl- $C_{1-4}alkyl-$ ,  $C_{1-6}alkylS-$ ,  $C_{1-6}alkylSO_2-$ ,  $(C_{1-4}alkyl)_2NSO_2-$  or  $(C_{1-4}alkyl)NHSO_2-$ ;  
 $R^3$  is hydrogen, halogen,  $NO_2$ , CN,  $N_3$ , trifluoromethyldiaziriny,  $C_{1-6}alkylo-$ ,  $C_{1-6}alkylS-$ ,  $C_{1-6}alkyl$ ,  $C_{3-6}cycloalkyl$ ,  $C_{3-6}cycloalkyl-C_{1-4}alkyl-$ ,  $C_{1-6}alkenyl$ ,  $C_{1-6}alkynyl$ ,  $CF_3CO-$ ,  $C_{1-6}alkylCO-$ ,  $C_{3-6}cycloalkylCO-$ ,  $C_{3-6}cycloalkyl-C_{1-4}alkylCO-$ , phenyl, phenoxy, benzyloxy, benzoyl, phenyl- $C_{1-4}alkyl-$ , or  $-NR^5R^6$  where  $R^5$  is hydrogen or  $C_{1-4}alkyl$ , and  
 $R^6$  is hydrogen,  $C_{1-4}alkyl$ ,  $-CHO$ ,  $-CO_2C_{1-4}alkyl$  or  $-COC_{1-4}alkyl$ ;  
 $R^4$  is hydrogen,  $C_{1-6}alkyl$ ,  $C_{1-6}alkenyl$ , or  $C_{1-6}alkynyl$ ;  
but excluding the compound 2,4,5-trimethoxy-N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)benzamide.

The compounds of this invention are typically (tetrahydroisoquinolin-5-yl)benzamides, (tetrahydroisoquinolin-6-yl)benzamides, (tetrahydroisoquinolin-7-yl)benzamides or (tetrahydroisoquinolin-8-yl)benzamides, especially (tetrahydroisoquinolin-7-yl)benzamides, and most suitably (tetrahydroisoquinolin-5-yl)benzamides; or (dihydroisoindol-4-yl)benzamides; or (tetrahydro-3-benzazepin-6-yl)benzamides.

In the formula (I),  $R^1$  alkoxy groups are typically based on straight chain alkyl groups, but in general alkyl groups may be straight chain or branched. Aromatic rings, especially the aromatic ring in the bicyclic heterocyclic moiety in formula (I) and phenyl groups, including phenyl groups that are part of other moieties, in  $R^2$  and  $R^3$  may optionally be substituted with one or more independently selected halogen or  $C_{1-6}alkyl$ ,  $C_{1-6}alkoxy$  or  $C_{1-6}alkylcarbonyl$ .

Suitable  $C_{3-6}cycloalkyl$  groups include cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

Suitable halo substituents include fluoro, chloro, iodo and bromo.

A suitable group of compounds of formula (I) have

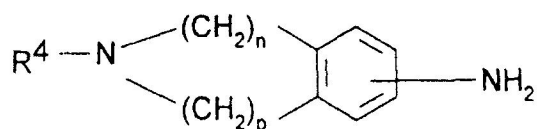
$R^1$  as methoxy, ethoxy or *n*-propoxy

$R^2$  as hydrogen, methoxy, bromo, chloro, iodo, acetyl, pivaloyl, *iso*-

butyryl, benzoyl, trifluoromethyl, trifluoroacetyl, *n*-propylsulfonyl, isopropylsulfonyl or dimethylsulfamoyl

107  
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11. A compound of formula (I), as defined in Claim 1, or a pharmaceutically acceptable salt or solvate, thereof as a therapeutic agent, in particular for the treatment and/or prophylaxis of of anxiety, mania, depression, panic disorders and/or aggression, disorders associated with a subarachnoid haemorrhage or neural shock, the effects
- 5 associated with withdrawal from substances of abuse such as cocaine, nicotine, alcohol and benzodiazepines, disorders treatable and/or preventable with anti-convulsive agents, such as epilepsy including post-traumatic epilepsy, Parkinson's disease, psychosis, migraine, cerebral ischaemia, Alzheimer's disease and other degenerative diseases such as Huntingdon's chorea, schizophrenia, obsessive compulsive disorders (OCD), neurological
- 10 deficits associated with AIDS, sleep disorders (including circadian rhythm disorders, insomnia & narcolepsy), tics (e.g. Gilles de la Tourette's syndrome), traumatic brain injury, tinnitus, neuralgia, especially trigeminal neuralgia, neuropathic pain, dental pain, cancer pain, inappropriate neuronal activity resulting in neurodysthesis in diseases such as diabetes, MS and motor neurone disease, ataxias, muscular rigidity (spasticity),
- 15 temporomandibular joint dysfunction, and amyotrophic lateral sclerosis (ALS).
12. A process for the preparation of compounds of formula (I), which comprises reacting a compound of formula (II)

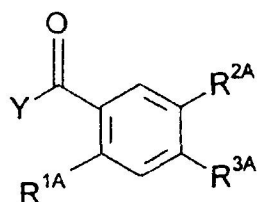


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(II)

where n and p are as defined for formula (I), as defined in Claim 1, and R<sup>4A</sup> is R<sup>4</sup> as defined for formula (I) or a group convertible to R<sup>4</sup>

- 25 with a compound of formula (III)



(III)

- where Y is Cl or OH, and R<sup>1A</sup>, R<sup>2A</sup>, and R<sup>3A</sup> are respectively R<sup>1</sup>, R<sup>2</sup>, and R<sup>3</sup> as defined
- 30 for formula (I) or groups convertible to R<sup>1</sup>, R<sup>2</sup>, and R<sup>3</sup>,  
and where required converting a R<sup>1A</sup>, R<sup>2A</sup>, R<sup>3A</sup> or R<sup>4A</sup> group to a R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> or R<sup>4</sup> group, converting one R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> or R<sup>4</sup> group to another R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> or R<sup>4</sup> group,