[illegible]
Folios: 68

70
68

Señor
SUPERINTENDENTE DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
E. S D.

Re: P1.- **ASTRAZENECA AB**.- Solicitud de Patente de Invención para **"COMPUESTOS NOVEDOSOS"**.- Clase A61.-Expediente número 00-093.169.-

1. Me refiero a mi solicitud arriba mencionada de fecha 6 de Diciembre de 2000.

2. Anexos me permito presentar a usted:

(1) Copia Certificada, de la solicitud de patente presentada para el invento arriba nombrado **respecto de la cual reclamo prioridad,** a saber la solicitud sueca número 9904505-6 de 9 de Diciembre de 1999, junto con su traducción oficial correspondiente a las legalizaciones y reivindicaciones de dicho documento;

(2) Copia debidamente autenticada por el Notario Sexto del Circulo de Bogotá, de los documentos que acreditan la calidad de Traductor Oficial del señor Gabriel Rueda Chadid quien elaboró la traducción de las legalizaciones y reivindicaciones de la solicitud sueca número 9904505-6 de 9 de Diciembre de 1999;

(3) Documento que acredita el traspaso que los autores del invento de la referencia hacen a favor de mi representando, de sus derechos sobre el mismo, debidamente legalizado hasta por el Ministerio de Relaciones Exteriores de Colombia bajo el número 490022 de 12 de Diciembre de 2000;

(4) Traducción Oficial No. 8187, debidamente legalizada hasta por el Ministerio de Relaciones Exteriores de Colombia bajo el número 494070 de 15 de Diciembre de 2000, correspondiente a las legalizaciones de dicho documento de traspaso;

(5) Documento que acredita el traspaso que el autor del invento de la referencia hace a favor de mi representando, de sus derechos sobre el mismo, debidamente legalizado hasta por el Ministerio de Relaciones Exteriores de Colombia bajo el número 494069 de 15 de Diciembre de 2000; y

(6) Traducción Oficial No. 8183, debidamente legalizada hasta por el Ministerio de Relaciones Exteriores de Colombia bajo el número 494069 de 15 de Diciembre de 2000, correspondiente a las legalizaciones de dicho documento de traspaso.

3. Ruego a usted tomar atenta nota de lo anterior y proceder de conformidad.

Señor Superintendente,

JOSE ANTONIO LLOREDA
T.P. 10.784
Código 231

República de Colombia

Ministerio de Justicia y del Derecho

74
71

COMO NOTARIO SEXTO DE SANTAFE DE BOGOTA
HAGO CONSTAR
QUE LA FOTOCOPIA CONCUERDE CON LA FOTOCOPIA AUTENTICA QUE HE TENIDO A LA VISTA
SANTAFE DE BOGOTA 13 DIC. 2000
JUAN MANUEL BOTERO MEDINA
NOTARIO

EL SECRETARIO GENERAL DEL MINISTERIO DE JUSTICIA Y DEL DERECHO

CERTIFICA:

Que por Resolución 5996 del 29 de noviembre de 1982, le fue expedida licencia para ejercer funciones de Traductor e Intérprete Oficial en los idiomas INGLES-ESPAÑOL, ESPAÑOL-INGLES a GABRIEL RUEDA CHADID, identificado con la cédula de ciudadanía No. 17.124.145 expedida en Bogotá. Que dicha resolución se encuentra vigente en la fecha.

A solicitud del interesado, en Santafé de Bogotá D.C., a los 17 días del mes de noviembre de 1994.

COMO NOTARIO SEXTO ENCARGADO DE SANTAFE DE BOGOTA
HAGO CONSTAR
QUE LA FOTOCOPIA CONCUERDE CON LA FOTOCOPIA AUTENTICA QUE HE TENIDO A LA VISTA
SANTAFE DE BOGOTA 31 AGO. 1998
PABLO [illegible]

JUSTICIA DE COLOMBIA
del Derecho
SECRETARIO GENERAL

JORGE LUIS SABOGAL SABOGAL

HAGO CONSTAR
QUE LA FOTOCOPIA CONCUERDE CON LA FOTOCOPIA AUTENTICA QUE HE TENIDO A LA VISTA
SANTAFE DE BOGOTA 01 SET. 2000

COMO NOTARIO SEXTO DE SANTAFE DE BOGOTA
HAGO CONSTAR
QUE LA FOTOCOPIA CONCUERDE CON LA FOTOCOPIA AUTENTICA QUE HE TENIDO A LA VISTA
SANTAFE DE BOGOTA
JUAN MANUEL BOTERO MEDINA
NOTARIO

LMR/mmc.

7572

TRIBUNAL SUPERIOR DEL DISTRITO JUDICIAL DE SANTAFE DE BOGOTA
SECRETARIA GENERAL

LA SUSCRITA SECRETARIA DEL H. TRIBUNAL SUPERIOR DEL DISTRITO JUDICIAL DE SANTAFE DE BOGOTA,

COMO NOTARIO SEXTO DE SANTAFE DE BOGOTA
HAGO CONSTAR
QUE LA FOTOCOPIA COINCIDE CON LA FOTOCOPIA AUTENTICA QUE HE TENIDO A LA VISTA
SANTAFE DE BOGOTA 13 DIC. 2000
JUAN MANUEL BOTERO MEDINA
NOTARIO

C E R T I F I C A :

Que el Acuerdo No. 183 de diciembre 3 de 1982 emanado de esta Corporación, por medio del cual dió posesión al señor GABRIEL RUEDA CHADID identificado con Cédula de Ciudadanía número 17.124.145 de Bogotá como TRADUCTOR E INTERPRETE OFICIAL de los idiomas INGLES-ESPAÑOL, ESPAÑOL-INGLES, en virtud de la Resolución No. 5996, se encuentra en VIGENTE.

COMO NOTARIO SEXTO ENCARGADO DE SANTAFE DE BOGOTA
HAGO CONSTAR
QUE LA FOTOCOPIA COINCIDE CON LA FOTOCOPIA AUTENTICA QUE HE TENIDO A LA VISTA
SANTAFE DE BOGOTA 01 SET. 2000
PABLO MEDINA GARAVITO
NOTARIO

COMO NOTARIO SEXTO ENCARGADO DE SANTAFE DE BOGOTA
HAGO CONSTAR
QUE LA FOTOCOPIA COINCIDE CON LA FOTOCOPIA AUTENTICA QUE HE TENIDO A LA VISTA
SANTAFE DE BOGOTA 21 AGO. 1998
PABLO MEDINA GARAVITO
NOTARIO

Se expide en Santafé de Bogotá D.C., a dieciseis (16) de noviembre mil novecientos noventa y cuatro (1994).

MARIA INES RODRIGUEZ TORRES
SECRETARIA

COMO NOTARIO SEXTO DE SANTAFE DE BOGOTA
HAGO CONSTAR
QUE LA FOTOCOPIA COINCIDE CON LA FOTOCOPIA AUTENTICA QUE HE TENIDO A LA VISTA
SANTAFE DE BOGOTA 01 JUL 1998
JUAN MANUEL BOTERO MEDINA
NOTARIO

COMO NOTARIO SEXTO ENCARGADO DE SANTAFE DE BOGOTA
HAGO CONSTAR
QUE LA FOTOCOPIA COINCIDE CON LA FOTOCOPIA AUTENTICA QUE HE TENIDO A LA VISTA
SANTAFE DE BOGOTA 08 SET 1998
PABLO MEDINA GARAVITO
NOTARIO

COMO NOTARIO SEXTO DE SANTAFE DE BOGOTA
HAGO CONSTAR
QUE LA FOTOCOPIA COINCIDE CON LA FOTOCOPIA AUTENTICA QUE HE TENIDO A LA VISTA
SANTAFE DE BOGOTA 06 ENE. 1999
JUAN MANUEL BOTERO MEDINA
NOTARIO

crm./

72 73

Astra Zeneca AB C-2292-ICO

REF: LLC-136-2000. La presente es Traducción Oficial de un documento presentado originalmente en inglés. Esta traducción es elaborada por Gabriel Rueda Chadid (Traductor Oficial).

PRV

Patent-OCH Registreringsverket

CERTIFICACION

Se certifica que anexo se encuentra fiel copia de los documentos tal y como fueron radicados originalmente ante la Oficina de Registros y Patentes en relación con la siguiente solicitud de patente.

La solicitud se presentó originalmente en inglés.

(71) Solicitante: AstraZeneca UK Ltd, London GB
(21) Número de Solicitud de Patente. 9904505-6
(86) Fecha de presentación: 1999-12-09

Estocolmo, 2000-11-03

Por y en representación de la Oficina de Registros y patentes.
Therese Friberger (Hay firma y sello)
Derechos: 170

GABRIEL RUEDA CHADID
TRADUCTOR OFICIAL
RESOLUCION 5996 DE NOV. 20-82
MINISTERIO DE JUSTICIA

La suscrita Anne-Marie Bonde, Notario Público de la Ciudad de Estocolmo, Suecia, certifica que THERESE FRIBERGER autorizado para firmar en nombre de la PRV, REGISTRO NACIONAL DE LA PROPIEDAD INDUSTRIAL DE SUECIA ha otorgado y firmado el documento que antecede.

Derechos: 250 Coronas

Estocolmo, 2000-11-08

Hay firma y Sello

CONSULADO DE COLOMBIA EN ESTOCOLMO, SUECIA

Fecha: 2000-11-09 No. 003790

Previa la confrontación correspondiente DA FE de que la firma que aparece en este documento es similar a la REGISTRADA aquí por Anne-marie Bonde, Notario Público de la Ciudad de Estocolmo, Suecia.

Firmado y Sellado por

MARIA SMITH RUEDA

Encargada de las Funciones Consulares

MINISTERIO DE RELACIONES EXTERIORES

No.

Fecha:

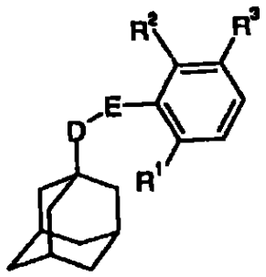
MARIA SMITH RUEDA, cuya firma aparece en el documento desempeña las funciones indicadas.

Jefe de Legalizaciones, Santafé de Bogotá D.C.

GABRIEL RUEDA CHADID
TRADUCTOR OFICIAL
RESOLUCION 5996 DE NOV. 29-95
MINISTERIO DE JUSTICIA

REIVINDICACIONES **PRV 99-12-09**

1. Un compuesto de la formula general



(I)

donde D representa CH_2 o CH_2CH_2;

E representa C(O)NH o NHC(O);

R^1 y R^2 representan cada uno y de manera independiente un átomo de hidrógeno o halógeno, o un grupo amino, nitro, alquilo C_1-C_8 o trifluorometilo;

R^3 representa un grupo de la formula

(II);

X representa un átomo de oxígeno o azufre o un grupo NH, SO o SO_2;

Y representa un átomo de oxígeno o azufre o un grupo NH, SO o SO_2;

Z representa un grupo -OH, $-CO_2H$, alcoxi C_1-C_8, $-NR^8R^7$, $-C(O)NR^8R^9$ o $-N(R^{10})C(O)$-alquilo C_1-C_8;

R^4 representa un grupo alquilo C_2-C_8;

R^5 representa un grupo alquilo C_1-C_8; y

R^6, R^7, R^8, R^9 y R^{10} representan cada uno y de manera independiente un átomo de hidrógeno o un grupo alquilo C_1-C_8;

con la condición de que (i) cuando E representa NHC(O), X representa O, S o NH y Y representa O, entonces Z representa NH_2, y (ii) cuando E representa NHC(O), X representa O, S o NH, Y representa NH y R^5 representa CH_2CH_2, entonces Z no es H o -OH;
o una de sus sales o solvatos farmacéuticamente aceptables.

2. Un compuesto de acuerdo con la reivindicación 1, donde D representa CH_2.

3. Un compuesto de acuerdo con las reivindicaciones 1 o 2, donde E representa NHC(O).

4. Un compuesto de acuerdo con una de las reivindicaciones 1 a 3, donde R^1 y R^2 representan cada uno y de manera independiente un átomo de hidrógeno, cloro o bromo o un grupo amino, nitro, alquilo C_1-C_2 o trifluorometilo.

5. Un compuesto de acuerdo con una de las reivindicaciones anteriores, donde X representa un átomo de oxígeno o grupo NH.

6. Un compuesto de acuerdo con una de las reivindicaciones anteriores, donde Z representa un grupo -OH, $-CO_2H$, metoxi, $-NR^6R^7$, $-C(O)NR^8R^9$ o $-N(R^{10})C(O)CH_3$.

7. Un compuesto de la formula (I), o una de sus sales o solvatos farmacéuticamente aceptables, de acuerdo con la reivindicación 1 que se selecciona a partir de:

hidrocloruro 2-Cloro-5-[2-(2-metoxietilamino)etilamino]-*N*-(triciclo[3.3.1.1^{3,7}]dec-1-ilmetil)-benzamida,

hidrocloruro [2-[4-Cloro-3-(triciclo[3.3.1.1^{3,7}]dec-1-ilmetil)carbamoil-fenilamino]-etiamino]-ácido acético,

hidrocloruro 2-Cloro-5-[3-(3-hidroxi-propilamino)-propoxi]-*N*-(triciclo[3.3.1.1^{3,7}]dec-1-ilmetil)-benzamida,

acetato 2-Cloro-5-[2-(3-hidroxipropilamino)etilamino]-*N*-(triciclo[3.3.1.1^{3,7}]dec-1-ilmetil)-benzamida,

acetato 5-[2-(2-Aminoetilamino)etilamino]-2-cloro-*N*-(triciclo[3.3.1.1^{3,7}]dec-1-ilmetil)-benzamida,

acetato 5-[2-(2-Acetilaminoetilamino)etilamino]-2-cloro-*N*-(triciclo[3.3.1.1^{3,7}]dec-1-ilmetil)-benzamida,

[2-[4-Cloro-3-(triciclo[3.3.1.1^{3,7}]dec-1-ilmetil)carbamoil-fenilamino]-etilamino]-ácido propionico,

acetato 2-Cloro-5-[2-(2-metilcarbamoiletilamino)etilamino]-*N*-(triciclo[3.3.1.1^{3,7}]dec-1-ilmetil)-benzamida,

acetato 2-Cloro-5-[2-(2-dimetilcarbamoiletilamino)etilamino]-*N*-(triciclo[3.3.1.1^{3,7}]dec-1-ilmetil)-benzamida,

2-Cloro-5-[3-(3-hidroxipropiltio)propoxi]-*N*-(triciclo-[3.3.1.1^{3,7}]dec-1-ilmetil)-benzamida,

hidrocloruro 5-[2-(2-Aminoetiltio)etoxi]-2-cloro-*N*-(triciclo-[3.3.1.1^{3,7}]dec-1-ilmetil)-benzamida,

hidrocloruro 2-Cloro-5-[2-(3-hidroxipropilamino)etoxi]-*N*-(triciclo[3.3.1.1^{3,7}]dec-1-ilmetil)-benzamida,

2-Cloro-5-[3-(3-hidroxipropilsulfonil)propoxi]-*N*-(triciclo-[3.3.1.1^{3,7}]dec-1-ilmetil)-benzamida,

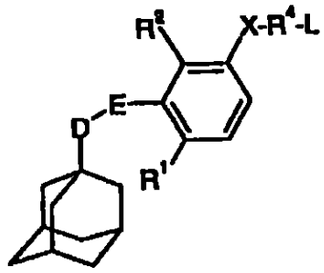
(±)-2-Cloro-5-[3-(3-hidroxipropilsulfinil)propoxi]-*N*-(triciclo[3.3.1.1^{3,7}]dec-1-ilmetil)-benzamida,

2-Cloro-5-[2-(3-hidroxipropiltio)etoxi]-*N*-(triciclo-[3.3.1.1^{3,7}]dec-1-ilmetil)-benzamida,

hidrocloruro *S*-2-Cloro-5-[2-(2-hidroxipropilamino)etoxi]-*N*-(triciclo[3.3.1.1^{3,7}]dec-1-ilmetil)-benzamida,
hidrocloruro *R*-2-Cloro-5-[2-(2-hidroxipropilamino)etoxi]-*N*-(triciclo[3.3.1.1^{3,7}]dec-1-ilmetil)-benzamida,
hidrocloruro *S*-2-Cloro-5-[2-(2-hidroxi-1-metiletilamino)-etoxi]-*N*-(triciclo[3.3.1.1^{3,7}]dec-1-ilmetil)-benzamida,
hidrocloruro *R*-2-Cloro-5-[2-(2-hidroxi-1-metiletilamino)-etoxi]-*N*-(triciclo[3.3.1.1^{3,7}]dec-1-ilmetil)-benzamida,
(±)-2-Cloro-5-[2-(3-hidroxipropilsulfinil)etoxi]-*N*-(triciclo[3.3.1.1^{3,7}]dec-1-ilmetil)-benzamida,
2-Cloro-5-[2-(3-hidroxipropilsulfonil)etoxi]-*N*-(triciclo-[3.3.1.1^{3,7}]dec-1-ilmetil)-benzamida,
hidrocloruro (±)-5-[2-(2-Aminoetilsulfinil)etoxi]-2-cloro-*N*-(triciclo[3.3.1.1^{3,7}]dec-1-ilmetil)-benzamida,
hidrocloruro 5-[2-(2-Aminoetilsulfonil)etoxi]-2-cloro-*N*-(triciclo[3.3.1.1^{3,7}]dec-1-ilmetil)-benzamida,
hidrocloruro 5-[3-(2-Aminoetiltio)propoxi]-2-cloro-*N*-(triciclo[3.3.1.1^{3,7}]dec-1-ilmetil)-benzamida,
hidrocloruro (±)-5-[3-(2-Aminoetilsulfinil)propoxi]-2-cloro-*N*-(triciclo[3.3.1.1^{3,7}]dec-1-ilmetil)-benzamida, y
hidrocloruro 5-[3-(2-Aminoetilsulfonil)propoxi]-2-cloro-*N*-(triciclo[3.3.1.1^{3,7}]dec-1-ilmetil)-benzamida.

8. Un proceso para la preparación de un compuesto de la formula (I) según se definió en la reivindicación 1 y que comprende:

a) cuando Y representa un átomo de azufre o un grupo NH, se hace reaccionar un compuesto de la formula general



(III)

donde L representa un grupo saliente (por ejemplo átomo de halógeno) y D, E, R^1, R^2, X y R^4 corresponden a las definiciones de la formula (I), con un compuesto de la formula general

$$R^{20} — R^5 — Z \qquad (IV)$$

donde R^{20} representa SH o NH_2 y R^5 y Z corresponden a las definiciones de la formula (I), o

(b) cuando Y representa SO o SO_2, se hace reaccionar un compuesto correspondiente de la formula (I) en la cual Y representa un átomo de azufre con un agente oxidante adecuado:

y opcionalmente después de (a) o (b) se convierte el compuesto de la formula (I) obtenido en una de sus sales o solvatos farmacéuticamente aceptables.

9. Una composición farmacéutica que comprende un compuesto de la formula (I), o una de sus sales o solvatos farmacéuticamente aceptables, según se describió en una de las reivindicaciones 1 a 7 en asocio con un adyuvante, diluyente o portador farmacéuticamente aceptable.

10. Un proceso para la preparación de una composición farmacéutica según se describió en la reivindicación 9 y que comprende la mezcla de un compuesto de la formula (I), o una de sus sales o solvatos farmacéuticamente aceptables, según se definió en una de las reivindicaciones 1 a 7 con un adyuvante, diluyente o portador farmacéuticamente aceptable.

11. Un compuesto de la formula (I), o una de sus sales o solvatos farmacéuticamente aceptables, según se describió en una de las reivindicaciones 1 a 7 para uso en terapia.

12. Un compuesto de la formula (I), o una de sus sales o solvatos farmacéuticamente aceptables, según se describió en una de las reivindicaciones 1 a 7 para uso en el tratamiento de artritis reumatoide.

13. El uso de un compuesto de la formula (I), o una de sus sales o solvatos farmacéuticamente aceptables, según se describió en una de las reivindicaciones 1 a 7 en la elaboración de un medicamento para uso en terapia.

14. Un método para efectuar inmunosupresión que comprende la administración a un paciente de una cantidad terapéuticamente eficaz de un compuesto de la formula (I), o una de sus sales o solvatos farmacéuticamente aceptables, según se describió en una de las reivindicaciones 1 a 7.

La anterior es Traducción Oficial de un documento presentado originalmente en inglés. Esta traducción fue realizada por

GABRIEL RUEDA CHADID
TRADUCTOR OFICIAL
RESOLUCION 5996 DE NOV. 29-93
MINISTERIO DE JUSTICIA

B3 81

GABRIEL RUEDA CHADID (Traductor Ofi ial). Resolución 5996 del Minjusticia, por lo cual estampo mi Sello y Firmo.

Bogotá D.C., Diciembre 18, 2000.

GABRIEL RUEDA CHADID
TRADUCTOR OFICIAL
RESOLUCION 5996 DE NOV. 29-82
MINISTERIO DE JUSTICIA

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leg 84 82

PRV

PATENT- OCH REGISTRERINGSVERKET
Patentavdelningen

Intyg
Certificate

PATENT- OCH REGISTRERINGSVERKET

Härmed intygas att bifogade kopior överensstämmer med de handlingar som ursprungligen ingivits till Patent- och registreringsverket i nedannämnda ansökan.

Ansökan ingavs ursprungligen på engelska.

This is to certify that the annexed is a true copy of the documents as originally filed with the Patent- and Registration Office in connection with the following patent application.

The application was originally filed in English.

(71) *Sökande* / *Applicant (s)* — *AstraZeneca UK Ltd, London GB*

(21) *Patentansökningsnummer* / *Patent application number* — *9904505-6*

(86) *Ingivningsdatum* / *Date of filing* — *1999-12-09*

Stockholm, 2000-11-03

För Patent- och registreringsverket
For the Patent- and Registration Office

Therese Friberger

Therese Friberger

Avgift
Fee *170:-*

La infrascrita Anne-Marie Bondo, Notaria Pública de Estocolmo, Suecia, certifica que Therese Friberger, autorizado para firmar en nombre de la PRV, DIRECCIÓN NACIONAL DE PATENTES Y REGISTROS EN SUECIA, ha otorgado y firmado el documento que antecede.
Derechos 230.- Estocolmo 2000-11-08
Coronas De oficio:

PATENT- CH REGISTRERINGSVERKET SWEDEN
Postadress/Adress Box 5055 S-102 42 STOCKHOLM
Telefon/Phone +46 8 782 25 00 Vx 08-782 25 00
Telex 17878 PATOREG S
Telefax +46 8 666 02 86 08-666 02 86

15

EL CONSULADO DE COLOMBIA EN
ESTOCOLMO, SUECIA

Fecha 2000 -11- 09 No: 003790

Previa la confrontación correspondiente DA FE de que la firma que aparece en este documento es similar a la REGISTRADA aquí por

Ana María Bonde, Notaria Pública, Estocolmo, Suecia

MARIA SMITH RUEDA
Encargada de las Funciones Consulares

PAGADO
Impuesto de Timbre
Siete ..... dólares US$ 7
Derechos Consulares
Quince ..... dólares US$ 15

CONSULADO DE COLOMBIA
ESTOCOLMO

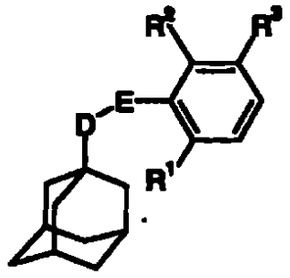
NOVEL COMPOUNDS

The present invention relates to adamantane derivatives, a process for their preparation, pharmaceutical compositions containing them, a process for preparing the pharmaceutical compositions, and their use in therapy.

The $P2X_7$ receptor (previously known as P2Z receptor), which is a ligand-gated ion channel, is present on a variety of cell types, largely those known to be involved in the inflammatory/immune process, specifically, macrophages, mast cells and lymphocytes (T and B). Activation of the $P2X_7$ receptor by extracellular nucleotides, in particular adenosine triphosphate, leads to the release of interleukin-1β (IL-1β) and giant cell formation (macrophages/microglial cells), degranulation (mast cells) and L-selectin shedding (lymphocytes). $P2X_7$ receptors are also located on antigen-presenting cells (APC), keratinocytes, salivary acinar cells (parotid cells), hepatocytes, erythrocytes, erythroleukaemic cells, monocytes, fibroblasts, bone marrow cells, neurones and renal mesangial cells.

It would be desirable to make compounds effective as $P2X_7$ receptor antagonists for use in the treatment of inflammatory, immune or cardiovascular diseases, in the aetiologies of which the $P2X_7$ receptor may play a role.

In accordance with the present invention, there is therefore provided a compound of general formula



(I)

wherein D represents CH_2 or CH_2CH_2, preferably CH_2;

E represents C(O)NH or, preferably, NHC(O);

R^1 and R^2 each independently represent a hydrogen or halogen (e.g. fluorine, chlorine, bromine or iodine) atom, or an amino (NH_2), nitro (NO_2), C_1-C_6 alkyl or trifluoromethyl group;

R^3 represents a group of formula

(II);

X represents an oxygen or sulphur atom or a group NH, SO or SO_2;

Y represents an oxygen or sulphur atom or a group NH, SO or SO_2;

Z represents a group -OH, $-CO_2H$, C_1-C_6 alkoxy, $-NR^6R^7$, $-C(O)NR^8R^9$ or $-N(R^{10})C(O)$-C_1-C_6 alkyl;

R^4 represents a C_2-C_6 alkyl group;

R^5 represents a C_1-C_6 alkyl group; and

R^6, R^7, R^8, R^9 and R^{10} each independently represent a hydrogen atom or a C_1-C_6 alkyl group;

with the provisos that (i) when E represents NHC(O), X represents O, S or NH and Y represents O, then Z represents NH_2, and (ii) when E represents NHC(O), X represents O, S or NH, Y represents NH and R^5 represents CH_2CH_2, then Z is not H or -OH;

or a pharmaceutically acceptable salt or solvate thereof.

In the context of the present specification, unless otherwise indicated, an alkyl substituent or alkyl moiety in a substituent group may be linear or branched. In the present invention, an alkyl group or moiety may contain up to 6 carbon atoms, examples of which include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl and hexyl.

Preferably, R^1 and R^2 each independently represent a hydrogen or halogen atom, or an amino, nitro, C_1-C_4 alkyl or trifluoromethyl group.

More preferably, R^1 and R^2 each independently represent a hydrogen, chlorine or bromine atom, or an amino, nitro, C_1-C_3 alkyl or trifluoromethyl group.

Most preferably, R^1 and R^2 each independently represent a hydrogen or chlorine atom.

Preferably X represents an oxygen atom or a group NH.

Preferably Z represents a group -OH, $-CO_2H$, C_1-C_4 alkoxy, $-NR^6R^7$, $-C(O)NR^8R^9$ or $-N(R^{10})C(O)$-C_1-C_4 alkyl.

More preferably, Z represents a group -OH, $-CO_2H$, methoxy, $-NR^6R^7$, $-C(O)NR^8R^9$ or $-N(R^{10})C(O)CH_3$.

R^4 preferably represents a C_2-C_4 alkyl group, for example a linear alkyl group such as $(CH_2)_2$ or $(CH_2)_3$.

R^5 preferably represents a C_1-C_4 alkyl group, for example CH_2, $(CH_2)_2$, $(CH_2)_3$, $CH_2CH(CH_3)$ or $CH(CH_3)CH_2$.

Preferably R^6, R^7, R^8, R^9 and R^{10} each independently represent a hydrogen atom or a C_1-C_4, more preferably C_1-C_2, alkyl, especially methyl, group.

Preferred compounds of the invention include:

2-Chloro-5-[2-(2-methoxyethylamino)ethylamino]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, hydrochloride,

[2-[4-Chloro-3-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)carbamoyl-phenylamino]-ethylamino]-acetic acid, hydrochloride,

2-Chloro-5-[3-(3-hydroxy-propylamino)-propoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, hydrochloride,

2-Chloro-5-[2-(3-hydroxypropylamino)ethylamino]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, acetate,

5-[2-(2-Aminoethylamino)ethylamino]-2-chloro-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, acetate,

5-[2-(2-Acetylaminoethylamino)ethylamino]-2-chloro-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, acetate,

[2-(4-Chloro-3-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)carbamoyl-phenylamino]-ethylamino]-propionic acid,

2-Chloro-5-[2-(2-methylcarbamoylethylamino)ethylamino]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, acetate,

2-Chloro-5-[2-(2-dimethylcarbamoylethylamino)ethylamino]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, acetate,

2-Chloro-5-[3-(3-hydroxypropylthio)propoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

5-[2-(2-Aminoethylthio)ethoxy]-2-chloro-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, hydrochloride,

2-Chloro-5-[2-(3-hydroxypropylamino)ethoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, hydrochloride,

2-Chloro-5-[3-(3-hydroxypropylsulfonyl)propoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

(±)-2-Chloro-5-[3-(3-hydroxypropylsulfinyl)propoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

2-Chloro-5-[2-(3-hydroxypropylthio)ethoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

S-2-Chloro-5-[2-(2-hydroxypropylamino)ethoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, hydrochloride,

R-2-Chloro-5-[2-(2-hydroxypropylamino)ethoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, hydrochloride,

S-2-Chloro-5-[2-(2-hydroxy-1-methylethylamino)ethoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, hydrochloride,

R-2-Chloro-5-[2-(2-hydroxy-1-methylethylamino)ethoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, hydrochloride,

(±)-2-Chloro-5-[2-(3-hydroxypropylsulfinyl)ethoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

2-Chloro-5-[2-(3-hydroxypropylsulfonyl)ethoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

(±)-5-[2-(2-Aminoethylsulfinyl)ethoxy]-2-chloro-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, hydrochloride,

5-[2-(2-Aminoethylsulfonyl)ethoxy]-2-chloro-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, hydrochloride,

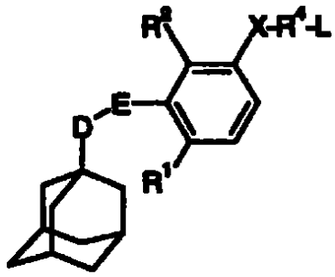
5-[3-(2-Aminoethylthio)propoxy]-2-chloro- *N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, hydrochloride,

(±)-5-[3-(2-Aminoethylsulfinyl)propoxy]-2-chloro-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, hydrochloride, and

5-[3-(2-Aminoethylsulfonyl)propoxy]-2-chloro-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, hydrochloride.

The present invention further provides a process for the preparation of a compound of formula (I) as defined above which comprises:

a) when Y represents a sulphur atom or a group NH, reacting a compound of general formula



(III)

wherein L represents a leaving group (e.g. a halogen atom) and D, E, R^1, R^2, X and R^4 are as defined in formula (I), with a compound of general formula

$R^{20}—R^5—Z$ (IV)

wherein R^{20} represents SH or NH_2 and R^5 and Z are as defined in formula (I), or

b) when Y represents SO or SO_2, reacting a corresponding compound of formula (I) in which Y represents a sulphur atom with a suitable oxidising agent;

and optionally after (a) or (b) converting the compound of formula (I) obtained to a pharmaceutically acceptable salt or solvate thereof.

The processes of the invention may conveniently be carried out in a solvent, e.g. an organic solvent such as dichloromethane, tetrahydrofuran, or an alcohol such a ethanol, isopropanol or butanol, at a temperature, e.g. in the range from 0 to 200 °C, preferably in the range from 0 to 150 °C. The oxidising agent used in (b) above may, for example, be 3-chloroperoxybenzoic acid or potassium peroxymonosulphate, commercially sold under the trade mark "Oxone".

Compounds of formula (III) are either known in the art, e.g. from WO 99/29660 and WO 99/29661 or may be prepared easily using known techniques.

Compounds of formula (IV) are either commercially available, are well known in the literature or may be prepared easily using known techniques.

It will be appreciated by those skilled in the art that in the processes of the present invention certain functional groups such as hydroxyl, carboxyl or amino groups in the starting reagents or intermediate compounds may need to be protected by protecting groups. Thus, the preparation of the compounds of formula (I) may involve at a certain stage the removal of one or more protecting groups.

The protection and deprotection of functional groups is described in 'Protective Groups in Organic Chemistry', edited by J.W.F. McOmie, Plenum Press (1973) and 'Protective Groups in Organic Synthesis', 2nd edition, T.W. Greene and P.G.M. Wuts, Wiley-Interscience (1991).

The compounds of formula (I) above may be converted to a pharmaceutically acceptable salt or solvate thereof, preferably an acid addition salt such as a hydrochloride, hydrobromide, phosphate, acetate, fumarate, maleate, tartrate, citrate, oxalate, methanesulphonate or *p*-toluenesulphonate, or an alkali metal salt such as a sodium or potassium salt.

Certain compounds of formula (I) are capable of existing in stereoisomeric forms. It will be understood that the invention encompasses all geometric and optical isomers of the compounds of formula (I) and mixtures thereof including racemates. Tautomers and mixtures thereof also form an aspect of the present invention.

The compounds of the present invention are advantageous in that they possess pharmacological activity and have utility as modulators of $P2X_7$ receptor activity. They are therefore indicated as pharmaceuticals for use in the treatment or prevention of rheumatoid arthritis, osteoarthritis, psoriasis, allergic dermatitis, asthma, hyperresponsiveness of the airway, chronic obstructive pulmonary disease (COPD), bronchitis, septic shock, glomerulonephritis, irritable bowel disease, Crohn's disease, ulcerative colitis, atherosclerosis, growth and metastases of malignant cells, myoblastic leukaemia, diabetes, neurodegenerative disease, Alzheimer's disease, meningitis, osteoporosis, burn injury, ischaemic heart disease, stroke, peripheral vascular disease and varicose veins.

Accordingly, the present invention provides a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined for use in therapy.

In another aspect, the invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined in the manufacture of a medicament for use in therapy.

In the context of the present specification, the term "therapy" also includes "prophylaxis" unless there are specific indications to the contrary. The terms "therapeutic" and "therapeutically" should be construed accordingly.

Prophylaxis is expected to be particularly relevant to the treatment of persons who have suffered a previous episode of, or are otherwise considered to be at increased risk of, the disease or condition in question. Persons at risk of developing a particular disease or condition generally include those having a family history of the disease or condition, or those who have been identified by genetic testing or screening to be particularly susceptible to developing the disease or condition.

The invention further provides a method of effecting immunosuppression (e.g. in the treatment of rheumatoid arthritis, irritable bowel disease, atherosclerosis, psoriasis, pulmonary disease, e.g. COPD or bronchitis, or diseases of the central nervous system, e.g. Alzheimer's disease or stroke) which comprises administering a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined to a patient.

For the above-mentioned therapeutic uses the dosage administered will, of course, vary with the compound employed, the mode of administration, the treatment desired and the disease or condition indicated. For effecting immunosuppression, the daily dosage of the compound of formula (I) will typically be in the range from 0.001 mg/kg to 30 mg/kg.

The compounds of formula (I) and pharmaceutically acceptable salts and solvates thereof may be used on their own but will generally be administered in the form of a

pharmaceutical composition in which the formula (I) compound/salt/solvate (active ingredient) is in association with a pharmaceutically acceptable adjuvant, diluent or carrier. Depending on the mode of administration, the pharmaceutical composition will preferably comprise from 0.05 to 99 %w (per cent by weight), more preferably from 0.10 to 70 %w, of active ingredient, and, from 1 to 99.95 %w, more preferably from 30 to 99.90 %w, of a pharmaceutically acceptable adjuvant, diluent or carrier, all percentages by weight being based on total composition.

Thus, the present invention also provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

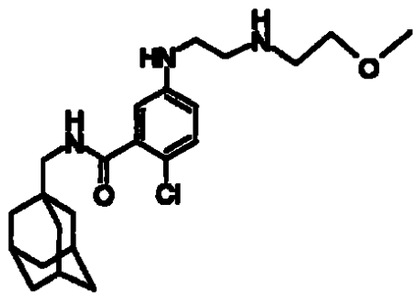
The invention further provides a process for the preparation of a pharmaceutical composition of the invention which comprises mixing a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined with a pharmaceutically acceptable adjuvant, diluent or carrier.

The pharmaceutical composition of the invention may be administered topically (e.g. to the lung and/or airways or to the skin) in the form of solutions, suspensions, heptafluoroalkane aerosols and dry powder formulations; or systemically, e.g. by oral administration in the form of tablets, capsules, syrups, powders or granules, or by parenteral administration in the form of solutions or suspensions, or by subcutaneous administration or by rectal administration in the form of suppositories or transdermally.

The present invention will now be further explained by reference to the following illustrative examples.

Example 1

2-Chloro-5-[2-(2-methoxyethylamino)ethylamino]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, hydrochloride



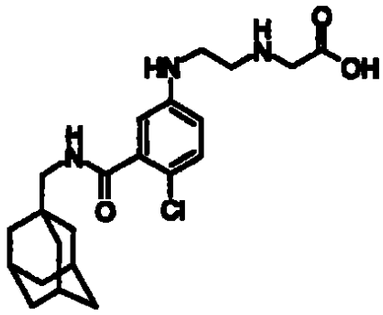
To a solution of 2-chloro-5-(2-chloroethylamino)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide (prepared according to the method of Example 63 of WO 99/29661) (0.2 g) and diisopropylethylamine (0.27 ml) in ethanol (5 ml) was added sodium iodide (0.08 g) and 2-methoxyethylamine (0.11 g) and reaction vessel sealed and reaction mixture heated at 90 °C for 15 hours before concentration under reduced pressure. Residue was partitioned between ethyl acetate and sodium hydrogencarbonate solution, aqueous phase extracted with additional ethyl acetate and organic phases combined, dried ($MgSO_4$) and concentrated under reduced pressure. Residue was purified by NPHPLC (eluting with 0-25% ethanol in dichloromethane) which gave 5-(*N*-(2-Methoxyethyl)-2-aminoethyl)amino-2-chloro-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide as a semi-solid which was converted to the hydrochloride salt by stirring with 4M HCl in dioxane and concentrated under reduced pressure to leave the title compound as a white solid (0.085 g).

MS (APCI +ve) 420/422 $(M+H)^+$

^{1}H NMR (CD_3OD) δ 8.27 (1H, t); 7.20(1H, d); 7.73 (2H, m); 3.63 (2H, t); 3.46 (2H, t); 3.40 (3H, s); 3.26 (2H, m); 3.04 (2H, d); 1.98 (3H, s); 1.77 (3H, d); 1.67 (3H, d); 1.62 (6H, s).

Example 2

[2-[4-Chloro-3-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)carbamoyl-phenylamino]-ethylamino]-acetic acid, hydrochloride



a) **[2-[4-Chloro-3-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)carbamoyl-phenylamino]-ethylamino]-acetic acid, 1,1-dimethylethyl ester**

Prepared according to the method of Example 1 using 2-chloro-5-(2-chloroethyl)amino-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide (prepared according to the method of Example 63 of WO 99/29661) (0.2 g) and *tert*butyl glycine (0.26 g) to deliver the sub-title compound as a brown foam (0.10 g).

^{1}H NMR (CD_3OD) δ 7.13(1H, d); 6.66 (2H, m); 3.20 (2H, t); 3.02 (2H, s); 2.79 (2H, t); 1.97 (3H, s); 1.76 (3H, d); 1.72 (3H, d); 1.61 (6H, s); 1.43 (9H, s).

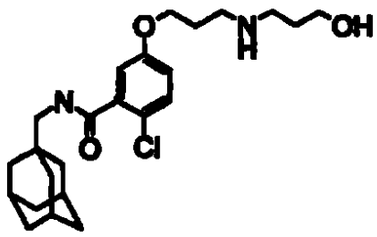
b) **[2-[4-Chloro-3-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)carbamoyl-phenylamino]-ethylamino]-acetic acid, hydrochloride**

To [2-[4-chloro-3-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)carbamoyl-phenylamino]-ethylamino]-acetic acid, 1,1-dimethylethyl ester (0.10 g) was added a solution of HCl in dioxane (5 ml of a 4*M* solution) and reaction mixture stirred at room temperature for 48 hours before concentration under reduced pressure. Residue was recrystallised (x2) from propan-2-ol/ethyl acetate/ether mixture to leave the title compound as a white solid (0.006 g).

^{1}H NMR (CD_3OD) δ 8.30 (1H, t); 7.20(1H, d); 6.72 (2H, m); 3.94 (2H, s); 3.47 (2H, s); 3.28 (2h, m); 3.03 (2H, s); 1.97 (3H, s); 1.76 (3H, d); 1.68 (3H, d); 1.61 (6H, s).

Example 3

2-Chloro-5-[3-(3-hydroxy-propylamino)-propoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, hydrochloride



a) **2-Chloro-5-[3-chloropropoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide**

To a solution of 2-chloro-5-hydroxy-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide (prepared according to the method of Example 51 of WO 99/29661) (0.48 g) in ethanol (5 ml) was added caesium carbonate (0.977 g) and reaction mixture heated to 85 °C for 10 minutes before addition of 1-bromo-3-chloropropane (0.74 ml) and heating continued for 24 hours before being cooled to room temperature and concentrated under reduced pressure. Residue was dissolved in ethyl acetate and washed with water (x2), $KHSO_4$ solution and brine, dried ($MgSO_4$), concentrated and residue purified by silica gel chromatography (eluting with 20% ethyl acetate in isohexanes) to deliver the sub-title compound as a pale yellow foam (0.50 g).

^{1}H NMR ($CDCl_3$) δ 7.28(2H, m); 6.91 (1H, m); 6.34 (1H, t); 4.13 (2H, t); 3.73 (2H, t); 3.58 (2H, d); 2.23 (2H, tt); 2.10 (2H, d); 1.73 (3H, d); 1.65 (3H, d); 1.59 (6H, s).

b) **2-Chloro-5-[3-(3-hydroxy-propylamino)-propoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, hydrochloride**

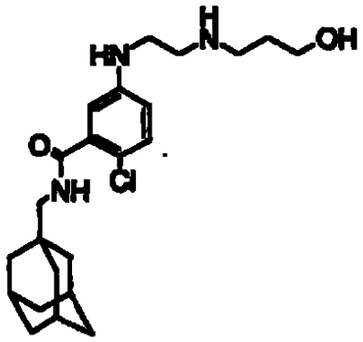
To a solution of 2-chloro-5-[3-chloropropoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide (0.25 g) and diisopropylethylamine (0.54 ml) in ethanol (5 ml) was added

sodium iodide (0.08 g) and 1-propanolamine (0.24 ml) and reaction vessel sealed and reaction mixture heated at 120 °C for 24 hours. The reaction mixture was concentrated under reduced pressure. Residue was partitioned between ethyl acetate and sodium hydrogencarbonate solution, aqueous phase extracted with additional ethyl acetate and organic phases combined, dried ($MgSO_4$) and concentrated under reduced pressure. Residue was purified by NPHPLC (eluting with 0-25% ethanol in dichloromethane) which gave 2-chloro-5-[3-(3-hydroxy-propylamino)-propoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide as a semi-solid which was converted to the hydrochloride salt by stirring with 4M HCl in dioxane and concentrated under reduced pressure to leave the title compound as a white solid (0.036 g).

MS (APCI +ve) 435.2396; $C_{22}H_{35}ClN_2O_3$ requires 435.2414 $(M+H)^+$
^1H NMR (CD_3OD) δ 8.28 (1H, t); 7.27 (1H, d); 6.93 (2H, m); 4.05 (2H, t); 3.62 (2H, t); 3.15 (2H, m); 3.09 (2H, t); 2.96 (2H, m); 2.10 (2H, tt); 1.89 (3H, s); 1.82 (2H, tt); 1.68 (3H, d); 1.59 (3H, d); 1.53 (6H, s).

Example 4

2-Chloro-5-[2-(3-hydroxypropylamino)ethylamino]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, acetate



To a solution of 2-chloro-5-(2-chloroethylamino)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide (prepared according to the method of Example 63 of WO 99/29661) (0.2 g) and diisopropylethylamine (0.5 ml) in 1-butanol (10 ml) was added sodium iodide (0.08 g) and 3-aminopropan-1-ol (0.12 g) and reaction vessel sealed and reaction mixture

MS (APCI +ve) 405/407 $(M+H\text{-}Boc)^+$

b) 5-[2-(2-Aminoethylamino)ethylamino]-2-chloro-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, acetate

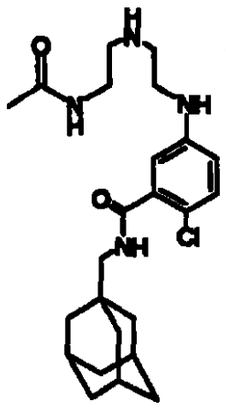
4M HCl in dioxane (2ml) was added to a solution of {2-[2-[4-chloro-3-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethylcarbamoyl)-phenylamino]-ethylamino]ethyl}-carbamic acid, 1,1-dimethylethyl ester (0.25g) in isopropanol (5ml). After 15 hours reaction mixture was concentrated and residue purified by RPHPLC (eluting with 15-95% MeCN in 0.1% $AcONH_4$ aqueous) concentrated under reduced pressure to leave the title compound as a solid (0.035g).

MS (APCI +ve) 405/407 $(M+H)^+$

^1H NMR ($CDCl_3$) δ 7.12 (1H, d); 7.00 (1H, d); 6.61 (1H, dd); 6.50 (1H, t); 3.28 (2H, s); 3.10 (2H, d); 3.02 (2H, s); 2.95 (4H, s); 2.20-2.80 (5H+water, s); 1.99 (6H, s); 1.68 (6H, q); 1.57 (6H, s).

Example 6

5-[2-(2-Acetylaminoethylamino)ethylamino]-2-chloro-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, acetate



Prepared according to the method of Example 4 using 2-chloro-5-(2-chloroethylamino)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide (prepared according to

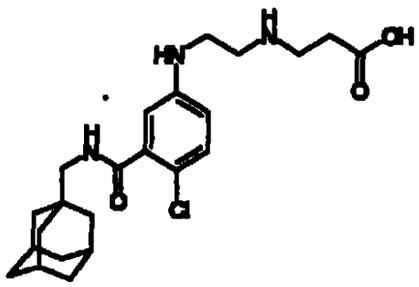
the method of Example 63 of WO 99/29661) (0.2g) and *N*-(2-amino-ethyl)-acetamide (0.16g) to deliver the title compound as a solid (0.03g).

MS (APCI +ve) 447/449 $(M+H)^+$

^{1}H NMR ($CDCl_3$) δ 7.15 (1H, d); 6.95 (1H, d); 6.68 (1H, s); 6.60 (1H, dd); 6.47 (1H, t); 3.41 (2H, q); 3.33 (2H, t); 3.15 (2H, d); 2.99 (2H, t); 2.87 (2H, t); 2.20-2.60 (3H+water, s); 1.99 (3H, s); 1.98 (3H, s); 1.95 (3H, s); 1.68 (6H, q); 1.58 (6H, s).

Example 7

[2-[4-Chloro-3-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)carbamoyl-phenylamino]-ethylamino]-propionic acid



a) [2-[4-Chloro-3-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)carbamoyl-phenylamino]-ethylamino]-propionic acid, 1,1-dimethylethyl ester

Prepared according to the method of Example 4 using 2-chloro-5-(2-chloroethyl)amino-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide (prepared according to the method of Example 63 of WO 99/29661) (0.2 g) and β-alanine 1,1-dimethylethyl ester (0.29 g) to deliver the sub-title compound as an oil (0.20 g).

MS (APCI +ve) 490/492 $(M+H)^+$

b) [2-[4-Chloro-3-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)carbamoyl-phenylamino]-ethylamino]-propionic acid

To a solution of [2-[4-chloro-3-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)carbamoyl-phenylamino]-ethylamino]-propionic acid, 1,1-dimethylethyl ester (0.20 g) in

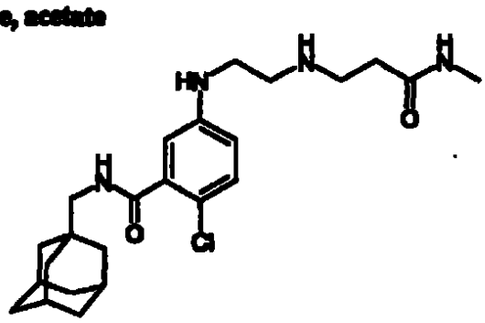
dichloromethane (5ml), was added trifluoroacetic acid (2 ml). After 15 hours concentrated, then purified by RPHPLC (eluting with 15-95% MeCN in 0.1% $AcONH_4$ aqueous) ~~concentrated under reduced pressure to leave the title compound as a solid (0.010 g).~~

MS (APCI +ve) 434/436 $(M+H)^+$

^1H NMR ($CDCl_3$/d_6-DMSO/d_1-TFA/CD_3OD) δ 7.18 (1H, d); 6.78 (1H, d); 6.68 (1H, dd); 3.50 (2H, t); 3.25 (2H, t); 3.22 (2H, t); 3.10 (2H, s); 2.78 (2H, t); 2.00 (3H, s); 1.69 (6H, q); 1.59 (6H, s).

Example 8

2-Chloro-5-[2-(2-methylcarbamoylethylamino)ethylamino]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, acetate



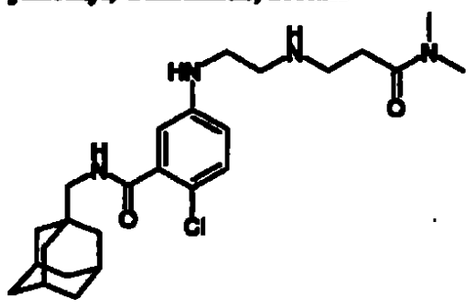
Prepared according to the method of Example 4 using 2-chloro-5-(2-chloroethylamino)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide (prepared according to the method of Example 63 of WO 99/29661) (0.2g) (0.2 g) and 3-amino-*N*-methylpropionamide (0.22 g) to give the title compound (0.08g).

MS (APCI +ve) 447/449 $(M+H)^+$

^1H NMR ($CDCl_3$) δ 7.13 (1H, d); 6.90 (1H, d); 6.59 (1H, dd); 6.20-6.40 (5H+water, m); 3.40 (2H, t); 3.14 (2H, d); 3.01-3.08 (4H, m); 2.73 (2H, d); 2.52 (2H, t); 2.00 (6H, s); 1.68 (6H, q); 1.58 (6H, s).

Example 9

2-Chloro-5-[2-(2-dimethylcarbamoylethylamino)ethylamino]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, acetate



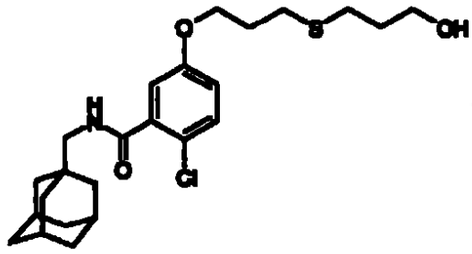
Prepared according to the method of Example 4 using 2-chloro-5-(2-chloroethylamino)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide (prepared according to the method of Example 63 of WO 99/29661) (0.2g) (0.2 g) and 3-amino-*N,N*-dimethylpropionamide (0.23 g) to deliver the title compound (0.005 g).

MS (APCI +ve) 461/463 $(M+H)^+$

^{1}H NMR ($CDCl_3$) δ 7.14 (1H, d); 6.95 (1H, d); 6.63 (1H, dd); 6.37 (1H, t); 3.35 (2H, t); 3.16 (2H, d); 2.99-3.02 (7H, m); 2.94 (3H, s); 2.63 (2H, t); 2.20-2.60 (3H+water, s); 2.05 (3H, s); 2.00 (3H, s); 1.69 (6H, q); 1.58 (6H, s).

Example 10

2-Chloro-5-[3-(3-hydroxypropylthio)propoxy]- *N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide



To a solution of 2-chloro-5-[3-chloropropoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide (prepared as described in Example 3a) above) (0.06 g) and

1,8-diazabicyclo(5.4.0)undec-7-ene (0.07 ml) in 1-butanol (5 ml) was added sodium iodide (0.023 g) and 3-mecaptopropan-1-ol (0.04 ml) and reaction vessel sealed and reaction mixture heated at 100 °C for 24 hours. The reaction mixture was diluted with ethyl acetate and extracted twice with 2*M* hydrochloric acid, twice with sodium hydrogencarbonate solution, once with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Residue was purified by NPHPLC (eluting with 0-2% ethanol in dichloromethane) to leave the title compound as a white solid (0.05g).

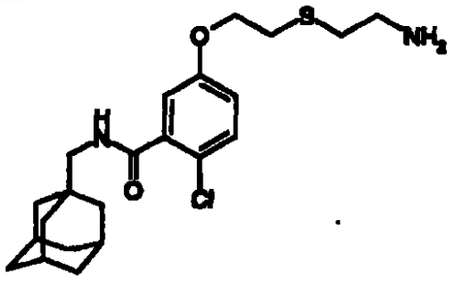
Mp 112-114 °C

MS (APCI +ve) 452/454 $(M+H)^+$

^1H NMR ($CDCl_3$) δ 7.26-7.29 (2H, m); 6.90 (1H, dd); 6.36 (1H, t); 4.09 (2H, t); 3.76 (2H, q); 3.17 (2H, d); 2.71 (2H, t); 2.65 (2H, t); 2.06 (2H, quin); 2.00 (3H, s); 1.85 (2H, quin); 1.69 (6H, q); 1.58 (6H, s).

Example 11

5-[2-(2-Aminoethylthio)ethoxy]-2-chloro-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, hydrochloride



a) **2-Chloro-5-[2-chloroethoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide**

To a solution of 2-chloro-5-hydroxy-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide (prepared according to the method of Example 51 of WO 99/29661) (0.30 g), triphenylphosphine (0.25 g) and 2-chloroethanol (0.07 ml) in tetrahydrofuran (4 ml) was added diethyl azodicarboxylate (0.15 ml) and the reaction mixture stirred at room temperature for 18 hours before further addition of triphenylphosphine (0.12 g) and diethyl azodicarboxylate (0.08 ml) and reaction stirred for additional 4 hours before addition of

silica and reaction mixture concentrated under reduced pressure. Residue was purified by silica gel chromatography (eluting with 20% ethyl acetate in isohexanes) to deliver the sub-title compound as a lightly coloured oil (0.31 g).

^{1}H NMR (d_6-DMSO) δ 8.30 (1H, t); 7.39(1H, d); 7.03 (1H, dd); 6.96 (1H, d); 4.29 (2H, t); 4.04 (2H, t); 2.92 (2H, d); 1.93 (3H, s); 1.72-1.44 (12H, m).

b) {2-[3-[4-chloro-3-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethylcarbamoyl)-phenoxy]-ethylthio]ethyl}-carbamic acid, 1,1-dimethylethyl ester

To a solution of 2-chloro-5-[2-chloroethoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide (0.1 g) and 1,8-diazabicyclo(5.4.0)undec-7-ene (0.12 ml) in isopropanol (3 ml) was added sodium iodide (0.04 g) and (2-mercapto-ethyl)-carbamic acid tert butyl ester (0.14 ml) and reaction vessel sealed and reaction mixture heated at 100 °C for 24 hours. The reaction mixture was diluted with ethyl acetate and extracted twice with 2M hydrochloric acid, twice with sodium hydrogencarbonate solution, once with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Residue was purified by NPHPLC (eluting with 0-2% ethanol in dichloromethane) to leave the sub-title compound contaminated with traces of (2-mercapto-ethyl)-carbamic acid *tert* butyl ester (0.32 g).

MS (APCI +ve) 523/525 $(M+H)^+$

c) 5-[2-(2-Aminoethylthio)ethoxy]-2-chloro-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, hydrochloride

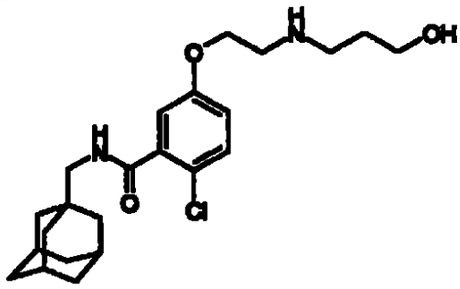
4M HCl in dioxane (2 ml) was added to a solution of {2-[3-[4-chloro-3-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethylcarbamoyl)-phenoxy]-ethylthio]ethyl}-carbamic acid, 1,1-dimethylethyl ester (230 mg) in methanol (5 ml). After 15 hours concentrated, then purified by RPHPLC (eluting with 15-50% MeCN in 0.1% $AcONH_4$ aqueous) concentrated under reduced pressure to leave the title compound as the acetate salt. Conversion to the hydrochloride salt by stirring with 4M HCl in dioxane and concentrated under reduced pressure. Trituration with diethyl ether gave the title compound as a solid (0.055 g).

MS (APCI +ve) 423/425 $(M+H)^+$

^1H NMR (DMSO) δ 8.30 (1H, t); 7.95 (3H, s); 7.39 (1H, d); 7.02 (1H, dd); 6.94 (1H, d); 4.19 (2H, t); 2.91-3.02 (6H, m); 2.85 (2H, t); 1.94 (3H, s); 1.63 (6H, q); 1.52 (6H, s).

Example 12

2-Chloro-5-[2-(3-hydroxypropylamino)ethoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, hydrochloride



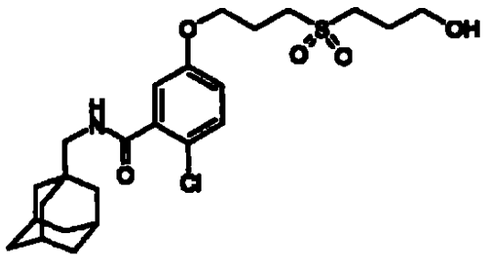
To a solution of 2-chloro-5-[2-chloroethoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide (prepared as described in Example 11a) above) (0.15 g) and diisopropylethylamine (0.50 ml) in 1-butanol (4 ml) was added sodium iodide (0.06 g) and 3-aminopropan-1-ol (0.09 ml) and reaction vessel sealed and reaction mixture heated at 110 °C for 24 hours. The reaction mixture was partitioned between ethyl acetate and sodium hydrogencarbonate solution, dried ($MgSO_4$) and concentrated under reduced pressure. Residue was purified by RPHPLC (eluting with 25-95% MeCN in 0.1% $AcONH_4$ aqueous) which gave 2-chloro-5-[2-[(3-hydroxypropyl)amino]ethoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide as the acetate salt which was converted to the hydrochloride salt by stirring with 4M HCl in dioxane and concentrated under reduced pressure. Recrystallisation from isohexane / isopropanol gave the title compound as a white solid (0.1g).

MS (APCI +ve) 421/423 $(M+H)^+$

^{1}H NMR(DMSO) δ 8.08 (2H, s); 8.32 (1H, t); 7.43 (1H, d); 7.06 (1H, dd); 6.98 (1H, d); 4.79 (1H, t); 4.27 (2H, t); 3.49 (2H, q); 3.40 (2H, s); 3.05 (2H, s); 2.93 (2H, d); 1.94 (3H, s); 1.79 (2H, quin); 1.58 (6H, q); 1.52 (6H, s).

Example 13

2-Chloro-5-[3-(3-hydroxypropylsulfonyl)propoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide



3-Chloroperoxybenzoic acid (0.14g, 70%) was added to a solution of 2-chloro-5-[3-(3-hydroxypropylthio)propoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide (prepared as described in Example 10 above) (0.1g) in dichloromethane (10ml). After 1 hour calcium hydroxide (0.1g) was added and stirring continued for a further 30 minutes. The reaction mixture was dried ($MgSO_4$), filtered through celite and concentrated. Residue was triturated with ethanol to leave the title compound as a white solid (0.030g).

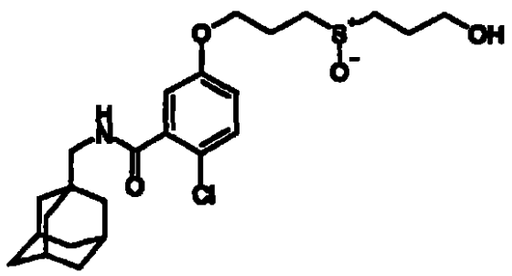
Mp 175-177 °C

MS (APCI +ve) 484/486 $(M+H)^+$

^{1}H NMR (DMSO) δ 8.29 (1H, t); 7.38 (1H, d); 7.00 (1H, dd); 6.93 (1H, d); 4.68 (1H, t); 4.11 (2H, t); 3.49 (2H, q); 3.25 (2H, t); 3.14 (2H, t); 2.92 (2H, d); 2.12 (2H, quin); 1.94 (3H, s); 1.85 (2H, quin); 1.63 (6H, q); 1.52 (6H, s).

Example 14

(±)-2-Chloro-5-[3-(3-hydroxypropylsulfinyl)propoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide



3-Chloroperoxybenzoic acid (0.065g, 70%) was added to a solution of 2-chloro-5-[3-(3-hydroxypropylthio)propoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide (prepared as described in Example 10 above) (0.11g) in dichloromethane (10ml). After 15 hours the crude reaction mixture was purified by NPHPLC (eluting 0-10% ethanol in dichloromethane) to leave the title compound as a white solid (0.055g).

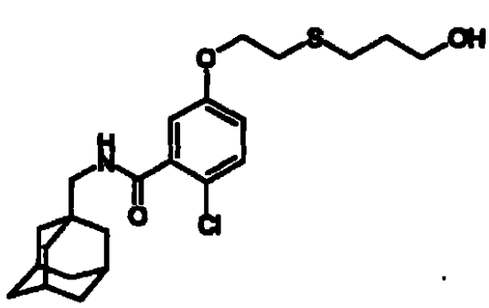
Mp 147-151 °C

MS (APCI +ve) 468/470 $(M+H)^+$

^{1}H NMR (DMSO) δ 8.29 (1H, t); 7.37 (1H, d); 7.00 (1H, dd); 6.93 (1H, d); 4.63 (1H, t); 4.12 (2H, t); 3.50 (2H, q); 2.64-3.00 (6H, m); 2.09 (2H, quin); 1.94 (3H, s); 1.80 (2H, quin); 1.62 (6H, q); 1.52 (6H, s).

Example 15

2-Chloro-5-[2-(3-hydroxypropylthio)ethoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide



Prepared according to the method of Example 10 using 2-chloro-5-(2-chloroethoxy)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide (prepared as described in Example 11a) above) (0.34g) and 3-mercaptopropan-1-ol (0.25ml) to give the title compound (0.4g).

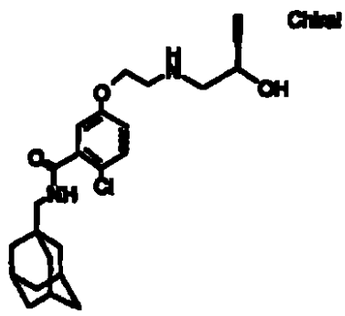
Mp 121-123 °C

MS (APCI +ve) 438/440 $(M+H)^+$

^{1}H NMR (DMSO) δ 8.28 (1H, t); 7.37 (1H, d); 7.00 (1H, dd); 6.92 (1H, d); 4.47 (1H, t); 4.15 (2H, t); 3.45 (2H, q); 2.92 (2H, d); 2.86 (2H, t); 2.63 (2H, t); 1.94 (3H, s); 1.57-1.72 (8H, m); 1.51 (6H, s).

Example 16

***S*-2-Chloro-5-[2-(2-hydroxypropylamino)ethoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, hydrochloride**



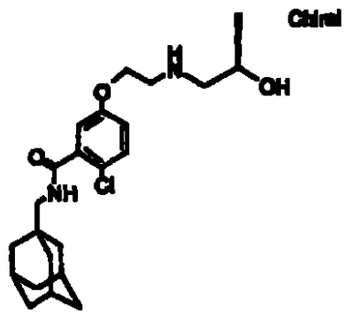
Prepared according to the method of Example 4 using 2-chloro-5-(2-chloroethoxy)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide (0.17 g) (prepared as described in Example 11a) above) and *S*-1-amino-2-propanol (0.11 ml). The reaction mixture was partitioned between ethyl acetate and sodium hydrogencarbonate solution, dried ($MgSO_4$) and concentrated under reduced pressure. Residue was purified by RPHPLC (eluting with 25-95% MeCN in 0.1% $AcONH_4$ aqueous) which gave the title compound as the acetate salt. This was converted to the hydrochloride salt by stirring with 4M HCl in dioxane and concentrated under reduced pressure. Recrystallisation from isohexane / isopropanol gave the title compound as a solid (0.05g).

MS (APCI +ve) 421/423 $(M+H)^+$

^{1}H NMR (DMSO) δ 8.60-9.00 (2H, d); 8.32 (1H, t); 7.42 (1H, d); 7.05 (1H, dd); 6.98 (1H, d); 5.36 (1H, d); 4.29 (2H, t); 3.95-4.05 (1H, m); 3.35 (2H, s); 3.00-3.10 (1H, m); 2.93 (2H, d); 2.80-2.90 (1H, m); 1.94 (3H, s); 1.63 (6H, q); 1.52 (6H, s); 1.12 (3H, d).

Example 17

***R*-2-Chloro-5-[2-(2-hydroxypropylamino)ethoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, hydrochloride**



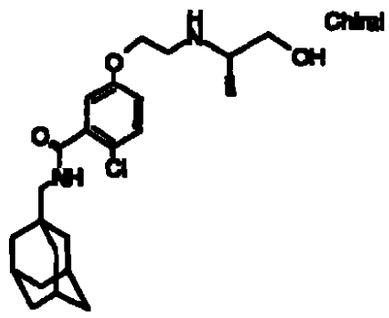
Prepared according to the method of Example 4 using 2-chloro-5-(2-chloroethoxy)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide (prepared as described in Example 11a) above) (0.17 g) and *R*-1-amino-2-propanol (0.11 ml). The reaction mixture was partitioned between ethyl acetate and sodium hydrogencarbonate solution, dried ($MgSO_4$) and concentrated under reduced pressure. Residue was purified by RPHPLC (eluting with 25-95% MeCN in 0.1% $AcONH_4$ aqueous) which gave the title compound as the acetate salt. This was converted to the hydrochloride salt by stirring with 4M HCl in dioxane and concentrated under reduced pressure. Trituration with diethyl ether gave the title compound as a solid (0.055g).

MS (APCI +ve) 421/423 $(M+H)^+$

^{1}H NMR (DMSO) δ 8.60-9.00 (2H, d); 8.32 (1H, t); 7.42 (1H, d); 7.05 (1H, dd); 6.98 (1H, d); 5.36 (1H, d); 4.29 (2H, t); 3.95-4.05 (1H, m); 3.35 (2H, s); 3.00-3.10 (1H, m); 2.93 (2H, d); 2.80-2.90 (1H, m); 1.94 (3H, s); 1.63 (6H, q); 1.52 (6H, s); 1.12 (3H, d).

Example 18

***S*-2-Chloro-5-[2-(2-hydroxy-1-methylethylamino)ethoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, hydrochloride**



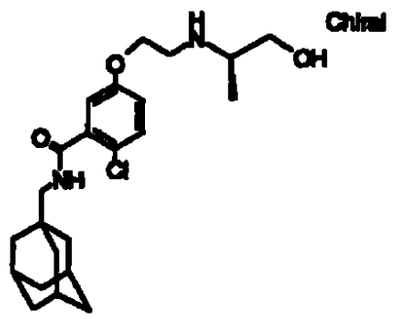
Prepared according to the method of Example 4 using 2-chloro-5-(2-chloroethoxy)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide (prepared as described in Example 11a) above) (0.17 g) and *S*-2-amino-1-propanol (0.11 ml). The reaction mixture was partitioned between ethyl acetate and sodium hydrogencarbonate solution, dried ($MgSO_4$) and concentrated under reduced pressure. Residue was purified by RPHPLC (eluting with 25-95% MeCN in 0.1% $AcONH_4$ aqueous) which gave the title compound as the acetate salt. This was converted to the hydrochloride salt by stirring with 4M HCl in dioxane and concentrated under reduced pressure. Trituration with diethyl ether gave the title compound as a solid (0.07g).

MS (APCI +ve) 421/423 $(M+H)^+$

^{1}H NMR (DMSO) δ 8.75 (2H, d); 8.32 (1H, t); 7.42 (1H, d); 7.05 (1H, dd); 6.99 (1H, d); 5.40 (1H, t); 4.29 (2H, t); 3.63-3.69 (1H, m); 3.50-3.56 (1H, m); 3.30-3.40 (3H+water, s); 2.93 (2H, d); 1.94 (3H, s); 1.63 (6H, q); 1.52 (6H, s); 1.22 (3H, d).

Example 19

***R*-2-Chloro-5-[2-(2-hydroxy-1-methylethylamino)ethoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, hydrochloride**



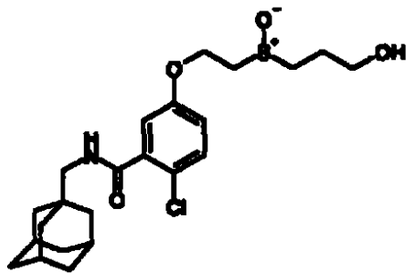
Prepared according to the method of Example 4 using 2-chloro-5-(2-chloroethoxy)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide (prepared as described in Example 11a) above) (0.17 g) and *R*-2-amino-1-propanol (0.11 ml). The reaction mixture was partitioned between ethyl acetate and sodium hydrogencarbonate solution, dried ($MgSO_4$) and concentrated under reduced pressure. Residue was purified by RPHPLC (eluting with 25-95% MeCN in 0.1% $AcONH_4$ aqueous) which gave the title compound as the acetate salt. This was converted to the hydrochloride salt by stirring with 4M HCl in dioxane and concentrated under reduced pressure. Trituration with diethyl ether gave the title compound as a solid (0.05g).

MS (APCI +ve) 421/423 $(M+H)^+$

^{1}H NMR (DMSO) δ 8.75 (2H, d); 8.32 (1H, t); 7.42 (1H, d); 7.05 (1H, dd); 6.99 (1H, d); 5.40 (1H, t); 4.29 (2H, t); 3.63-3.69 (1H, m); 3.50-3.56 (1H, m); 3.30-3.40 (3H+water, s); 2.93 (2H, d); 1.94 (3H, s); 1.63 (6H, q); 1.52 (6H, s); 1.22 (3H, d).

Example 20

(±)-2-Chloro-5-[2-(3-hydroxypropylsulfinyl)ethoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide



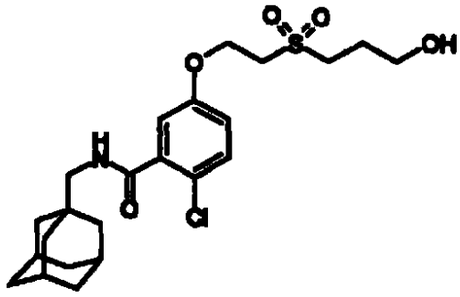
Prepared according to the method of Example 14 using 2-chloro-5-[2-(3-hydroxypropylthio)ethoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide (prepared as described in Example 15 above) (0.12g) and 3-chloroperoxybenzoic acid (0.07g, 70%) to give the title compound (0.07 g).

MS (APCI +ve) 454/456 $(M+H)^+$

^{1}H NMR (DMSO) δ 8.31 (1H, t); 7.39 (1H, d); 7.05 (1H, dd); 6.97 (1H, d); 4.64 (1H, t); 4.30-4.50 (2H, m); 3.55 (2H, q); 3.22-3.30 (1H, m); 3.01-3.07 (1H, m); 2.83-2.93 (3H, m); 2.74-2.81 (1H, m); 1.94 (3H, s); 1.80 (2H, quin); 1.66 (6H, q); 1.52 (6H, s).

Example 21

2-Chloro-5-[2-(3-hydroxypropylsulfonyl)ethoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide



Prepared according to the method of Example 13 using 2-chloro-5-[2-(3-hydroxypropylthio)ethoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide (prepared as

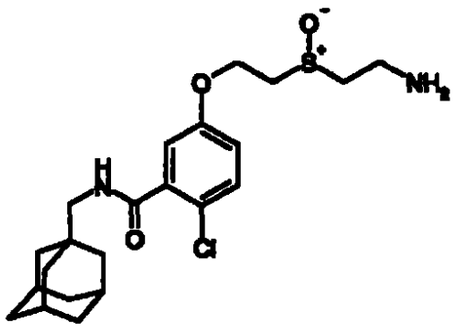
described in Example 15 above) (0.12g) and 3-chloroperoxybenzoic acid (0.14g, 70%), with purification by NPHPLC (eluting 0-5% EtOH in dichloromethane) to give the title compound (0.07 g).

MS (APCI +ve) 470/472 $(M+H)^+$

^1H NMR (DMSO) δ 8.31 (1H, t); 7.40 (1H, d); 7.05 (1H, dd); 6.98 (1H, d); 4.70 (1H, t); 4.38 (2H, t); 3.62 (2H, t); 3.50 (2H, q); 3.20 (2H, t); 2.92 (2H, d); 1.94 (3H, s); 1.85 (2H, quin); 1.66 (6H, q); 1.52 (6H, s).

Example 22

(±)-5-[2-(2-Aminoethylsulfinyl)ethoxy]-2-chloro-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, hydrochloride



a) **{2-[3-[4-chloro-3-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethylcarbamoyl)-phenoxy]-ethylsulfinyl]ethyl}-carbamic acid, 1,1-dimethylethyl ester**

3-Chloroperoxybenzoic acid (0.1g, 70%) was added to a solution of {2-[3-[4-chloro-3-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethylcarbamoyl)-phenoxy]-ethylthio]ethyl}-carbamic acid, 1,1-dimethylethyl ester (prepared as described in Example 11b) above) (0.2g) in dichloromethane (10ml). After 2 hours calcium hydroxide (0.3g) was added and stirring continued for a further 30minutes. The reaction mixture was dried ($MgSO_4$), filtered through celite and concentrated. Purification by NPHPLC (eluting with 0-10% ethanol in dichloromethane) gave the sub-title compound (0.14g).

MS (APCI +ve) 439/441 $(M+H\text{-}BOC)^+$

b) (±)-5-[2-(2-Aminoethylsulfinyl)ethoxy]-2-chloro-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, hydrochloride

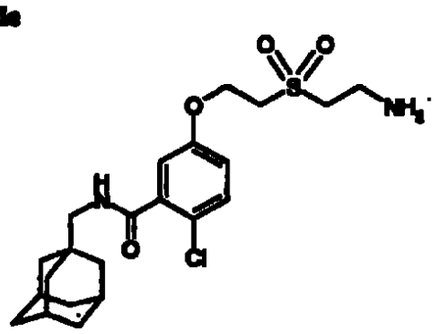
4M hydrochloric acid in dioxane (2ml) was added to a solution of {2-[3-[4-chloro-3-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethylcarbamoyl)-phenoxy]-ethylsulfinyl]ethyl}-carbamic acid, 1,1-dimethylethyl ester (0.14g) in methanol (10ml). After 15 hours the reaction mixture was concentrated and the residue recrystallised from isohexane / isopropanol, to leave the title product (0.05g).

MS (APCI +ve) 439/441 $(M+H)^+$

^{1}H NMR (DMSO) δ 8.32 (1H, t); 8.06 (3H, s); 7.40 (1H, d); 7.07 (1H, dd); 6.99 (1H, d); 4.30-4.45 (2H, m); 3.05-3.45 (6H, m); 2.92 (2H, d); 1.94 (3H, s); 1.85 (2H, quin); 1.63 (6H, q); 1.52 (6H, s).

Example 23

5-[2-(2-Aminoethylsulfonyl)ethoxy]-2-chloro-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, hydrochloride



a) {2-[3-[4-chloro-3-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethylcarbamoyl)-phenoxy]-ethylsulfonyl]ethyl}-carbamic acid, 1,1-dimethylethyl ester

3-Chloroperoxybenzoic acid (0.3g, 70%) was added to a solution of {2-[3-[4-chloro-3-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethylcarbamoyl)-phenoxy]-ethylthio]ethyl}-carbamic acid, 1,1-dimethylethyl ester (prepared as described in Example 11b) above) (0.2g) in dichloromethane (10ml). After 2 hours calcium hydroxide (0.3g) was added and stirring continued for a further 30 minutes. The reaction mixture was dried ($MgSO_4$), filtered

through celite and concentrated. Purification by NPHPLC (eluting with 0-10% ethanol in dichloromethane) to leave the sub-title compound (0.12g).

MS (APCI +ve) 455/457 $(M+H\text{-}BOC)^+$

b) 5-[2-(2-Aminoethylsulfonyl)ethoxy]-2-chloro-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, hydrochloride

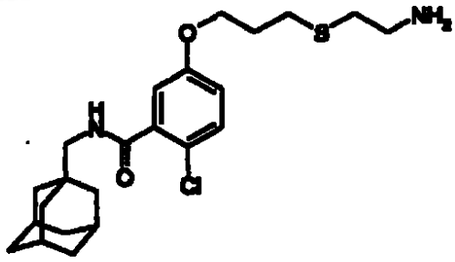
4M hydrochloric acid in dioxane (2ml) was added to a solution of {2-[3-[4-chloro-3-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethylcarbamoyl)-phenoxy]-ethylsulfonyl]ethyl}-carbamic acid, 1,1-dimethylethyl ester (0.14g) in methanol (10ml). After 15 hours the reaction mixture was concentrated and the residue recrystallised from isohexane / isopropanol, to leave the title product (0.05g).

MS (APCI +ve) 455/457 $(M+H)^+$

^{1}H NMR (DMSO) δ 8.32 (1H, t); 8.10 (3H, s); 7.42 (1H, d); 7.10 (1H, dd); 7.04 (1H, d); 4.40 (2H, t); 3.80 (2H, t); 3.55 (2H, t); 3.25 (2H t); 2.95 (2H, d); 1.94 (3H, s); 1.63 (6H, q); 1.52 (6H, s).

Example 24

5-[3-(2-Aminoethylthio)propoxy]-2-chloro- *N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, hydrochloride



a) {2-[3-[4-chloro-3-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethylcarbamoyl)-phenoxy]-propylthio]ethyl}-carbamic acid, 1,1-dimethylethyl ester

Prepared according to the method of Example 11b) using 2-chloro-5-(3-chloropropoxy)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide (prepared as described in Example 3a) above) (0.47g), to leave the sub-title compound contaminated with (2-mercapto-ethyl)-carbamic acid tert butyl ester (1.0g).

MS (APCI +ve) 537/539 $(M+H)^+$

b) 5-[3-(2-Aminoethylthio)propoxy]-2-chloro- *N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, hydrochloride

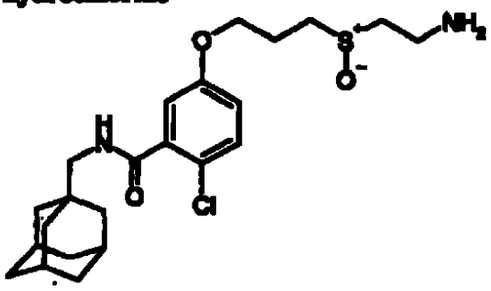
Prepared according to the method of Example 11c) using {2-[3-[4-chloro-3-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethylcarbamoyl)-phenoxy]-propylthio]ethyl}-carbamic acid, 1,1-dimethylethyl ester (0.34g), to give the title compound (0.065g).

MS (APCI +ve) 437/439 $(M+H)^+$

^{1}H NMR (DMSO) δ 8.29 (1H, t); 7.94 (3H, s); 7.37 (1H, d); 7.00 (1H, dd); 6.92 (1H, d); 4.07 (2H, t); 2.98 (2H, t); 2.92 (2H, d); 2.71 (2H, t); 2.66 (2H, t); 1.95-2.02 (5H, m); 1.63 (6H, q); 1.52 (6H, s).

Example 25

(±)-5-[3-(2-Aminoethylsulfinyl)propoxy]-2-chloro- *N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, hydrochloride



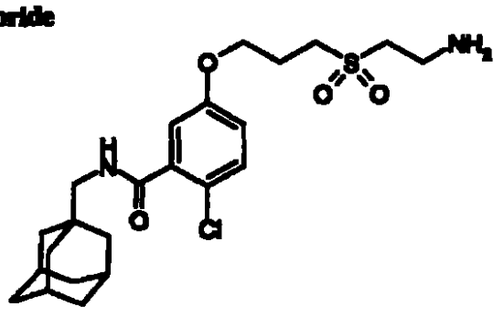
Prepared according to the method of Example 22 using {2-[3-[4-chloro-3-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethylcarbamoyl)-phenoxy]-propylthio]ethyl}-carbamic acid, 1,1-dimethylethyl ester (prepared as described in Example 24a) above) (0.3g), to give the title compound (0.16g).

MS (APCI +ve) 453/455 $(M+H)^+$

^{1}H NMR (DMSO) δ 8.30 (1H, t); 8.05 (3H, s); 7.38 (1H, d); 7.01 (1H, dd); 6.93 (1H, d); 4.13 (2H, t); 2.87-3.30 (8H, m); 2.10 (2H, quin); 1.94 (3H, s); 1.63 (6H, q); 1.52 (6H, s).

Example 26

5-[3-(2-Aminoethylsulfonyl)propoxy]-2-chloro-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, hydrochloride



Prepared according to the method of Example 23 using {2-[3-[4-chloro-3-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethylcarbamoyl)-phenoxy]-propylthio]ethyl}-carbamic acid, 1,1-dimethylethyl ester (prepared as described in Example 24a) above) (0.2g), to give the title compound (0.07g).

MS (APCI +ve) 469/471 $(M+H)^+$

^{1}H NMR (DMSO) δ 8.30 (1H, t); 8.12 (3H, s); 7.39 (1H, d); 7.02 (1H, dd); 6.94 (1H, d); 4.15 (2H, t); 3.20-3.60 (6H+water, m); 2.92 (2H, d); 2.12 (2H, quin); 1.94 (3H, s); 1.63 (6H, q); 1.53 (6H, s).

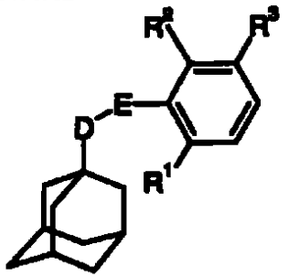
Pharmacological Analysis

Certain compounds such as benzoylbenzoyl adenosine triphosphate (bbATP) are known to be agonists of the $P2X_7$ receptor, effecting the formation of pores in the plasma membrane (Drug Development Research (1996), 37(3), p.126). Consequently, when the receptor is activated using bbATP in the presence of ethidium bromide (a fluorescent DNA probe), an increase in the fluorescence of intracellular DNA-bound ethidium bromide is observed. The increase in fluorescence can be used as a measure of $P2X_7$ receptor activation and therefore to quantify the effect of a compound on the $P2X_7$ receptor.

In this manner, each of the title compounds of Examples 1 to 26 was tested for antagonist activity at the $P2X_7$ receptor. Thus, the test was performed in 96-well flat bottomed microtitre plates, the wells being filled with 250 µl of test solution comprising 200 µl of a suspension of THP-1 cells (2.5×10^6 cells/ml) containing 10^{-4}M ethidium bromide, 25 µl of a high potassium buffer solution containing 10^{-5}M bbATP, and 25 µl of the high potassium buffer solution containing 3×10^{-5}M test compound. The plate was covered with a plastics sheet and incubated at 37 °C for one hour. The plate was then read in a Perkin-Elmer fluorescent plate reader, excitation 520 nm, emission 595 nm, slit widths: Ex 15 nm, Em 20 nm. For the purposes of comparison, bbATP (a $P2X_7$ receptor agonist) and pyridoxal 5-phosphate (a $P2X_7$ receptor antagonist) were used separately in the test as controls. From the readings obtained, a pIC_{50} figure was calculated for each test compound, this figure being the negative logarithm of the concentration of test compound necessary to reduce the bbATP agonist activity by 50%. Each of the compounds of Examples 1 to 26 demonstrated antagonist activity, having a pIC_{50} figure > 5.0.

CLAIMS

1. A compound of general formula



(I)

wherein D represents CH_2 or CH_2CH_2;

E represents C(O)NH or NHC(O);

R^1 and R^2 each independently represent a hydrogen or halogen atom, or an amino, nitro, C_1-C_6 alkyl or trifluoromethyl group;

R^3 represents a group of formula

(II);

X represents an oxygen or sulphur atom or a group NH, SO or SO_2;

Y represents an oxygen or sulphur atom or a group NH, SO or SO_2;

Z represents a group -OH, $-CO_2H$, C_1-C_6 alkoxy, $-NR^6R^7$, $-C(O)NR^8R^9$ or $-N(R^{10})C(O)$-C_1-C_6 alkyl;

R^4 represents a C_2-C_6 alkyl group;

R^5 represents a C_1-C_6 alkyl group; and

R^6, R^7, R^8, R^9 and R^{10} each independently represent a hydrogen atom or a C_1-C_6 alkyl group;

with the provisos that (i) when E represents NHC(O), X represents O, S or NH and Y represents O, then Z represents NH_2, and (ii) when E represents NHC(O), X represents O, S or NH, Y represents NH and R^5 represents CH_2CH_2, then Z is not H or -OH;

or a pharmaceutically acceptable salt or solvate thereof.

2. A compound according to claim 1, wherein D represents CH_2.

3. A compound according to claim 1 or claim 2, wherein E represents NHC(O).

4. A compound according to any one of claims 1 to 3, wherein R^1 and R^2 each independently represent a hydrogen, chlorine or bromine atom, or an amino, nitro, C_1-C_3 alkyl or trifluoromethyl group.

5. A compound according to any one of the preceding claims, wherein X represents an oxygen atom or a group NH.

6. A compound according to any one of the preceding claims, wherein Z represents a group -OH, $-CO_2H$, methoxy, $-NR^6R^7$, $-C(O)NR^8R^9$ or $-N(R^{10})C(O)CH_3$.

7. A compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, according to claim 1 which is selected from:

2-Chloro-5-[2-(2-methoxyethylamino)ethylamino]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, hydrochloride,

[2-[4-Chloro-3-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)carbamoyl-phenylamino]-ethylamino]-acetic acid, hydrochloride,

2-Chloro-5-[3-(3-hydroxy-propylamino)-propoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, hydrochloride,

2-Chloro-5-[2-(3-hydroxypropylamino)ethylamino]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, acetate,

5-[2-(2-Aminoethylamino)ethylamino]-2-chloro-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, acetate,

5-[2-(2-Acetylaminoethylamino)ethylamino]-2-chloro-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, acetate,

[2-[4-Chloro-3-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)carbamoyl-phenylamino]-ethylamino]-propionic acid,

2-Chloro-5-[2-(2-methylcarbamoylethylamino)ethylamino]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, acetate,

2-Chloro-5-[2-(2-dimethylcarbamoylethylamino)ethylamino]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, acetate,

2-Chloro-5-[3-(3-hydroxypropylthio)propoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

5-[2-(2-Aminoethylthio)ethoxy]-2-chloro-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, hydrochloride,

2-Chloro-5-[2-(3-hydroxypropylamino)ethoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, hydrochloride,

2-Chloro-5-[3-(3-hydroxypropylsulfonyl)propoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

(±)-2-Chloro-5-[3-(3-hydroxypropylsulfinyl)propoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

2-Chloro-5-[2-(3-hydroxypropylthio)ethoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

S-2-Chloro-5-[2-(2-hydroxypropylamino)ethoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, hydrochloride,

R-2-Chloro-5-[2-(2-hydroxypropylamino)ethoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, hydrochloride,

S-2-Chloro-5-[2-(2-hydroxy-1-methylethylamino)ethoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, hydrochloride,

R-2-Chloro-5-[2-(2-hydroxy-1-methylethylamino)ethoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, hydrochloride,

(±)-2-Chloro-5-[2-(3-hydroxypropylsulfinyl)ethoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

2-Chloro-5-[2-(3-hydroxypropylsulfonyl)ethoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

(±)-5-[2-(2-Aminoethylsulfinyl)ethoxy]-2-chloro-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, hydrochloride,

5-[2-(2-Aminoethylsulfonyl)ethoxy]-2-chloro-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, hydrochloride,

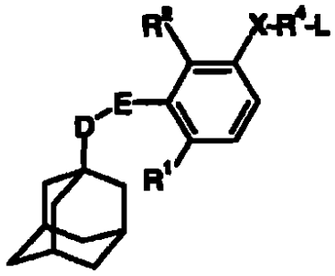
5-[3-(2-Aminoethylthio)propoxy]-2-chloro- *N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, hydrochloride,

(±)-5-[3-(2-Aminoethylsulfinyl)propoxy]-2-chloro-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, hydrochloride, and

5-[3-(2-Aminoethylsulfonyl)propoxy]-2-chloro-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, hydrochloride.

8. A process for the preparation of a compound of formula (I) as defined in claim 1 which comprises:

a) when Y represents a sulphur atom or a group NH, reacting a compound of general formula



(III)

wherein L represents a leaving group (e.g. a halogen atom) and D, E, R^1, R^2, X and R^4 are as defined in formula (I), with a compound of general formula

$$R^{20}—R^5—Z \quad \text{(IV)}$$

wherein R^{20} represents SH or NH_2 and R^5 and Z are as defined in formula (I), or

b) when Y represents SO or SO_2, reacting a corresponding compound of formula (I) in which Y represents a sulphur atom with a suitable oxidising agent;

and optionally after (a) or (b) converting the compound of formula (I) obtained to a pharmaceutically acceptable salt or solvate thereof.

9. A pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 7 in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

10. A process for the preparation of a pharmaceutical composition as claimed in claim 9 which comprises mixing a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as defined in any one of claims 1 to 7 with a pharmaceutically acceptable adjuvant, diluent or carrier.

11. A compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 7 for use in therapy.

12. A compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 7 for use in the treatment of rheumatoid arthritis.

13. Use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 7 in the manufacture of a medicament for use in therapy.

14. A method of effecting immunosuppression which comprises administering to a patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 7.

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ABSTRACT

NOVEL COMPOUNDS

The invention provides adamantane derivatives, a process for their preparation, pharmaceutical compositions containing them, a process for preparing the pharmaceutical compositions, and their use in therapy.

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TRADUCCION OFICIAL NO. 8183

De un documento escrito en inglés.

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Legalizaciones de un traspaso de patente a AstraZeneca AB escrito simultáneamente en inglés y en español, firmado ilegiblemente por Michael Paul Mortimore con la siguiente legalización notarial: Suscrito y confirmado por Michael Paul Mortimore este día diez de noviembre de dos mil ante mí.

Firmado: Christine Ann Chater Notario Público.

Sello de caucho: Christine Ann Chater – Notario Público – Swindon Wiltshire – Inglaterra

Sello en relieve estampado sobre lámina de papel color vino tinto: Christine Ann Chater – Notario Público

Expediente A2292-I-CO

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A TODOS LOS QUE LLEGUEN LOS PRESENTES YO CHRISTINE ANN CHATER DOMICILIADA EN Swindon Inglaterra, Notario Público debidamente admitido y juramentado POR EL PRESENTE CERTIFICO la autenticidad de la firma MICHAEL PAUL MORTIMORE al pié del documento adjunto al presente,

dicha firma fue suscrita hoy en mi presencia por MICHAEL PAUL MORTIMORE, quien se identificó ante mí mediante presentación del pasaporte británico número 033750747 y estaba nombrado y descrito en él.

EN FE Y TESTIMONIO DE ELLO, yo el Notario mencionado he suscrito mi nombre y he puesto y estampado el sello de mi despacho en Vertex Pharmaceuticals, 88 Milton Park Abingdon, Oxfordshire Inglaterra, este día diez de noviembre de dos mil.

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Christine Ann Chater Notario Público.

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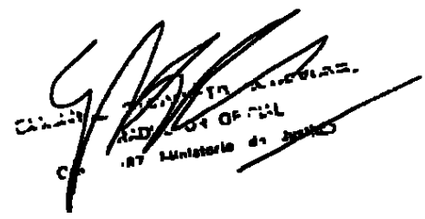
No. D 644388

Fecha: noviembre 13 de 2000



Este documento tiene la firma/sello de C.A Chater

Actuando en su condición de Notario Público.

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Firmado por A. Beckwith

Por el Secretario de Estado Principal de Su Magestad para Asuntos Extranjeros y de la Comunidad.

Sello impreso: Ministerio de Relaciones Exteriores y de la Comunidad - Londres - con el escudo inglés en el centro.

Sello en relive: Ministerio de Relaciones Exteriores y de la Comunidad - 3 -

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Bogotá, .D.C. 13 de diciembre de 2000

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D.E. ASUNTOS CONSULARES Y DIPLOMATICOS

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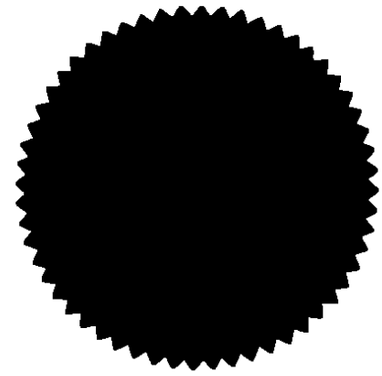
T ALL TO WHOM THESE PRESENTS shall come I CHRISTINE ANN CHATER of Swindon England Notary Public duly admitted and sworn DO HEREBY CERTIFY the genuiness of the signature MICHAEL PAUL MORTIMORE at the foot of the document hereunto annexed such signature having been this day subscribed in my presence by MICHAEL PAUL MORTIMORE who identified himself to me by production of British Passport number 033750547 and was therein named and described

IN FAITH AND TESTIMONY whereof I the said Notary have subscribed my name and set and affixed my seal of office at Vertex Pharmaceuticals 88 Milton Park Abingdon Oxfordshire England this Tenth day of November Two Thousand



Christine Ann Chater
Notary Public

Christine Ann Chater
Notary Public
Swindon Wiltshire
England

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CONSULADO GENERAL DE COLOMBIA
LONDRES

AUTENTICACION N° 02077-11 .

EL CONSUL DE COLOMBIA DE FE DE QUE A. BECKNELL.
EJERCIA EN LA FECHA LAS FUNCIONES DE SECRETARIO MINISTERIO RELACIONES EXTERIORES
Y QUE SU FIRMA Y SELLOS SON LOS QUE ACOSTUMBRA EN SUS ACTOS OFICIALES 15 NOV 2006
LONDRES
PAGADO IMPUESTO DE TIMBRE
DERECHOS: US$ 225

ANA GEORGINA ESPINOSA
Primer Consul

CONSULADO GENERAL DE COLOMBIA
LONDRES

UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND

No. **D644388**

Date **13 November, 2000**

This document bears
the signature / seal of **C A Chater**

Acting in the capacity of **Notary Public**

Signed by: **A. Beckwith**

FOREIGN AND COMMONWEALTH OFFICE
LONDON

For Her Majesty's Principal Secretary of State
For Foreign and Commonwealth Affairs

2292 I CO

leg. 128 129

ASSIGNMENT

The undersigned,

Lilian Alcaraz a French citizen, Mark Furber, Timothy Luker, Philip Thorne all British citizens

domiciled in
AstraZeneca R&D Charnwood, Bakewell Road, Loughborough, Leics. LE11 5RH, United Kingdom
and
Michael Mortimore a British citizen

Domiciled in
Vertex Pharmaceuticals Ltd., 88 Milton Park Abingdon, Oxfordshire OX14 4RY, United Kingdom

hereby state under oath to be the sole and true inventor of

NOVEL COMPOUNDS

We state as well that we assign, without reservations or limitation, in favor of

AstraZeneca AB

a corporation organized and existing under the laws of

Sweden

domiciled in

S-151 85 Södertälje, Sweden

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

TRASPASO

abajo firmado

Lilian Alcaraz un ciudadano Francés, Mark Furber, Timothy Luker, Philip Thorne todos ciudadanos Británicos

domiciliado en
AstraZeneca R&D Charnwood, Bakewell Road, Loughborough, Leics. LE11 5RH, Reino Unido
y
Michael Paul Mortimore un ciudadano Británico

Domiciliado en
Vertex Pharmaceuticals Ltd., 88 Milton Park Abingdon, Oxfordshire OX14 4RY, Reino Unido

declaramos bajo juramento ser únicos y verdaderos inventores de.

COMPUESTOS NOVEDOSOS

Declaramos asimismo que cedemos y transferimos sin reserva ni limitación, a favor de la sociedad

AstraZeneca AB

organizada y existente de conformidad con la leyes de

Suecia

domiciliada en

S-151 85 Södertälje, Suecia

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

.....
Lilian Alcaraz

.....
Mark Furber

Subscribed and affirmed by Michael Paul Mortimore

.....
Timothy Luker

.....
Michael Mortimore

This 7th day of November 2000
Before me
Christine Ann Chater
Notary Public

.....
Philip Thorne

Christine Ann Chater
Notary Public
Swindon Wiltshire
England

[redacted]

60

CERTIFICADO NOTARIAL (INDIVIDU)

A los días del mes de 19 , compareci personalmente ante mi, Notario Publico,

a quien doy fé de conocer y me consta que la persona descrita y firmante del documento que precede, declarado ante mí que otorga el mismo para los fines y propósitos que en él se expresan.

NOTARY PUBLIC (Notario Público)

NOTARIAL CERTIFICATE (INDIVIDUAL)

On this day of 19 personally appeared before me, a Notary Public,

to me known and known to me to be the person described in and who executed the foregoing document, and duly acknowledged to me that executed the same for the uses and purposes therein expressed.

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TRADUCCION OFICIAL NO. 8187

De un documento escrito en inglés.

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Legalizaciones de un traspaso de patente a AstraZeneca AB escrito simultáneamente en inglés y en español, firmado ilegiblemente por Lilian Alcaraz, Timothy Luker, Philip Thorne y Mark Furber. Firmado ilegiblemente por Notario Público de (ilegible)

Sello en relieve estampado sobre lámina de papel color vino tinto: Keneth Peter Byass – Notario Público

Expediente # A 2292-1-CO.

= = = = = =

REINO UNIDO DE LA GRAN BRETAÑA E IRLANDA DEL NORTE

No. D 647588

Fecha: noviembre 29 de 2000

Este documento tiene la firma/sello de Kenneth Peter Byass

Actuando en su condición de Notario Público.

Firma ilegible

Firmado por B.J. Clark

Por el Secretario de Estado Principal de Su Magestad para Asuntos Extranjeros y de la Comunidad.

Sello impreso: Ministerio de Relaciones Exteriores y de la Comunidad - Londres - con el escudo inglés en el centro.

Sello en relieve: Ministerio de Relaciones Exteriores y de la Comunidad – 2 – con el escudo inglés en el centro.

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Es traducción fiel y completa, de la cual queda copia en el archivo de esta Oficina de traducciones para su confrontación, a la cual me remito.

El documento fué legalizado en el Ministerio de Relaciones Exteriores bajo el No. 490022 de Diciembre 12 de 2000.

Derechos de traducción: $12.000.00

Bogotá, .D.C. 13 de diciembre de 2000

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TRADUCTOR OFICIAL

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JEFE DE LEGALIZACIONES SANTAFE DE BOGOTA D.C.

2292-1 CO
AstraZeneca
leg. 131

ASSIGNMENT

The undersigned,

Lilian Alcaraz a French citizen, Mark Furber, Timothy Luker, Philip Thorne all British citizens

domiciled in
AstraZeneca R&D Charnwood, Bakewell Road, Loughborough, Leics. LE11 5RH, United Kingdom
and
Michael Mortimore a British citizen

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.....
Lilian Alcaraz

.....
Timothy Luker

.....
Philip Thorne

TRASPASO

abajo firmado

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

M Luke.
.....
Mark Furber

.....
Michael Mortimore

RCJ 5240A

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CERTIFICADO NOTARIAL (INDIVIDUO)

A los 22 días del mes de Noviembre 2000, comparecieron personalmente ante mi, Notario Publico,
Lilian Alcaraz, Mark Furber, Timothy Luker, Philip Thorne, Paul Willis, Austen Pinn y Moya Catherin

a quienes doy fé de conocer y me consta que las personas descritas y firmantes del documento que precede, declarado ante mí que otorga el mismo para los fines y propósitos que en él se expresan.

NOTARY PUBLIC (Notario Público)

NOTARIAL CERTIFICATE (INDIVIDUAL)

On this 22 day of November 2000 personally appeared before me, a Notary Public,
Lilian Alcaraz, Mark Furber, Timothy Luker, Philip Thorne, Paul Willis, Austen Pinn and Moya Catherin

to me known and known to me to be the persons described in and who executed the foregoing document, and they duly acknowledged to me that they executed the same for the uses and purposes therein expressed.

Notary Public

[redacted]

CERTIFICADO NOTARIAL (INDIVIDUO)

A los días del mes de 19 , compareci personalmente ante mi, Notario Publico,

a quien doy fé de conocer y me consta que la persona descrita y firmante del documento que precede, declarado ante mí que otorga el mismo para los fines y propósitos que e xpresan.

NOTARIAL CERTIFICATE (INDIVIDUAL)

On this day of 19 personally appeared before me, a Notary Public,

to me known and known to me to be the person described in and who executed the foregoing document, and duly acknowledged to me that executed the same for the uses and purposes therein expressed.

MINISTERIO DE RELACIONES EXTERIORES
CUYA FIRMA APARECE EN EL DOCUMENTO DE SERIE Y NO. 490022
LAS FUNCIONES LEGALIZADORAS

DIC 12

JEFE DE LEGALIZACIONES
SANTAFE DE BOGOTA D.C.