



Industria y Comercio
SUPERINTENDENCIA

Organización CSA Ltda

PC7

DELEGATURA DE PROPIEDAD INDUSTRIAL
DIVISIÓN DE NUEVAS CREACIONES

07-62883

SOLICITUD DE PATENTE DE
INVENCION

TITULO: INHIBIDORES DEL TRASPORTE DE GLICINA

SOLICITANTE: GLAXO GROUP LIMITED.

DIRECCIÓN: Glaxo Wellcome House, Berkeley Avenue, Greenford,
Middlesex UB6 0NN, Inglaterra

A 61 K 31/166

APODERADO: J. IAN RAISBECK

BOGOTÁ 21 de Junio de 2007

301
2207/000135

OlarteRaisbeck

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 07-062883- -00000-0000

Dep 2020 NULCRLACIONES
Lve 379 FASENACIONALII
Folios 361

Industria y Comercio
SUPERINTENDENCIA

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE

PCT

ENTRADA EN FASE NACIONAL

P2007/000105

SOLICITUD DE:

1

☒

Patente de Invención.

☐

Patente de Modelo de Utilidad.

☐

Capítulo I.

☒

Capítulo II.

2

**SOLICITANTE
(71)**

Nombre: GLAXO GROUP LIMITED

Dirección: Glaxo Wellcome House, Berkeley
Avenue, Greenford, Middlesex UB6 ONN

Nacionalidad o Domicilio: BRITANICA

Lugar de Constitución: INGLATERRA

Teléfono: _____

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C.C. ☐ NIT ☐

C.E. ☐ Otro ☐

Cual _____

Número _____

3

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O APODERADO**

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Número 79.376.996 Btá
TP 135.799

4

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PCT (86)

Solicitud Internacional No. PCT/GB2005/004951

Fecha Diciembre 21, 2005

Publicación Internacional No. WO 2006/067423

Fecha Junio 29, 2006

6

Título (54) INHIBIDORES DEL TRASPORTE DE GLICINA

7

Clasificación Internacional (51) C07C 233/78, C07C 211/36, A61K 31/166.

8

Prioridad

SI

☒

NO

☐

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GB

GB

GB

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Diciembre 23, 2004

Mayo 5, 2005

Noviembre 29, 2005

(31) Número de Solicitud

0428231.5

0509204.4

0524320.9

9

Comprobante de pago No. 07 - 49.157

Fecha 20 de junio de 2007

10

ANEXOS

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

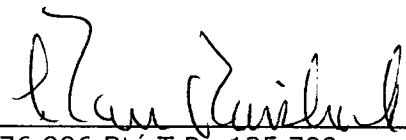
12

Solicito la concesión de la patente,

NOMBRE: J. IAN RAISBECK

FIRMA:

C.C. 79.376.996 Btá T.P. 135.799



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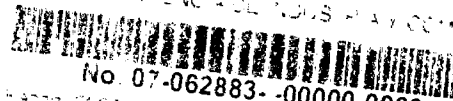
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Nacionalidad: Británica

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 07-062883-00000-0000

FECHA: 2007-06-20 18:53:20 Dep. 2026 Y. - CONSIGNACIONES
 TR 11-04-1N E.Y. - 379 FASE NACIONAL
 Aut 411 PRESENTACION Folios 36*

NIT : 900170099 2

RECIBO OFICIAL DE CAJA : 07 49,157
 FECHA : JUNIO 20 DE 2007

***** CONSIGNACION *****

DEPORTE	TE	TIPO PAGO	BANCO	CUENTA	Nº. PAGO	FECHA PGO	VT. PAGO
OLARTE RAISBECK		CONSIGNACION	BANCO POPULAR	050 00110-6	52331002	19/06/2007	3,403,000.00

***** CONCEPTO *****

CANT.	CONCEPTO	TOTAL CONCEPTO
1	50005-01 01 SOLICITUDES	
	1 TRAMITES DE SOL. DE PATENTE DE IN	402,000.00
	TOTAL :	\$ 402,000.00

SON: CUATROCIENTOS OCHENTA Y DOS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE N°. _____

APOSTILLA EN PODER DE REPRESENTACIÓN DE
GLAXO GROUP LIMITED

PODER DE REPRESENTACION

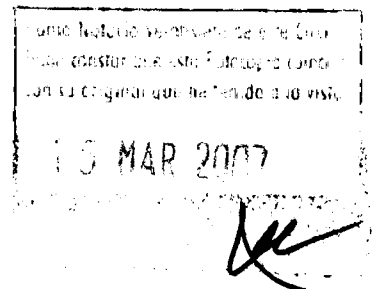
Bilingüe inglés- español otorgado en Brentford, Middlesex, Inglaterra el 13 de agosto de 2003 y firmado por Peter John Giddings, Apoderado y Funcionario autorizado.

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

APOSTILLA

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

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



CERTIFICADO

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

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

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

Marlen Neira C

Marlen Neira C
MARLEN NEIRA CASTRO
Traductor e Intérprete Oficial
Inglés - Español - Inglés
Resolución No. 2117 del 7 de

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

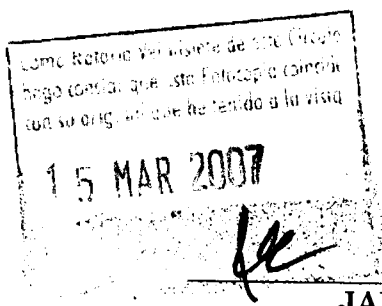
CERTIFICO:

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

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

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

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



JAMES KERR MILLIGAN
Notario Público de Londres, Inglaterra



APOSTILLE

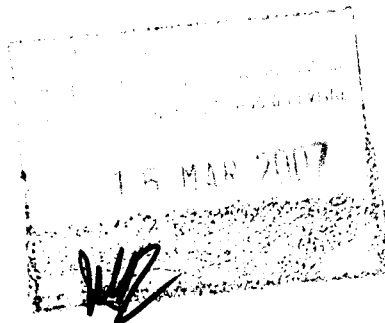
(Hague Convention of 5 October 1961 / Convention de La Haye du 5 octobre 1961)

UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND

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

This public document / Le présent acte public

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



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

8. Number/sous No **G229474**

9. Stamp:
timbre:
10. Signature: **J. Garbrah**



A handwritten signature in dark ink, appearing to be "J. Garbrah", written over a horizontal line.

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

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

OLARTE RAISBECK

OLARTE RAISBECK & FRIERI, LTDA.
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Power of Attorney

The undersigned,

domiciled in

Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN, GB
by means of these presents hereby grants to **Carlos R. Olarte, J. Ian Raisbeck and Ana Maria Frieri** full and sufficient Power of Attorney to file, prosecute, obtain, defend and enforce any and all of the company's **Patents, Utility Models and Industrial Designs** in the Republic of Colombia, to which end it empowers them to take all steps necessary before any administrative or judicial authority of any class for the objects stated, to file petitions, appeals, replies and oppositions, pay taxes and annuities, request testimonies, receive documents and securities, abandon applications and collect refunds. Sufficient power is hereby granted to receive notifications on behalf of the Company, to confer powers on those who are to represent the company judicially and extrajudicially, to answer in court in the matter of all claims and demands that may be presented in connection with the objects stated, giving them likewise power to substitute these presents and revoke such substitutions.

Poder

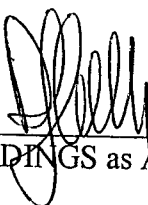
El suscrito,

Glaxo Group Limited

domiciliado en

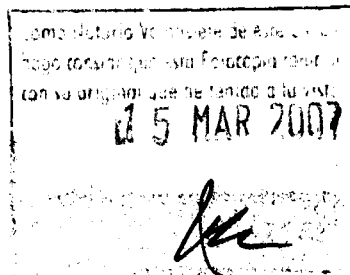
por medio del presente otorga a **Carlos R. Olarte, J. Ian Raisbeck y Ana María Frieri** poder especial, amplio y suficiente para presentar, tramitar, obtener, defender y hacer respetar todas y cualquiera de **Patentes, Modelos de Utilidad y Diseños Industriales** de la compañía en la República de Colombia,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

Signature/Firma: _____


Peter John GIDDINGS as Attorney and Authorised Official

Date/Fecha: 13 August 2003

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



(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
29 June 2006 (29.06.2006)

PCT

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WO 2006/067423 A1

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0428231.5 23 December 2004 (23.12.2004) GB
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0524320.9 29 November 2005 (29.11.2005) GB(71) Applicant (for all designated States except US): **GLAXO GROUP LIMITED** [GB/GB]; Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).

(72) Inventors; and

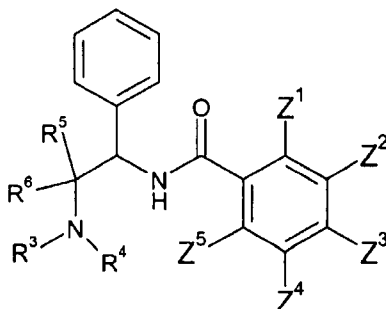
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(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU,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

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI,

[Continued on next page]

(54) Title: GLYCINE TRANSPORT INHIBITORS



(I)

(57) Abstract: The present invention relates to compounds of formula (I), or to salts or solvates thereof, their use in the manufacture of medicaments for treating neurological and neuropsychiatric disorders, in particular psychoses, dementia or attention deficit disorder. The invention further comprises processes to make these compounds and pharmaceutical formulations thereof.



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FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT,
RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA,
GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

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

Declarations under Rule 4.17:

- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))
- of inventorship (Rule 4.17(iv))

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

GLYCINE TRANSPORT INHIBITORS

17

The present invention relates to glycine transporter inhibiting compounds, their use in the manufacture of medicaments for treating neurological and neuropsychiatric disorders, in particular psychoses, dementia or attention deficit disorder. The invention further comprises processes to make these compounds and pharmaceutical formulations thereof.

Molecular cloning has revealed the existence in mammalian brains of two classes of glycine transporters, termed GlyT1 and GlyT2. GlyT1 is found predominantly in the forebrain and its distribution corresponds to that of glutamatergic pathways and NMDA receptors (Smith, *et al.*, *Neuron*, 8, 1992: 927-935). Molecular cloning has further revealed the existence of three variants of GlyT1, termed GlyT-1a, GlyT-1b and GlyT-1c (Kim *et al.*, *Molecular Pharmacology*, 45, 1994: 608-617), each of which displays a unique distribution in the brain and peripheral tissues. The variants arise by differential splicing and exon usage, and differ in their N-terminal regions. GlyT2, in contrast, is found predominantly in the brain stem and spinal cord, and its distribution corresponds closely to that of strychnine-sensitive glycine receptors (Liu *et al.*, *J. Biological Chemistry*, 268, 1993: 22802-22808; Jursky and Nelson, *J. Neurochemistry*, 64, 1995 : 1026-1033). Another distinguishing feature of glycine transport mediated by GlyT2 is that it is not inhibited by sarcosine as is the case for glycine transport mediated by GlyT1. These data are consistent with the view that, by regulating the synaptic levels of glycine, GlyT1 and GlyT2 selectively influence the activity of NMDA receptors and strychnine-sensitive glycine receptors, respectively.

NMDA receptors are critically involved in memory and learning (Rison and Staunton, *Neurosci. Biobehav. Rev.*, 19 533-552 (1995); Danysz *et al.*, *Behavioral Pharmacol.*, 6 455-474 (1995)); and, furthermore, decreased function of NMDA-mediated neurotransmission appears to underlie, or contribute to, the symptoms of schizophrenia (Olney and Farber, *Archives General Psychiatry*, 52, 998-1007 (1996)). Thus, agents that inhibit GlyT1 and thereby increase glycine activation of NMDA receptors can be used as novel antipsychotics and anti-dementia agents, and to treat other diseases in which cognitive processes are impaired, such as attention deficit disorders and organic brain syndromes. Conversely, over-activation of NMDA receptors has been implicated in a number of disease states, in particular the neuronal death associated with stroke and possibly neurodegenerative diseases, such as Alzheimer's disease, multi-infarct dementia, AIDS dementia, Huntington's disease, Parkinson's disease, amyotrophic lateral

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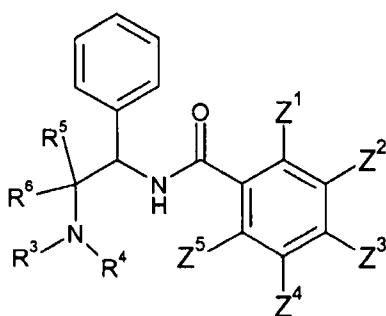
sclerosis or other conditions in which neuronal cell death occurs, such as stroke or head trauma. Coyle & Puttfarcken, Science, **262**, 689-695 (1993); Lipton and Rosenberg, New Engl. J. of Medicine, **330**, 613-622 (1993); Choi, Neuron, **1**, 623-634 (1988). Thus, pharmacological agents that increase the activity of GlyT1 will result in decreased glycine-activation of NMDA receptors, which activity can be used to treat these and related disease states. Similarly, drugs that directly block the glycine site of the NMDA receptors can be used to treat these and related disease states.

Glycine transport inhibitors are already known in the art, for example as disclosed in published international patent application WO03/055478 (SmithKline Beecham).

However, there still remains the need to identify further compounds that can inhibit GlyT1 transporters, including those that inhibit GlyT1 transporters selectively over GlyT2 transporters.

It has now been found that a novel class of compounds inhibit GlyT1 transporters and are thus useful in the treatment of certain neurological and neuropsychiatric disorders, including schizophrenia.

Thus, in a first aspect, there is provided a compound of formula (I) or a salt or solvate thereof:



(I)

wherein

Z¹ is selected from the group consisting of C₁₋₄alkyl, C₃₋₆cycloalkyl, C₁₋₄alkoxy, C₁₋₄alkylthio, haloC₁₋₄alkyl, phenyl, haloC₁₋₄alkoxy, halophenyl, C₁₋₄alkylsulfoxy, C₁₋₄alkylsulfonyl, bromo and chloro;

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Z² is selected from the group consisting of hydrogen, halogen, cyano, C₁₋₄alkyl, phenyl, haloC₁₋₄alkyl, haloC₁₋₄alkoxy, halophenyl, C₁₋₄alkoxyC₁₋₄alkyl and C₃₋₆cycloalkyl;

5 Z³ is selected from the group consisting of hydrogen, halogen, C₁₋₄alkyl, C₁₋₄alkoxy, C₁₋₄alkylthio, haloC₁₋₄alkyl, haloC₁₋₄alkoxy, and C₃₋₆cycloalkyl;

10 Z⁴ is selected from the group consisting of hydrogen, halogen, C₁₋₃alkyl, haloC₁₋₄alkyl, C₁₋₄alkoxy, C₁₋₄alkylthio, phenyl, haloC₁₋₄alkoxy, halophenyl, C₁₋₄alkoxyC₁₋₄alkyl and C₃₋₆cycloalkyl;

15 Z⁵ is selected from the group consisting of hydrogen, fluoro, chloro, bromo, iodo, hydroxy, C₁₋₄alkyl, C₁₋₄alkoxy, C₁₋₄alkylthio, phenyl, haloC₁₋₄alkyl, haloC₁₋₄alkoxy, halophenyl, C₁₋₄alkoxyC₁₋₄alkyl and C₃₋₆cycloalkyl;

20 whereby if more than one of Z¹ to Z⁵ is methoxy, then only Z¹ and Z⁵ are methoxy

R³ and R⁴ are independently selected from hydrogen and C₁₋₄alkyl, optionally substituted with one or more groups Y; or R³ and R⁴ together with the nitrogen atom to which they are attached form a saturated or partially unsaturated 4-, 5- 6- or 7-membered carbocyclic ring optionally substituted with a group Y';

Y is selected from the group consisting of C₁₋₄alkoxy, hydroxy, haloC₁₋₄alkoxy and C₃₋₅cycloalkyl;

25 Y' is selected from the group consisting of C₁₋₄alkyl, C₁₋₄alkoxy, halogen, hydroxy, haloC₁₋₄alkoxy, C₃₋₅cycloalkyl and C₅₋₁₀aryl or Y' forms a -CH₂- or -CH₂-CH₂- bridge between two atoms on the 4-, 5-, 6-, or 7-membered carbocyclic ring;

30 R⁵ and R⁶ are independently C₁₋₄alkyl, optionally substituted with one or more groups X; or R⁵ and R⁶ together with the carbon atom to which they are attached form a saturated 5- or 6-membered carbocyclic ring optionally substituted with one or more groups X', in the case of R⁵ and R⁶ together with the carbon atom to which they are attached forming a 5-membered saturated carbocyclic ring, that ring may optionally further comprise an additional heteroatom group selected from O, N and S(O)_m; where m = 0, 1 or 2.

35

19

X is selected from the group consisting of halogen, hydroxy, C₁₋₄alkoxy, haloC₁₋₄alkyl, haloC₁₋₄alkoxy and C₅₋₁₀aryl; and

X' is selected from the group consisting of halogen, hydroxy, C₁₋₄alkyl, C₁₋₄alkoxy, haloC₁₋₄alkyl, haloC₁₋₄alkoxy and C₅₋₁₀aryl;

whereby R³, R⁴, R⁵ and R⁶ are not all simultaneously unsubstituted methyl;

with the provisos that

- 10 - when simultaneously Z1 is propyloxy, Z3 is chloro, Z2=Z4=Z5=H, and R5 and R6 are both methyl, then R³ and R⁴ together with the nitrogen atom to which they are attached do not form a 2-methylpyrrolidine group;
- when simultaneously Z1 is methyl, Z3 is methoxy, Z2=Z4=Z5=H, and R5 and R6 are both methyl, then R³ and R⁴ together with the nitrogen atom to which they are attached do not form a pyrrolidine group.

As used herein, the term "alkyl" refers to a straight or branched alkyl group in all isomeric forms. Examples of C₁₋₄alkyl include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl and tert-butyl.

20

As used herein, the term "cycloalkyl" refers to a non-aromatic cyclic saturated hydrocarbon ring. Examples of C₃₋₆cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

25 As used herein, the term "alkoxy" refers to the group -O-alkyl wherein alkyl is as defined above. The term "methoxy" refers to the group -O-methyl.

As used herein, the term "alkylthio" refers to the group -S-alkyl wherein alkyl is as defined above. The term "methylthio" refers to the group -S-methyl.

30

As used herein, the term "alkylsulfoxy" refers to the group -S(O)-alkyl wherein alkyl is as defined above.

35 As used herein, the term "alkylsulfonyl" refers to the group -S(O)₂-alkyl wherein alkyl is as defined above.

15

As used herein, the term "C₅₋₁₀aryl" refers to a 5- or 6- membered monocyclic aromatic group or a 8- to 10- membered bicyclic aromatic group. Examples of C₅₋₁₀aryl include phenyl, indenyl, azulenyl and naphthyl.

- 5 As used herein, the terms "halogen" and its abbreviation "hal" refer to fluorine, chlorine, bromine, or iodine.

As used herein, the term "haloalkyl" refers to an alkyl group as defined above which is substituted with any number of fluorine, chlorine, bromine, or iodine atoms, including with
10 mixtures of those atoms. A haloalkyl group may, for example contain 1, 2 or 3 halogen atoms. For example, a haloalkyl group may have all hydrogen atoms replaced with halogen atoms. Examples of haloalkyl groups include fluoromethyl, difluoromethyl and trifluoromethyl.

- 15 As used herein, the term "salt" refers to any salt of a compound according to the present invention prepared from an inorganic or organic acid or base, quaternary ammonium salts and internally formed salts. Physiologically acceptable salts are particularly suitable for medical applications because of their greater aqueous solubility relative to the parent compounds. Such salts must clearly have a physiologically acceptable anion or cation.
- 20 Suitably physiologically acceptable salts of the compounds of the present invention include acid addition salts formed with inorganic acids such as hydrochloric, hydrobromic, hydroiodic, phosphoric, metaphosphoric, nitric and sulfuric acids, and with organic acids, such as tartaric, acetic, trifluoroacetic, citric, malic, lactic, fumaric, benzoic, formic, propionic, glycolic, gluconic, maleic, succinic, camphorsulfuric, isothionic, mucic, gentisic,
- 25 isonicotinic, saccharic, glucuronic, furoic, glutamic, ascorbic, anthranilic, salicylic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, pantothenic, stearic, sulfinilic, alginic, galacturonic and arylsulfonic, for example benzenesulfonic and p-toluenesulfonic, acids; base addition salts formed with alkali metals and alkaline earth metals and organic bases such as N,N-dibenzylethylenediamine, chlorprocaine, choline,
- 30 diethanolamine, ethylenediamine, meglumine (N-methylglucamine), lysine and procaine; and internally formed salts. Salts having a non-physiologically acceptable anion or cation are within the scope of the invention as useful intermediates for the preparation of physiologically acceptable salts and/or for use in non-therapeutic, for example, *in vitro*, situations. The salts may have any suitable stoichiometry. For example, a salt may have
- 35 1:1 or 2:1 stoichiometry. Non-integral stoichiometry ratios are also possible.

16

As used herein, the term "solvate" refers to a complex of variable stoichiometry formed by a solute (in this invention, a compound of formula (I) or a salt thereof) and a solvent. Such solvents for the purpose of the invention may not interfere with the biological activity of the solute. Examples of suitable solvents include, but are not limited to, water, methanol, ethanol and acetic acid. Preferably the solvent used is a pharmaceutically acceptable solvent. Examples of suitable pharmaceutically acceptable solvents include water, ethanol and acetic acid. Most preferably the solvent used is water.

10 In one embodiment, R^3 and R^4 are both simultaneously the same C_{1-4} alkyl, the same C_{1-4} alkyl substituted with one or more groups Y, or R^3 and R^4 together with the nitrogen atom to which they are attached form a saturated 5- or 6-membered carbocyclic ring optionally substituted with a group Y'.

15 In one embodiment, R^3 and R^4 are both C_{1-4} alkyl, for example methyl or ethyl, for example methyl.

Y may, for example, be selected from the group consisting of C_{1-4} alkoxy, halo C_{1-4} alkoxy and C_{5-10} aryl. In one embodiment, Y is selected from the group consisting of C_{1-4} alkoxy, C_{5-10} aryl.

20 Y' may, for example, be selected from the group consisting of halogen, C_{1-4} alkyl, C_{1-4} alkoxy, halo C_{1-4} alkoxy and C_{5-10} aryl. In one embodiment, Y' is selected from the group consisting of C_{1-4} alkyl, C_{1-4} alkoxy, C_{5-10} aryl.

25 In one embodiment, R^3 and R^4 are independently selected from hydrogen, methyl and ethyl, optionally substituted with a group Y, or R^3 and R^4 together with the nitrogen atom to which they are attached form a saturated or partially unsaturated (for example saturated) 4-, 5-, 6- or 7-membered carbocyclic ring optionally substituted with a group Y'.

30 In a further embodiment, R^3 and R^4 are selected from methyl and ethyl, optionally substituted with a group Y, or R^3 and R^4 together with the nitrogen atom to which they are attached form a saturated 4-, 5- or 6-membered carbocyclic ring optionally substituted with a group Y'. For example, R^3 and R^4 are both unsubstituted methyl, or R^3 and R^4 together with the nitrogen atom to which they are attached form a saturated 5- or 6-
35 membered carbocyclic ring.

17

Y may, for example, be selected from the group consisting of C₁₋₄alkoxy, hydroxy and C₃₋₅cycloalkyl.

Y' may, for example, be selected from the group consisting of halogen and C₁₋₄alkyl or Y' may form a -CH₂- bridge between two atoms on the 5- or 6- membered carbocyclic ring.

In one embodiment, R⁵ and R⁶ are both simultaneously the same C₁₋₄alkyl, the same C₁₋₄alkyl substituted with one or more groups X, or R⁵ and R⁶ together with the carbon atom to which they are attached form a saturated 5- or 6-membered carbocyclic ring optionally substituted with a group X', the 5- or 6-membered saturated carbocyclic ring optionally further comprising an additional heteroatom group selected from O, N and S(O)_m (where m is 0, 1, or 2);

In a further embodiment, R⁵ and R⁶ together with the carbon atom to which they are attached form a saturated 5- or 6-membered carbocyclic ring, for example a 5-membered carbocyclic ring.

X is, for example, selected from the group consisting of halogen, C₁₋₄alkoxy, haloC₁₋₄alkyl, haloC₁₋₄alkoxy and C₅₋₁₀aryl.

In one embodiment, R⁵ and R⁶ are independently selected from methyl and ethyl, optionally substituted with one or more groups X; or R⁵ and R⁶ together with the carbon atom to which they are attached form a saturated 5- or 6-membered carbocyclic ring and in the case of R⁵ and R⁶ together with the carbon atom to which they are attached forming a 5-membered saturated carbocyclic ring, that ring may optionally further comprise an oxygen heteroatom. In one embodiment one of R⁵ and R⁶ is ethyl and the other is methyl.

For example, in one embodiment R⁵ and R⁶ are independently selected from methyl and ethyl, or R⁵ and R⁶ together with the carbon atom to which they are attached form a saturated 5-membered carbocyclic ring. For example, in a further embodiment, R⁵ and R⁶ are both methyl, or R⁵ and R⁶ together with the carbon atom to which they are attached form a saturated 5- membered carbocyclic ring.

X may, for example, be selected from the group consisting of hydroxy and C₁₋₄alkoxy.

X' may, for example, be selected from the group consisting of hydroxy and C₁₋₄alkoxy.

18

In one embodiment, at least one of the pairs of groups R^3 / R^4 and R^5 / R^6 forms a cyclic group with the Nitrogen or Carbon atom to which they are respectively attached. For example, that cyclic group may be a 5-membered carbocyclic ring.

5

In one embodiment of the invention, Z^1 is selected from the group consisting of chloro, C_{1-4} alkyl, halo C_{1-4} alkyl, C_{1-4} alkoxy, halo C_{1-4} alkoxy, C_{1-4} alkylthio, phenyl, and halophenyl;

Z^2 is selected from the group consisting of hydrogen, iodo, bromo, chloro, fluoro, C_{1-4} alkyl, halo C_{1-4} alkyl, halo C_{1-4} alkoxy, phenyl, and halophenyl;

10

Z^3 is selected from the group consisting of hydrogen, iodo, bromo, chloro, C_{1-4} alkyl, halo C_{1-4} alkyl, C_{1-4} alkoxy, halo C_{1-4} alkoxy;

Z^4 is selected from the group consisting of hydrogen, iodo, bromo, chloro, fluoro, C_{1-4} alkoxy, halo C_{1-4} alkoxy, phenyl, and halophenyl; and

15

Z^5 is selected from the group consisting of hydrogen, iodo, bromo, chloro, C_{1-4} alkyl, C_{1-4} alkoxy, halo C_{1-4} alkoxy, phenyl, and halophenyl;

20

wherein no more than three of Z^1 , Z^2 , Z^3 , Z^4 , and Z^5 are hydrogen.

In another embodiment, Z^1 is selected from the group consisting of chloro, halo C_{1-4} alkyl, C_{1-4} alkoxy, halo C_{1-4} alkoxy, phenyl, and halophenyl, and Z^2 , Z^3 , Z^4 and Z^5 are hydrogen.

25

In a further embodiment,

Z^1 is selected from the group consisting of, chloro, C_{1-4} alkyl, and C_{1-4} alkoxy;

Z^2 is selected from the group consisting of hydrogen, halo C_{1-4} alkyl, and C_{1-4} alkyl;

30

Z^3 is hydrogen;

Z^4 is hydrogen; and

Z^5 is selected from the group consisting of hydrogen, and C_{1-4} alkyl;

35

19

wherein no more than three of Z^1 , Z^2 , Z^3 , Z^4 , and Z^5 are hydrogen.

In one embodiment, Z^1 is selected from the group consisting of C_{1-4} alkyl, C_{3-6} cycloalkyl, C_{1-2} alkoxy, C_{1-4} alkylthio, halo C_{1-4} alkyl, phenyl, halo C_{1-4} alkoxy, halophenyl, C_{1-4} alkylsulfoxy,
5 C_{1-4} alkylsulfonyl, bromo and chloro.

In one embodiment, Z^1 is selected from the group consisting of C_{1-4} alkyl, C_{1-2} alkoxy, C_{1-4} alkylthio, halo C_{1-4} alkyl, phenyl, halo C_{1-4} alkoxy, halophenyl and chloro;

10 For example, Z^1 is selected from the group consisting of C_{1-4} alkyl, C_{1-2} alkoxy, C_{1-4} alkylthio, halo C_{1-4} alkyl, and chloro, particularly from the group consisting of C_{1-4} alkyl and C_{1-2} alkoxy. For example, Z^1 may be selected from methyl, methylthio, ethoxy and methoxy.

In one embodiment, Z^2 is selected from the group consisting of hydrogen, halogen, C_{1-4} alkyl, phenyl and halo C_{1-4} alkyl. For example, Z^2 may be selected from the group
15 consisting of hydrogen, halogen, and C_{1-4} alkyl. For example Z^2 may be selected from hydrogen, bromo and methyl. For example Z^2 may be hydrogen

In one embodiment, Z^3 is selected from the group consisting of hydrogen, halogen, C_{1-4} alkyl, C_{1-4} alkoxy and halo C_{1-4} alkyl. For example, Z^3 may be selected from the group
20 consisting of hydrogen, halogen, C_{1-4} alkyl and halo C_{1-4} alkyl. For example Z^3 may be selected from hydrogen, fluoro, chloro and trifluoromethyl.

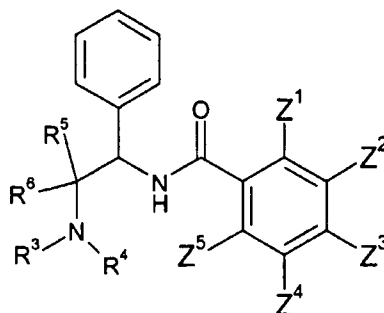
In one embodiment, Z^4 is selected from the group consisting of hydrogen, halogen, C_{1-3} alkyl, phenyl, C_{1-4} alkoxy and halo C_{1-4} alkyl. For example Z^4 may be selected from the
25 group consisting of hydrogen and halogen. For example Z^4 may be hydrogen.

In one embodiment, Z^5 is selected from the group consisting of hydrogen, hydroxy, fluoro, chloro, bromo, C_{1-4} alkyl, C_{1-4} alkoxy, halo C_{1-4} alkyl and halo C_{1-4} alkoxy; Z^5 may be selected
30 from the group consisting of chloro, bromo, C_{1-4} alkyl, C_{1-4} alkoxy and halo C_{1-4} alkyl. For example, Z^5 may be selected from the group consisting of bromo, methyl, and trifluoromethyl.

In one embodiment, Z^1 and Z^5 are both simultaneously not hydrogen. In a further
35 embodiment, Z^1 , Z^3 and Z^5 are all simultaneously not hydrogen.

20

Accordingly, in one embodiment, the present invention provides a compound of formula (Ia) or a salt or solvate thereof:



(Ia)

wherein

5 Z^1 is selected from the group consisting of C_{1-4} alkyl, C_{1-2} alkoxy, C_{1-4} alkylthio, halo C_{1-4} alkyl, and chloro;

10 Z^2 is selected from the group consisting of hydrogen, halogen, halo C_{1-4} alkyl, and C_{1-4} alkyl;

15 Z^3 is selected from the group consisting of hydrogen, halogen, halo C_{1-4} alkyl and C_{1-4} alkyl;

Z^4 is selected from the group consisting of hydrogen and halogen;

Z^5 is selected from the group consisting of bromo, C_{1-4} alkyl, C_{1-4} alkoxy and halo C_{1-4} alkyl;

20 R^3 and R^4 are independently unsubstituted methyl or ethyl, or R^3 and R^4 together with the nitrogen atom to which they are attached form a saturated 5- or 6-membered carbocyclic ring;

25 R^5 and R^6 are independently methyl or ethyl, or R^5 and R^6 together with the carbon atom to which they are attached form a saturated 5- membered carbocyclic ring;

and at least one of the pairs of groups R^3 / R^4 and R^5 / R^6 forms a cyclic group with the Nitrogen or Carbon atom to which they are respectively attached.

21

It is to be understood that features of an embodiment of the invention described with reference to one parameter can be combined with the features of another embodiment. The disclosure herein thus includes the combination of the features of any one embodiment with the features of any other embodiment described. All embodiments and
5 features of compounds of formula (I) apply to compounds of formula (Ia).

Examples of compounds of the invention include Examples 1 to 260 shown below, as well as salts and solvates thereof.

10 The compounds of formula (I) may have the ability to crystallise in more than one form. This is a characteristic known as polymorphism, and it is understood that such polymorphic forms ("polymorphs") are within the scope of formula (I). Polymorphism generally can occur as a response to changes in temperature or pressure or both and can also result from variations in the crystallisation process. Polymorphs can be distinguished
15 by various physical characteristics known in the art such as x-ray diffraction patterns, solubility, and melting point.

Certain of the compounds described herein may exist in stereoisomeric forms (i.e. they may contain one or more asymmetric carbon atoms or may exhibit *cis-trans* isomerism).
20 The individual stereoisomers (enantiomers and diastereoisomers) and mixtures of these are included within the scope of the present invention. Likewise, it is understood that compounds of formula (I) may exist in tautomeric forms other than that shown in the formula and these are also included within the scope of the present invention.

25 As referred to above, individual enantiomers of compounds of formula (I) may be prepared. In a preferred embodiment, an optically pure enantiomer is desired. The term "optically pure enantiomer" means that the compound contains greater than about 90 % of the desired isomer by weight, preferably greater than about 95 % of the desired isomer by weight, and most preferably greater than about 99 % of the desired isomer by weight, said
30 weight percent based upon the total weight of the isomer(s) of the compound. In some cases, one enantiomer of a particular structure may have a significantly higher activity than the other enantiomer of the same structure. Chirally pure, or chirally enriched compounds may be prepared by chirally selective synthesis or by separation of enantiomers. The separation of enantiomers may be carried out on the final product or,
35 alternatively on a suitable intermediate.

22

The compounds of this invention may be made by a variety of methods, including standard chemistry. Any previously defined variable will continue to have the previously defined meaning unless otherwise indicated. Illustrative general synthetic methods are set out below and then specific compounds of the invention are prepared in the working

5 Examples.

Compounds of general formula (I) may be prepared by methods known in the art of organic synthesis as set forth in part by the following synthesis schemes. It is also recognised that in all of the schemes described below, it is well understood that protecting

10 groups for sensitive or reactive groups are employed where necessary in accordance with general principles of chemistry. Protecting groups are manipulated according to standard methods of organic synthesis (T. W. Greene and P. G. M. Wuts (1991) Protecting Groups in Organic Synthesis, John Wiley & Sons). These groups are removed at a convenient stage of the compound synthesis using methods that are readily apparent to those skilled

15 in the art. The selection of processes as well as the reaction conditions and order of their execution shall be consistent with the preparation of compounds of formula (I). Those skilled in the art will recognise if a stereocentre exists in compounds of formula (I). Accordingly, the present invention includes both possible stereoisomers and includes not only racemic compounds but the individual enantiomers as well. Where the

20 stereochemistry is indicated as being variable at certain positions, a mixture of stereoisomers may be obtained, this mixture having been separated where indicated. Stereoisomers may be separated by high-performance liquid chromatography or other appropriate means. When a compound is desired as a single enantiomer, it may be obtained by stereospecific synthesis or by resolution of the final product or any convenient

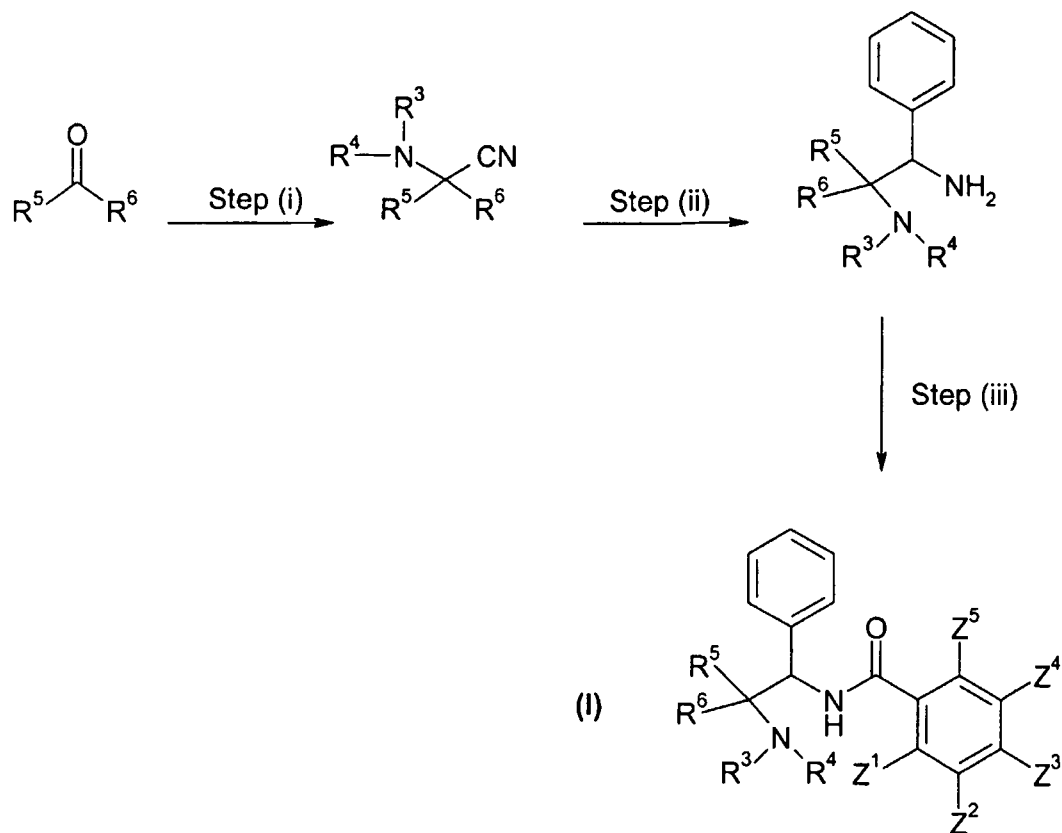
25 intermediate. Resolution of the final product, an intermediate, or a starting material may be effected by any suitable method known in the art. See, for example, Stereochemistry of Organic Compounds by E. L. Eliel, S. H. Wilen, and L. N. Mander (Wiley-Interscience, 1994).

30 Typical reaction routes for the preparation of a compound of formula (I) as hereinbefore defined, are shown in the following schemes. The starting materials and reagents are known to the skilled person in the art and/or can be prepared using methods known in the art.

35 Compounds of formula (I) can be synthesised by known methods; for example by, but not limited to, the synthetic route outlined in the scheme below

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Scheme 1



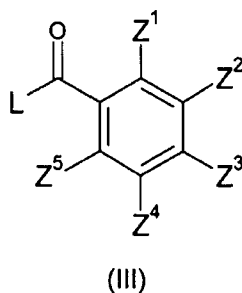
- 5 wherein $R^3, R^4, R^5, R^6, Z^1, Z^2, Z^3, Z^4$ and Z^5 are as defined for the compound of formula (I).

Step (i) is carried out for example by reaction of a ketone with an amine or amine salt in the presence of inorganic cyanide, for example potassium cyanide, in solvent such as water or by reaction of a ketone with an amine and trimethylsilyl cyanide in either the absence of solvent or in a solvent such as acetic acid.

Step (ii) can be achieved by successive reaction with an appropriate organometallic reagent, for example phenyllithium, in a suitable inert solvent for example tetrahydrofuran, followed by reduction with a reducing agent, for example, sodium borohydride in a suitable solvent, for example methanol.

Acylation step (iii) can be achieved by reaction with a compound of formula (III):

24



5 wherein Z^1 , Z^2 , Z^3 , Z^4 and Z^5 are as defined in formula (I) and L represents a suitable leaving group. Examples of leaving groups include halogen, hydroxy, $OC(=O)$ alkyl, $OC(=O)O$ -alkyl and OSO_2Me . L may be halogen and acylation in step (iii) may be carried out in an inert solvent such as dichloromethane, in the presence of a base such as triethylamine. When L represents hydroxy, the reaction preferably takes place in an inert solvent such as dichloromethane in the presence of a coupling reagent, for example a diimide reagent such as N,N dicyclohexylcarbodiimide (DCC), N-(3-(dimethylamino)propyl)-N-ethylcarbodiimide hydrochloride (EDC), polymer-supported EDC, polymer-supported DCC or O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluoro phosphate (HATU).

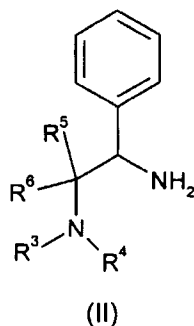
15

Within the scheme there is scope to convert a group R^3 into another group R^3 and similarly for groups R^4 , R^5 and R^6 , and Z^1 , Z^2 , Z^3 , Z^4 and Z^5 .

Accordingly, in a second aspect, the present invention provides a method of preparing a compound of formula (I), comprising the step of:

20

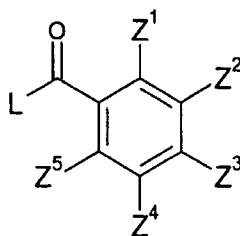
reacting a compound of formula (II):



25

25

wherein R^3 , R^4 , R^5 and R^6 are as defined in formula (I), with a compound of formula (III):



(III)

5

wherein Z^1 , Z^2 , Z^3 , Z^4 and Z^5 are as defined in formula (I) and L represents a suitable leaving group;

and thereafter optionally:

- 10
- removing any protecting groups and/or
 - converting a compound of formula (I) into another compound of formula (I) and/or
 - forming a salt or solvate.

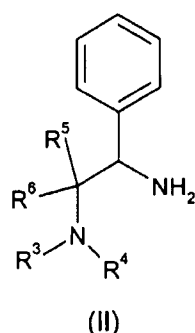
15 Suitable leaving groups L include halogen, hydroxy, $OC(=O)alkyl$, $OC(=O)O-alkyl$ and OSO_2Me .

Compounds of formula (I) can be converted into further compounds of formula (I) using standard techniques. For example, and by way of illustration rather than limitation, possible conversion reactions include acylation with an appropriate acylating agent such as acetyl chloride, alkylation using an appropriate alkylating reagent such as methyl iodide, and sulfonylation using a sulfonylating agent such as methanesulfonic anhydride and N-alkylation by reductive amination using a ketone or an aldehyde in the presence of a reducing agent such as sodiumtriacetoxymethylborohydride.

25 Pharmaceutically acceptable salts may be prepared conventionally by reaction with the appropriate acid or acid derivative.

In a further aspect, the present invention provides a compound of formula (II):

26



wherein R^3 , R^4 , R^5 and R^6 are as defined in formula (I), with the proviso that the
5 compound of formula (II) is not the compound wherein simultaneously R^3 and R^4 together
with the nitrogen atom to which they are attached form an unsubstituted piperidine ring
and R^5 and R^6 together with the carbon atom to which they are attached form an
unsubstituted cyclopentyl ring.

10 Compounds of formula (II) are useful as intermediates in the synthesis of compounds of
the invention.

The compounds of the present invention inhibit the GlyT1 transporter. The compounds
may selectively inhibit the GlyT1 transporter over the GlyT2 transporter.

15 Such compounds would be suitable for the treatment of certain neurological and
neuropsychiatric disorders. As used herein, the terms "treatment" and "treating" refer to
the alleviation and/or cure of established symptoms as well as prophylaxis.

20 The affinities of the compounds of this invention for the GlyT1 transporter can be
determined by the following assay:

HEK293 cells expressing the Glycine (Type 1) transporter were grown in cell culture
medium [DMEM/NUT mix F12 containing 2mM L-Glutamine, 0.8mg/mL G418 and 10%
25 heat inactivated fetal calf serum] at 37°C and 5% CO₂. Cells grown to 70-80% confluency
in T175 flasks were harvested and resuspended at 1.32×10^6 cells/mL in assay buffer
[140mM NaCl, 5.4mM KCl, 1.8mM CaCl₂, 0.8mM MgSO₄, 20mM HEPES, 5mM glucose
and 5mM alanine, pH 7.4]. Compounds were serially diluted 2.5-fold in DMSO from a top
concentration of 2.5mM with each compound giving a 11 data point dose-response.
30 100nL of compound at each concentration was added to the assay plate. An equal

27

volume of Leadseeker™ WGA SPA beads (12.5mg/ml suspended in assay buffer) was added to the cell suspension (1.32×10^6) and 5 μ L of the cell/bead suspension transferred to each well of a 384-well white solid bottom plate (3300 cells/well) containing 100nL of test compounds. Substrate (5 μ L) was added to each well [1:100 dilution of [^{3} H]-glycine stock in assay buffer containing 2.5 μ M glycine). Final DMSO concentration was 1% v/v. Data was collected using a Perkin Elmer Viewlux. pIC₅₀ values were determined using ActivityBase.

The following assay may also be used:

HEK293 cells expressing the Glycine (Type 1) transporter are grown in cell medium (DMEM/NUT mix F12) containing 2 mM L-Glutamine, 0.8 mg/mL G418 and 10% heat inactivated fetal calf serum (Gibco BRL) at 37°C in 5% CO₂. Cells grown to 70-80% confluency in T175 flasks are harvested and resuspended at 4×10^5 cells/ml in assay buffer [NaCl (140 mM), KCl (5.4 mM), CaCl₂ (1.8 mM), MgSO₄ (0.8 mM), HEPES (20mM), glucose (5 mM) and alanine (5 mM), pH 7.4]. An equal volume of Leadseeker™ SPA beads (12.5mg/ml suspended in assay buffer) is added to the cell suspension. Compounds are prepared as 10mM stocks in DMSO. 2.5 fold serial dilutions of the compounds are made in DMSO from a top conc of 2.5 mM. 100 nL of compound at each concentration is added to the assay plate (384-well white solid bottom plate) using the hummingbird dispenser. 5 μ L of the cell/bead mix is then added on top of the compound using a multidrop dispenser. Substrate (5 μ L) is then added to each well (1:100 dilution of H³-glycine in assay buffer containing 2.5 μ M glycine) Data is collected using a PerkinElmer Viewlux as 5 minute exposures. pIC₅₀ data values are determined using Activity Base.

Compounds may be assayed in their free base form or in the form of a salt, for example the hydrochloride salt or the formate salt. The assays described above are generally considered to provide data that is correct to ± 3 standard deviations = ± 0.5 .

Compounds having a pIC₅₀ at the GlyT1 transporter of greater than or equal to 5.0 are considered to be active at the GlyT1 transporter. The example compounds below were found to have a pIC₅₀ at the GlyT1 transporter of greater than or equal to 5.0.

Accordingly, in a further aspect of the invention, there is provided a compound of formula (I) or a salt or solvate thereof: for use in therapy.

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In another aspect of the invention, there is provided a compound of formula (I) as hereinbefore described or a salt or solvate thereof, for use in the treatment of a disorder mediated by GlyT1.

- 5 As used herein, the term "a disorder mediated by GlyT1" refers to a disorder that may be treated by the administration of a medicament that alters the activity of the GlyT1 transporter. As hereinbefore described, the action of GlyT1 transporters affects the local concentration of glycine around NMDA receptors. As a certain amount of glycine is needed for the efficient functioning of NMDA receptors, any change to that local
10 concentration can affect NMDA-mediated neurotransmission. As hereinbefore described, changes in NMDA-mediated neurotransmission have been implicated in certain neuropsychiatric disorders such as dementia, depression and psychoses, for example schizophrenia, and learning and memory disorders, for example attention deficit disorders and autism. Thus, alterations in the activity of the GlyT1 transporter are expected to
15 influence such disorders.

The disorders mediated by GlyT1 referred to herein include neurological and neuropsychiatric disorders, including psychoses such as schizophrenia, dementia and other forms of impaired cognition such as attention deficit disorders and organic brain
20 syndromes. Other neuropsychiatric disorders include drug-induced (phencyclidine, ketamine and other dissociative anesthetics, amphetamine and other psychostimulants and cocaine) psychosis, psychosis associated with affective disorders, brief reactive psychosis, schizoaffective psychosis, and psychosis NOS, "schizophrenia-spectrum" disorders such as schizoid or schizotypal personality disorders, or illness associated with
25 psychosis (such as major depression, manic depressive (bipolar) disorder, Alzheimer's disease and post-traumatic stress syndrome), and NMDA receptor-related disorders such as autism, depression, benign forgetfulness, childhood learning disorders and closed head injury.

- 30 The compounds of formula (I) are of use as antipsychotic agents for example in the treatment of schizophrenia, schizo-affective disorders, schizophreniform diseases, psychotic depression, mania, acute mania, paranoid and delusional disorders.

Within the context of the present invention, the terms used herein are classified in the
35 Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, published by the American Psychiatric Association (DSM-IV) and/or the International Classification of

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Diseases, 10th Edition (ICD-10). The various subtypes of the disorders mentioned herein are contemplated as part of the present invention. Numbers in brackets after the listed diseases below refer to the classification code in DSM-IV.

- 5 In particular, the compounds of formula (I) are of use in the treatment of schizophrenia including the subtypes Paranoid Type (295.30), Disorganised Type (295.10), Catatonic Type (295.20), Undifferentiated Type (295.90) and Residual Type (295.60); Schizophreniform Disorder (295.40); Schizoaffective Disorder (295.70) including the subtypes Bipolar Type and Depressive Type; Delusional Disorder (297.1) including the subtypes Erotomanic Type, Grandiose Type, Jealous Type, Persecutory Type, Somatic Type, Mixed Type and Unspecified Type; Brief Psychotic Disorder (298.8); Shared Psychotic Disorder (297.3); Psychotic Disorder Due to a General Medical Condition including the subtypes With Delusions and With Hallucinations; Substance-Induced Psychotic Disorder including the subtypes With Delusions (293.81) and With Hallucinations (293.82); and Psychotic Disorder Not Otherwise Specified (298.9).

- The compounds of formula (I) are also of use in the treatment of mood disorders including Major Depressive Episode, Manic Episode, Mixed Episode and Hypomanic Episode; Depressive Disorders including Major Depressive Disorder, Dysthymic Disorder (300.4), Depressive Disorder Not Otherwise Specified (311); Bipolar Disorders including Bipolar I Disorder, Bipolar II Disorder (Recurrent Major Depressive Episodes with Hypomanic Episodes) (296.89), Cyclothymic Disorder (301.13) and Bipolar Disorder Not Otherwise Specified (296.80); Other Mood Disorders including Mood Disorder Due to a General Medical Condition (293.83) which includes the subtypes With Depressive Features, With Major Depressive-like Episode, With Manic Features and With Mixed Features), Substance-Induced Mood Disorder (including the subtypes With Depressive Features, With Manic Features and With Mixed Features) and Mood Disorder Not Otherwise Specified (296.90).

- 30 The compounds of formula (I) are also of use in the treatment of anxiety disorders including Panic Attack, Agoraphobia, Panic Disorder, Agoraphobia Without History of Panic Disorder (300.22), Specific Phobia (300.29) including the subtypes Animal Type, Natural Environment Type, Blood-Injection-Injury Type, Situational Type and Other Type), Social Phobia (300.23), Obsessive-Compulsive Disorder (300.3), Posttraumatic Stress Disorder (309.81), Acute Stress Disorder (308.3), Generalized Anxiety Disorder (300.02),

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Anxiety Disorder Due to a General Medical Condition (293.84), Substance-Induced Anxiety Disorder and Anxiety Disorder Not Otherwise Specified (300.00).

The compounds of formula (I) are also of use in the treatment of substance-related disorders including Substance Use Disorders such as Substance Dependence and Substance Abuse; Substance-Induced Disorders such as Substance Intoxication, Substance Withdrawal, Substance-Induced Delirium, Substance-Induced Persisting Dementia, Substance-Induced Persisting Amnesic Disorder, Substance-Induced Psychotic Disorder, Substance-Induced Mood Disorder, Substance-Induced Anxiety Disorder, Substance-Induced Sexual Dysfunction, Substance-Induced Sleep Disorder and Hallucinogen Persisting Perception Disorder (Flashbacks); Alcohol-Related Disorders such as Alcohol Dependence (303.90), Alcohol Abuse (305.00), Alcohol Intoxication (303.00), Alcohol Withdrawal (291.81), Alcohol Intoxication Delirium, Alcohol Withdrawal Delirium, Alcohol-Induced Persisting Dementia, Alcohol-Induced Persisting Amnesic Disorder, Alcohol-Induced Psychotic Disorder, Alcohol-Induced Mood Disorder, Alcohol-Induced Anxiety Disorder, Alcohol-Induced Sexual Dysfunction, Alcohol-Induced Sleep Disorder and Alcohol-Related Disorder Not Otherwise Specified (291.9); Amphetamine (or Amphetamine-Like)-Related Disorders such as Amphetamine Dependence (304.40), Amphetamine Abuse (305.70), Amphetamine Intoxication (292.89), Amphetamine Withdrawal (292.0), Amphetamine Intoxication Delirium, Amphetamine Induced Psychotic Disorder, Amphetamine-Induced Mood Disorder, Amphetamine-Induced Anxiety Disorder, Amphetamine-Induced Sexual Dysfunction, Amphetamine-Induced Sleep Disorder and Amphetamine-Related Disorder Not Otherwise Specified (292.9); Caffeine Related Disorders such as Caffeine Intoxication (305.90), Caffeine-Induced Anxiety Disorder, Caffeine-Induced Sleep Disorder and Caffeine-Related Disorder Not Otherwise Specified (292.9); Cannabis-Related Disorders such as Cannabis Dependence (304.30), Cannabis Abuse (305.20), Cannabis Intoxication (292.89), Cannabis Intoxication Delirium, Cannabis-Induced Psychotic Disorder, Cannabis-Induced Anxiety Disorder and Cannabis-Related Disorder Not Otherwise Specified (292.9); Cocaine-Related Disorders such as Cocaine Dependence (304.20), Cocaine Abuse (305.60), Cocaine Intoxication (292.89), Cocaine Withdrawal (292.0), Cocaine Intoxication Delirium, Cocaine-Induced Psychotic Disorder, Cocaine-Induced Mood Disorder, Cocaine-Induced Anxiety Disorder, Cocaine-Induced Sexual Dysfunction, Cocaine-Induced Sleep Disorder and Cocaine-Related Disorder Not Otherwise Specified (292.9); Hallucinogen-Related Disorders such as Hallucinogen Dependence (304.50), Hallucinogen Abuse (305.30), Hallucinogen Intoxication (292.89), Hallucinogen Persisting Perception Disorder (Flashbacks) (292.89),

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Hallucinogen Intoxication Delirium, Hallucinogen-Induced Psychotic Disorder, Hallucinogen-Induced Mood Disorder, Hallucinogen-Induced Anxiety Disorder and Hallucinogen-Related Disorder Not Otherwise Specified (292.9); Inhalant-Related Disorders such as Inhalant Dependence (304.60), Inhalant Abuse (305.90), Inhalant Intoxication (292.89), Inhalant Intoxication Delirium, Inhalant-Induced Persisting Dementia, Inhalant-Induced Psychotic Disorder, Inhalant-Induced Mood Disorder, Inhalant-Induced Anxiety Disorder and Inhalant-Related Disorder Not Otherwise Specified (292.9); Nicotine-Related Disorders such as Nicotine Dependence (305.1), Nicotine Withdrawal (292.0) and Nicotine-Related Disorder Not Otherwise Specified (292.9); Opioid-Related Disorders such as Opioid Dependence (304.00), Opioid Abuse (305.50), Opioid Intoxication (292.89), Opioid Withdrawal (292.0), Opioid Intoxication Delirium, Opioid-Induced Psychotic Disorder, Opioid-Induced Mood Disorder, Opioid-Induced Sexual Dysfunction, Opioid-Induced Sleep Disorder and Opioid-Related Disorder Not Otherwise Specified (292.9); Phencyclidine (or Phencyclidine-Like)-Related Disorders such as Phencyclidine Dependence (304.60), Phencyclidine Abuse (305.90), Phencyclidine Intoxication (292.89), Phencyclidine Intoxication Delirium, Phencyclidine-Induced Psychotic Disorder, Phencyclidine-Induced Mood Disorder, Phencyclidine-Induced Anxiety Disorder and Phencyclidine-Related Disorder Not Otherwise Specified (292.9); Sedative-, Hypnotic-, or Anxiolytic-Related Disorders such as Sedative, Hypnotic, or Anxiolytic Dependence (304.10), Sedative, Hypnotic, or Anxiolytic Abuse (305.40), Sedative, Hypnotic, or Anxiolytic Intoxication (292.89), Sedative, Hypnotic, or Anxiolytic Withdrawal (292.0), Sedative, Hypnotic, or Anxiolytic Intoxication Delirium, Sedative, Hypnotic, or Anxiolytic Withdrawal Delirium, Sedative-, Hypnotic-, or Anxiolytic-Persisting Dementia, Sedative-, Hypnotic-, or Anxiolytic- Persisting Amnestic Disorder, Sedative-, Hypnotic-, or Anxiolytic-Induced Psychotic Disorder, Sedative-, Hypnotic-, or Anxiolytic-Induced Mood Disorder, Sedative-, Hypnotic-, or Anxiolytic-Induced Anxiety Disorder, Sedative-, Hypnotic-, or Anxiolytic-Induced Sexual Dysfunction, Sedative-, Hypnotic-, or Anxiolytic-Induced Sleep Disorder and Sedative-, Hypnotic-, or Anxiolytic-Related Disorder Not Otherwise Specified (292.9); Polysubstance-Related Disorder such as Polysubstance Dependence (304.80); and Other (or Unknown) Substance-Related Disorders such as Anabolic Steroids, Nitrate Inhalants and Nitrous Oxide.

The compounds of formula (I) are also of use in the treatment of sleep disorders including primary sleep disorders such as Dyssomnias such as Primary Insomnia (307.42), Primary Hypersomnia (307.44), Narcolepsy (347), Breathing-Related Sleep Disorders (780.59), Circadian Rhythm Sleep Disorder (307.45) and Dyssomnia Not Otherwise Specified

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- (307.47); primary sleep disorders such as Parasomnias such as Nightmare Disorder (307.47), Sleep Terror Disorder (307.46), Sleepwalking Disorder (307.46) and Parasomnia Not Otherwise Specified (307.47); Sleep Disorders Related to Another Mental Disorder such as Insomnia Related to Another Mental Disorder (307.42) and
- 5 Hypersomnia Related to Another Mental Disorder (307.44); Sleep Disorder Due to a General Medical Condition; and Substance-Induced Sleep Disorder including the subtypes Insomnia Type, Hypersomnia Type, Parasomnia Type and Mixed Type.

- The compounds of formula (I) are also of use in the treatment of eating disorders such as
- 10 Anorexia Nervosa (307.1) including the subtypes Restricting Type and Binge-Eating/Purging Type; Bulimia Nervosa (307.51) including the subtypes Purging Type and Nonpurging Type; Obesity; Compulsive Eating Disorder; and Eating Disorder Not Otherwise Specified (307.50).

- 15 The compounds of formula (I) are also of use in the treatment of Autistic Disorder (299.00); Attention-Deficit /Hyperactivity Disorder including the subtypes Attention-Deficit /Hyperactivity Disorder Combined Type (314.01), Attention-Deficit /Hyperactivity Disorder Predominantly Inattentive Type (314.00), Attention-Deficit /Hyperactivity Disorder Hyperactive-Impulse Type (314.01) and Attention-Deficit /Hyperactivity Disorder Not
- 20 Otherwise Specified (314.9); Hyperkinetic Disorder; Disruptive Behaviour Disorders such as Conduct Disorder including the subtypes childhood-onset type (321.81), Adolescent-Onset Type (312.82) and Unspecified Onset (312.89), Oppositional Defiant Disorder (313.81) and Disruptive Behaviour Disorder Not Otherwise Specified; and Tic Disorders such as Tourette's Disorder (307.23).

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- The compounds of formula (I) are also of use in the treatment of Personality Disorders including the subtypes Paranoid Personality Disorder (301.0), Schizoid Personality Disorder (301.20), Schizotypal Personality Disorder (301.22), Antisocial Personality Disorder (301.7), Borderline Personality Disorder (301.83), Histrionic Personality Disorder
- 30 (301.50), Narcissistic Personality Disorder (301.81), Avoidant Personality Disorder (301.82), Dependent Personality Disorder (301.6), Obsessive-Compulsive Personality Disorder (301.4) and Personality Disorder Not Otherwise Specified (301.9).

- The compounds of Formula (I) are also of use in the enhancement of cognition including
- 35 the treatment of cognition impairment in other diseases such as schizophrenia, bipolar disorder, depression, other psychiatric disorders and psychotic conditions associated with

cognitive impairment. Within the context of the present invention, the term cognitive impairment includes for example the treatment of impairment of cognitive functions including attention, orientation, learning disorders, memory (i.e. memory disorders, amnesia, amnesic disorders, transient global amnesia syndrome and age-associated memory impairment) and language function; cognitive impairment as a result of stroke, Alzheimer's disease, Huntington's disease, Pick disease, Aids-related dementia or other dementia states such as Multiinfarct dementia, alcoholic dementia, hypothyroidism-related dementia, and dementia associated to other degenerative disorders such as cerebellar atrophy and amyotrophic lateral sclerosis; other acute or sub-acute conditions that may cause cognitive decline such as delirium or depression (pseudodementia states) trauma, head trauma, age related cognitive decline, stroke, neurodegeneration, drug-induced states, neurotoxic agents, mild cognitive impairment, age related cognitive impairment, autism related cognitive impairment, Down's syndrome, cognitive deficit related to psychosis, and post-electroconvulsive treatment related cognitive disorders; and dyskinetic disorders such as Parkinson's disease, neuroleptic-induced parkinsonism, and tardive dyskinesias.

The compounds of formula (I) are also of use in the treatment of sexual dysfunctions including Sexual Desire Disorders such as Hypoactive Sexual Desire Disorder (302.71), and Sexual Aversion Disorder (302.79); sexual arousal disorders such as Female Sexual Arousal Disorder (302.72) and Male Erectile Disorder (302.72); orgasmic disorders such as Female Orgasmic Disorder (302.73), Male Orgasmic Disorder (302.74) and Premature Ejaculation (302.75); sexual pain disorder such as Dyspareunia (302.76) and Vaginismus (306.51); Sexual Dysfunction Not Otherwise Specified (302.70); paraphilias such as Exhibitionism (302.4), Fetishism (302.81), Frotteurism (302.89), Pedophilia (302.2), Sexual Masochism (302.83), Sexual Sadism (302.84), Transvestic Fetishism (302.3), Voyeurism (302.82) and Paraphilia Not Otherwise Specified (302.9); gender identity disorders such as Gender Identity Disorder in Children (302.6) and Gender Identity Disorder in Adolescents or Adults (302.85); and Sexual Disorder Not Otherwise Specified (302.9).

The invention also provides a compound of formula (I) as hereinbefore described or a pharmaceutically acceptable salt or solvate thereof for use in the treatment of schizophrenia, mood disorders, anxiety disorders, substance-related disorders, sleep disorders, eating disorders, autistic disorder, attention-deficit/hyperactivity disorder, disruptive behaviour disorder, tic disorders, personality disorders, cognition impairment in

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other diseases, sexual dysfunction, Parkinson's disease, dyskinetic disorders, depression, bipolar disorder, cognitive impairment, obesity, emesis, movement disorders, obsessive-compulsive disorders, amnesia, aggression, vertigo, dementia and circadian rhythm disorders.

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The invention also provides a compound of formula (I) as hereinbefore described or a pharmaceutically acceptable salt or solvate thereof for use in the treatment of psychotic disorders, substance abuse, cognitive impairment, obesity, and gastric motility disorders.

10 In another aspect of the invention, there is provided a method of treating a mammal, including a human, suffering from or susceptible to a disorder mediated by GlyT1, which comprises administering an effective amount of a compound of formula (I) as hereinbefore defined or a salt or solvate thereof.

15 The invention also provides a method of treating schizophrenia, mood disorders, anxiety disorders, substance-related disorders, sleep disorders, eating disorders, autistic disorder, attention-deficit/hyperactivity disorder, disruptive behaviour disorder, tic disorders, personality disorders, cognition impairment in other diseases, sexual dysfunction, Parkinson's disease, dyskinetic disorders, depression, bipolar disorder, cognitive
20 impairment, obesity, emesis, movement disorders, obsessive-compulsive disorders, amnesia, aggression, vertigo, dementia and circadian rhythm disorders which comprises administering to a mammal in need thereof an effective amount of a compound of formula (I) as hereinbefore described or a pharmaceutically acceptable salt or solvate thereof.

25 The invention also provides a method of treating psychotic disorders, substance abuse, cognitive impairment, obesity and gastric motility disorders which comprises administering to a mammal in need thereof an effective amount of a compound of formula (I) as hereinbefore described or a pharmaceutically acceptable salt or solvate thereof.

30 The compounds of formula (I) are also of use as anticonvulsants. The compounds of formula (I) are thus useful in the treatment of convulsions in mammals, and particularly epilepsy in humans. "Epilepsy" is intended to include the following seizures: simple partial seizures, complex partial seizures, secondary generalised seizures, generalised seizures including absence seizures, myoclonic seizures, clonic seizures, tonic seizures, tonic
35 clonic seizures and atonic seizures. The invention also provides a method of treating convulsions, which comprises administering to a mammal in need thereof an effective

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amount of a compound of formula (I) as hereinbefore described or a pharmaceutically acceptable salt or solvate thereof. Treatment of epilepsy may be carried out by the administration of a non-toxic anticonvulsant effective amount of a compound of the formula (III) or a pharmaceutically acceptable salt, or a composition as hereinbefore defined.

The compounds of formula (I) also find use in the treatment of neuropathic pain, for example in diabetic neuropathy, sciatica, non-specific lower back pain, multiple sclerosis pain, fibromyalgia, HIV-related neuropathy, neuralgia such as post-herpetic neuralgia and trigeminal neuralgia and pain resulting from physical trauma, amputation, cancer, toxins or chronic inflammatory conditions.

In another aspect of the invention, there is provided use of a compound of formula (I) as hereinbefore defined or a salt or solvate thereof in the preparation of a medicament for the treatment of a disorder mediated by GlyT1.

Preferably, the disorder mediated by GlyT1 to be treated by the use or method as hereinbefore described is a psychosis, including schizophrenia, dementia and attention deficit disorders, particularly schizophrenia.

The invention also provides the use of a compound of formula (I) as hereinbefore described or a pharmaceutically acceptable salt or solvate thereof in the manufacture of a medicament for the treatment of schizophrenia, mood disorders, anxiety disorders, substance-related disorders, sleep disorders, eating disorders, autistic disorder, attention-deficit/hyperactivity disorder, disruptive behaviour disorder, tic disorders, personality disorders, cognition impairment in other diseases, sexual dysfunction, Parkinson's disease, dyskinetic disorders, depression, bipolar disorder, cognitive impairment, obesity, emesis, movement disorders, obsessive-compulsive disorders, amnesia, aggression, vertigo, dementia and circadian rhythm disorders.

The invention also provides the use of a compound of formula (I) as hereinbefore described or a pharmaceutically acceptable salt or solvate thereof in the manufacture of a medicament for the treatment of psychotic disorders, substance abuse, cognitive impairment, obesity and gastric motility disorders.

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As used herein, the term "effective amount" means that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system, animal or human that is being sought, for instance, by a researcher or clinician.

- 5 Compounds for use according to the invention may be administered as the raw material but the active ingredients are preferably provided in the form of pharmaceutical compositions.

- 10 Accordingly, in a further aspect of the invention, there is provided a pharmaceutical composition comprising a compound of formula (I) as hereinbefore described or a salt or solvate thereof, and at least one pharmaceutically acceptable carrier, diluent or excipient.

- 15 These pharmaceutical compositions may be used in the treatment of clinical conditions for which a GlyT1 inhibitor is indicated such as, for example, schizophrenia. The carrier must be pharmaceutically acceptable to the recipient and must be compatible with, i.e. not have a deleterious effect upon, the other ingredients in the composition. The carrier may be a solid or a liquid and is preferably formulated with at least one compound of formula (I) or a salt or solvate thereof as a unit dose formulation. If desired, other physiologically active ingredients may also be incorporated in the pharmaceutical compositions of the invention.

- 20 It will be appreciated by those skilled in the art that the compounds according to the invention may advantageously be used in conjunction with one or more other therapeutic agents, for instance, different antidepressant agents such as 5HT3 antagonists, serotonin agonists, NK-1 antagonists, selective serotonin reuptake inhibitors (SSRI), noradrenaline re-uptake inhibitors (SNRI), tricyclic antidepressants, dopaminergic antidepressants, H3 antagonists, 5HT1A antagonists, 5HT1B antagonists, 5HT1D antagonists, D1 agonists, M1 agonists and/or anticonvulsant agents, as well as atypical antipsychotic drugs and cognitive enhancers.

- 25 30 Suitable 5HT3 antagonists which may be used in combination of the compounds of the inventions include for example ondansetron, granisetron, metoclopramide.

Suitable serotonin agonists which may be used in combination with the compounds of the invention include sumatriptan, rauwolscine, yohimbine, metoclopramide.

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Suitable SSRIs which may be used in combination with the compounds of the invention include fluoxetine, citalopram, femoxetine, fluvoxamine, paroxetine, indalpine, sertraline, zimeldine.

- 5 Suitable SNRIs which may be used in combination with the compounds of the invention include venlafaxine and reboxetine.

Suitable tricyclic antidepressants which may be used in combination with a compound of the invention include imipramine, amitriptyline, chlomipramine and nortriptyline.

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Suitable dopaminergic antidepressants which may be used in combination with a compound of the invention include bupropion and amineptine.

- 15 Suitable anticonvulsant agents which may be used in combination of the compounds of the invention include for example divalproex, carbamazepine and diazepam.

Suitable atypical antipsychotic drugs which which may be used in combination of the compounds of the invention include for example risperidone, olanzapine, ziprasidone, aripiprazole and clozapine.

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It will be appreciated that the compounds of the combination or composition may be administered simultaneously (either in the same or different pharmaceutical formulations), separately or sequentially.

- 25 The compounds of formula (I) and their pharmaceutically acceptable salts and solvates thereof are also suitable for combination with other typical and atypical antipsychotics to provide improved treatment of psychotic disorders. Particular advantages associated with the combinations, uses and methods of treatment of compounds of formula (I) and their pharmaceutically acceptable salts and solvates thereof include equivalent or improved
- 30 efficacy at doses of administration which are lower than those commonly used for the individual components. Improved treatments of positive symptoms and/or negative symptoms and/or cognitive symptoms of the psychotic disorder may also be observed. The combinations, uses and methods of treatment of the invention may also provide advantages in treatment of patients who fail to respond adequately or who are resistant to
- 35 treatment with certain neuroleptic agents.

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The combination therapies of the invention are preferably administered adjunctively. By adjunctive administration is meant the coterminous or overlapping administration of each of the components in the form of separate pharmaceutical compositions or devices. This regime of therapeutic administration of two or more therapeutic agents is referred to generally by those skilled in the art and herein as adjunctive therapeutic administration; it is also known as add-on therapeutic administration. Any and all treatment regimes in which a patient receives separate but coterminous or overlapping therapeutic administration of the compounds of formula (I) or a pharmaceutically acceptable salt or solvate thereof and at least one neuroleptic agent are within the scope of the current invention. In one embodiment of adjunctive therapeutic administration as described herein, a patient is typically stabilised on a therapeutic administration of one or more of the components for a period of time and then receives administration of another component. Within the scope of this invention, it is preferred that the compounds of formula (I) or a pharmaceutically acceptable salt or solvate thereof is administered as adjunctive therapeutic treatment to patients who are receiving administration of at least one neuroleptic agent, but the scope of the invention also includes the adjunctive therapeutic administration of at least one neuroleptic agent to patients who are receiving administration of compounds of formula (I) or a pharmaceutically acceptable salt or solvate thereof.

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The combination therapies of the invention may also be administered simultaneously. By simultaneous administration is meant a treatment regime wherein the individual components are administered together, either in the form of a single pharmaceutical composition or device comprising or containing both components, or as separate compositions or devices, each comprising one of the components, administered simultaneously. Such combinations of the separate individual components for simultaneous combination may be provided in the form of a kit-of-parts.

In a further aspect therefore, the invention provides a method of treatment of a psychotic disorder by adjunctive therapeutic administration of compounds of formula (I) or a pharmaceutically acceptable salt or solvate thereof to a patient receiving therapeutic administration of at least one neuroleptic agent. In a further aspect, the invention provides the use of compounds of formula (I) or a pharmaceutically acceptable salt or solvate thereof in the manufacture of a medicament for adjunctive therapeutic administration for the treatment of a psychotic disorder in a patient receiving therapeutic administration of at least one neuroleptic agent. The invention further provides

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compounds of formula (I) or a pharmaceutically acceptable salt or solvate thereof for use for adjunctive therapeutic administration for the treatment of a psychotic disorder in a patient receiving therapeutic administration of at least one neuroleptic agent.

- 5 In a further aspect, the invention provides a method of treatment of a psychotic disorder by adjunctive therapeutic administration of at least one neuroleptic agent to a patient receiving therapeutic administration of compounds of formula (I) or a pharmaceutically acceptable salt or solvate thereof. In a further aspect, the invention provides the use of at least one neuroleptic agent in the manufacture of a medicament for adjunctive
10 therapeutic administration for the treatment of a psychotic disorder in a patient receiving therapeutic administration of compounds of formula (I) or a pharmaceutically acceptable salt or solvate thereof. The invention further provides at least one neuroleptic agent for adjunctive therapeutic administration for the treatment of a psychotic disorder in a patient receiving therapeutic administration of compounds of formula (I) or a pharmaceutically
15 acceptable salt or solvate thereof.

- In a further aspect, the invention provides a method of treatment of a psychotic disorder by simultaneous therapeutic administration of compounds of formula (I) or a pharmaceutically acceptable salt or solvate thereof in combination with at least one
20 neuroleptic agent. The invention further provides the use of a combination of compounds of formula (I) or a pharmaceutically acceptable salt or solvate thereof and at least one neuroleptic agent in the manufacture of a medicament for simultaneous therapeutic administration in the treatment of a psychotic disorder. The invention further provides the use of compounds of formula (I) or a pharmaceutically acceptable salt thereof in the
25 manufacture of a medicament for simultaneous therapeutic administration with at least one neuroleptic agent in the treatment of a psychotic disorder. The invention further provides compounds of formula (I) or a pharmaceutically acceptable salt thereof for use for simultaneous therapeutic administration with at least one neuroleptic agent in the treatment of a psychotic disorder. The invention further provides the use of at least one
30 neuroleptic agent in the manufacture of a medicament for simultaneous therapeutic administration with compounds of formula (I) or a pharmaceutically acceptable salt thereof in the treatment of a psychotic disorder.

- In further aspects, the invention provides a method of treatment of a psychotic disorder
35 by simultaneous therapeutic administration of a pharmaceutical composition comprising compounds of formula (I) or a pharmaceutically acceptable salt or solvate thereof and at

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least one mood stabilising or antimanic agent, a pharmaceutical composition comprising compounds of formula (I) or a pharmaceutically acceptable salt or solvate thereof and at least one mood stabilising or antimanic agent, the use of a pharmaceutical composition comprising compounds of formula (I) or a pharmaceutically acceptable salt or solvate thereof and at least one mood stabilising or antimanic agent in the manufacture of a medicament for the treatment of a psychotic disorder, and a pharmaceutical composition comprising compounds of formula (I) or a pharmaceutically acceptable salt or solvate thereof and at least one mood stabilising or antimanic agent for use in the treatment of a psychotic disorder.

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In a further aspect, the invention provides a kit-of-parts for use in the treatment of a psychotic disorder comprising a first dosage form comprising compounds of formula (I) or a pharmaceutically acceptable salt or solvate thereof and one or more further dosage forms each comprising a neuroleptic agent for simultaneous therapeutic administration.

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Within the context of the present invention, the term psychiatric disorder includes those disorders mentioned above, such as schizophrenia, mood disorders, anxiety disorders, substance-related disorders, sleep disorders, eating disorders, autistic disorder, attention-deficit/hyperactivity disorder, disruptive behaviour disorder, tic disorders, personality disorders, cognition impairment in other diseases, sexual dysfunction, dyskinetic disorders, depression, bipolar disorder, cognitive impairment and obsessive-compulsive disorders and all the various forms of the disorders as mentioned herein. which are contemplated as part of the present invention.

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Examples of neuroleptic/antipsychotic drugs that are useful in the present invention include, but are not limited to: butyrophenones, such as haloperidol, pimozide, and droperidol; phenothiazines, such as chlorpromazine, thioridazine, mesoridazine, trifluoperazine, perphenazine, fluphenazine, thiflupromazine, prochlorperazine, and acetophenazine; thioxanthenes, such as thiothixene and chlorprothixene ; thienobenzodiazepines; dibenzodiazepines; benzisoxazoles; dibenzothiazepines; imidazolidinones ; benzisothiazolyl-piperazines; triazine such as lamotrigine; dibenzoxazepines, such as loxapine; dihydroindolones, such as molindone; aripiprazole; and derivatives thereof that have antipsychotic activity.

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Examples of neuroleptic drugs that are preferred for use in the present invention are shown in Table A.

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A1

Table A
Neuroleptic drugs

Common Name	Trade Name	Route of Administration	Form	Dosage Range and (Median) ^a
Clozapine	CLOZARIL	oral	tablets	12.5-900 mg/day (300-900 mg/day)
Olanzapine	ZYPREXA	oral	tablets	5-25 mg/day (10-25 mg/day)
Ziprasidone	GEODON	oral	capsules	20-80mg/twice a day (80-160 mg/day)
Risperidone	RISPERDAL	oral	solution tablets	2-16 mg/day tablets (4-12 mg/day)
Quetiapine fumarate	SEROQUEL	oral	tablets	50-900 mg/day (300-900 mg/day)
Sertindole	SERLECT			(4-24 mg/day)
Amisulpride				
Haloperidol	HALDOL	oral	tablets	1-100 mg/day (1-15 mg/day)
Haloperidol Decanoate	HALDOL Decanoate	parenteral	injection	
Haloperidol lactate	HALDOL INTENSOL	oral	solution	

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Common Name	Trade Name	Route of Administration	Form	Dosage Range and (Median) ^a
		parenteral	injection	
Chlorpromazine	THORAZINE	rectal	suppositories	30-800 mg/day (200-500 mg/day)
		oral	capsules solution tablets	
		parenteral	injection	
Fluphenazine	PROLIXIN			0.5-40 mg/day (1-5 mg/day)
Fluphenazine decanoate	PROLIXIN Decanoate	parenteral	injection	(about one-half the dosage shown for oral)
Fluphenazine enanthate	PROLIXIN	parenteral	injection	(same as above)
Fluphenazine hydrochloride	PROLIXIN	oral	elixir solution	
		parenteral	injection	
Thiothixene	NAVANE	oral	capsules	6-60 mg/day (8-30 mg/day)
Thiothixene hydrochloride	NAVANE	oral	solution	
		parenteral	injection	
Trifluoperazine	STELAZINE			(2-40 mg/day)
Perphenazine	TRILAFON	oral	solution tablets	12-64 mg/day (16-64 mg/day)
		parenteral	injection	
Perphenazine and Amitriptyline hydrochloride	ETRAFON TRIAVIL	oral	tablets	
Thioridazine	MELLARIL	oral	suspension solution tablets	150-800 mg/day (100-300 mg/day)

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Common Name	Trade Name	Route of Administration	Form	Dosage Range and (Median) ^a
Mesoridazine				(30-400 mg/day)
Molindone	MOBAN			50-225 mg/day (15-150 mg/day)
Molindone hydrochloride	MOBAN	oral	solution	
Loxapine	LOXITANE			20-250 mg/day (60-100 mg/day)
Loxapine hydrochloride	LOXITANE	oral	solution	
		parenteral	injection	
Loxapine succinate	LOXITANE	oral	capsules	
Pimozide				(1-10 mg/day)
Flupenthixol				
Promazine	SPARINE			
Triflupromazine	VESPRIN			
Chlorprothixene	TARACTAN			
Droperidol	INAPSINE			
Acetophenazine	TINDAL			
Prochlorperazine	COMPAZINE			
Methotrimeprazine	NOZINAN			
Pipotiazine	PIPOTRIL			

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Common Name	Trade Name	Route of Administration	Form	Dosage Range and (Median) ^a
Aripiprazole				
Hoperidone				

Examples of tradenames and suppliers of selected neuroleptic drugs are as follows :
 clozapine (available under the tradename CLOZARIL®, from Mylan, Zenith Goldline,
 UDL, Novartis); olanzapine (available under the tradename ZYPREX®, from Lilly ;
 5 ziprasidone (available under the tradename GEODON®, from Pfizer); risperidone
 (available under the tradename RISPERDAL®, from Janssen); quetiapine fumarate
 (available under the tradename SEROQUEL®, from AstraZeneca); haloperidol (available
 under the tradename HALDOL®, from Ortho-McNeil); chlorpromazine (available under the
 tradename THORAZINE®, from SmithKline Beecham (GSK); fluphenazine (available
 10 under the tradename PROLIXIN®, from Apothecon, Copley, Schering, Teva, and
 American Pharmaceutical Partners, Pasadena); thiothixene (available under the
 tradename NAVANE®, from Pfizer); trifluoperazine (10-[3-(4-methyl-1-piperazinyl)propyl]-
 2-(trifluoromethyl)phenothiazine dihydrochloride, available under the tradename
 STELAZINE®, from Smith Klein Beckman; perphenazine (available under the tradename
 15 TRILAFON®; from Schering); thioridazine (available under the tradename MELLARIL®;
 from Novartis, Roxane, HiTech, Teva, and Alparma) ; molindone (available under the
 tradename MOBAN®, from Endo); and loxapine (available under the tradename
 LOXITANE®, from Watson). Furthermore, benperidol (Glianimon®), perazine (Taxilan®)
 or melperone (Eunerpan®) may be used.

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Other preferred neuroleptic drugs include promazine (available under the tradename
 SPARINE®), triflupromazine (available under the tradename VESPRIN®),
 chlorprothixene (available under the tradename TARACTAN®), droperidol (available
 under the tradename INAPSINE®), acetophenazine (available under the tradename
 25 TINDAL®), prochlorperazine (available under the tradename COMPAZINE®),
 methotrimeprazine (available under the tradename NOZINAN®), pipotiazine (available
 under the tradename PIPOTRIL®), ziprasidone, and hoperidone.

15

Particularly preferred neuroleptic agents for use in the invention are olanzapine, risperidone, quetiapine, aripiprazole, haloperidol, clozapine, ziprasidone and osanetant.

5 It will be appreciated by those skilled in the art that the compounds according to the invention may advantageously be used in conjunction with one or more other therapeutic agents, for instance, different antidepressant agents such as 5HT3 antagonists, serotonin agonists, NK-1 antagonists, selective serotonin reuptake inhibitors (SSRI), noradrenaline re-uptake inhibitors (SNRI), tricyclic antidepressants, dopaminergic antidepressants, H3
10 antagonists, 5HT1A antagonists, 5HT1B antagonists, 5HT1D antagonists, D1 agonists, M1 agonists and/or anticonvulsant agents, as well as atypical antipsychotic drugs and cognitive enhancers.

Suitable 5HT3 antagonists which may be used in combination of the compounds of the
15 inventions include for example ondansetron, granisetron, metoclopramide.

Suitable serotonin agonists which may be used in combination with the compounds of the invention include sumatriptan, rauwolscine, yohimbine, metoclopramide.

Suitable SSRIs which may be used in combination with the compounds of the invention
20 include fluoxetine, citalopram, femoxetine, fluvoxamine, paroxetine, indalpine, sertraline, zimeldine.

Suitable SNRIs which may be used in combination with the compounds of the invention include venlafaxine and reboxetine.

25 Suitable tricyclic antidepressants which may be used in combination with a compound of the invention include imipramine, amitriptyline, chlomipramine and nortriptyline.

Suitable dopaminergic antidepressants which may be used in combination with a
30 compound of the invention include bupropion and amineptine.

Suitable anticonvulsant agents which may be used in combination of the compounds of the invention include for example divalproex, carbamazepine and diazepam.

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Suitable atypical antipsychotic drugs which which may be used in combination of the compounds of the invention include for example risperidone, olanzapine, ziprasidone, aripiprazole and clozapine.

- 5 It will be appreciated that the compounds of the combination or composition may be administered simultaneously (either in the same or different pharmaceutical formulations), separately or sequentially.

10 For use in medicine, the compounds of the present invention are usually administered as a standard pharmaceutical composition. The present invention therefore provides in a further aspect a pharmaceutical composition comprising a compound of formula (I) as hereinbefore described or a pharmaceutically (i.e. physiologically) acceptable salt thereof and a pharmaceutically (i.e. physiologically) acceptable carrier. The pharmaceutical composition can be for use in the treatment of any of the conditions described herein.

15 Possible formulations include those suitable for oral, sub-lingual, buccal, parenteral (for example, subcutaneous, intramuscular, or intravenous), rectal, topical and intranasal administration and in forms suitable for administration by inhalation or insufflation (either through the mouth or nose). The most suitable means of administration for a particular patient will depend on the nature and severity of the conditions being treated and on the nature of the active compound, but, where possible, oral administration is preferred.

25 Formulations suitable for oral administration may be provided as discrete units, such as tablets, capsules, cachets, or lozenges, each containing a predetermined amount of the active compound; as powders or granules; as solutions or suspensions in aqueous or non-aqueous liquids; or as oil-in-water or water-in-oil emulsions. For example, a compound of the invention may be prepared as a formulation with a controlled release profile. This may be in any of the above mentioned pharmaceutical forms. For example, it may be a gel formulation in a non aqueous oily vehicle, for example Miglyol, with a suitable gelling agent if required, for example methyl cellulose or hydrophobic colloidal silica.

35 Formulations suitable for sublingual or buccal administration include lozenges comprising the active compound and, typically, a flavoured base, such as sugar and acacia or tragacanth and pastilles comprising the active compound in an inert base, such as gelatin and glycerin or sucrose and acacia.

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Formulations suitable for parenteral administration typically comprise sterile aqueous solutions containing a predetermined concentration of the active compound; the solution is preferably isotonic with the blood of the intended recipient. Although such solutions are preferably administered intravenously, they may also be administered by subcutaneous or intramuscular injection.

Formulations suitable for rectal administration are preferably provided as unit-dose suppositories comprising the active ingredient and one or more solid carriers forming the suppository base, for example, cocoa butter.

Formulations suitable for topical or intranasal application include ointments, creams, lotions, pastes, gels, sprays, aerosols and oils. Suitable carriers for such formulations include petroleum jelly, lanolin, polyethylene glycols, alcohols, and combinations thereof.

Formulations of compounds of the invention may, for example, be composed so as to improve the exposure profile of the compound of the invention.

Compositions suitable for transdermal administration include ointments, gels and patches.

Preferably the composition is in unit dose form such as a tablet, capsule or ampoule.

The formulations of the invention may be prepared by any suitable method, typically by uniformly and intimately admixing the active compound(s) with liquids or finely divided solid carriers, or both, in the required proportions and then, if necessary, shaping the resulting mixture into the desired shape.

For example, a tablet may be prepared by compressing an intimate mixture comprising a powder or granules of the active ingredient and one or more optional ingredients, such as a binder, lubricant, inert diluent, or surface active dispersing agent, or by moulding an intimate mixture of powdered active ingredient and inert liquid diluent.

Aqueous solutions for parenteral administration are typically prepared by dissolving the active compound in sufficient water to give the desired concentration and then rendering the resulting solution sterile and isotonic.

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It will be appreciated that the precise dose administered will depend on the age and condition of the patient and the frequency and route of administration and will be at the ultimate discretion of the attendant physician. The compound may be administered in single or divided doses and may be administered one or more times, for example 1 to 4 times per day.

A proposed dose of the active ingredient for use according to the invention for oral, sublingual, parenteral, buccal, rectal, intranasal or topical administration to a human (of approximately 70 kg bodyweight) for the treatment of neurological and neuropsychiatric disorders mediated by a GlyT1 inhibitor, including schizophrenia, may be about 1 to about 1000 mg, preferably about 5 to about 500 mg, more preferably about 10 to about 100 mg of the active ingredient per unit dose which could be administered, for example, 1 to 4 times per day.

Compounds of the invention may be used as PET ligands (for example labelled with carbon-11 or fluorine-18) or as SPECT ligands (for example labelled with iodine-123 or meta stable technetium-99) for *in vivo* visualisation and quantification of the GlyT1 transporter. For example, they may be used in PET or SPECT imaging of the brain. In the context of this patent, PET shall mean: positron emission tomography and SPECT (= SPET) shall mean: single photon emission (computed) tomography.

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

The invention is further illustrated by the following non-limiting examples.

Abbreviations:

THF	tetrahydrofuran
DCM	dichloromethane
DMF	dimethylformamide
HATU	O-(7-azabenzotriazol-1-yl) - N,N,N',N'-tetramethyluroniumhexafluorophosphate
EDC	N-(3-(dimethylamino)propyl)-N-ethylcarbodiimide hydrochloride
HOAt	3H-(1,2,3)-triazolo(4,5-b)pyridine-3-ol

NMP N-methylpyrrolidinone
DIPEA N,N-diisopropylethylamine
HOBt 1-hydroxybenzotriazole hydrate

5 **Analytical LC/MS chromatography conditions:**

Method A

Column: Waters Atlantis 50mm x 4.6mm, 3um particle size

Mobile phase: A: 0.05% Formic acid + Water
 B: Acetonitrile +0.05% Formic acid

10 Gradient: 5-min runtime: 3%B to 97%B over 4min

Flow rate: 3 ml/min

UV wavelength range: 220 -330 nm

Temperature: 30°C

15 Method B *

Column: Waters Atlantis 20mm x 4.6mm, 3um particle size

Mobile phase: A: 0.1% Formic acid + Water
 B: Acetonitrile +0.1% Formic acid

Gradient: 5.5-min runtime: 3%B to 97%B over 5.3min

20 Flow rate: 1 ml/min

UV wavelength range: 210 -350 nm

Temperature: Ambient

Mass Directed Auto-Purification System chromatography conditions:

25 Column: Waters Atlantis 19mm x 100mm or 30mm X 100mm, 5um
 particle size

Mobile phase: A: 0.1% Formic acid + Water
 B: Acetonitrile +0.1% Formic acid

30 Gradient: 13.5 min runtime with 10min gradient dependant on
 analytical retention time

Flow rate: 20 or 40 ml/min

General:

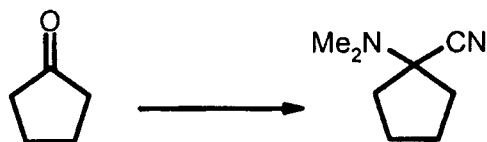
35 Throughout the examples section, the following terminology is adopted with regard to
chiral compounds: when a mixture of two enantiomers has been prepared, the compound
is described as (±). When a single enantiomer (that is to say mixture chirally enriched in

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one of the enantiomers) has been prepared, it is referred to as "chiral". The absolute stereochemistry has not been ascertained at the time of filing. Individual enantiomers of some materials prepared are identified by virtue of optical rotations and such materials are identified as the (+) or (-) enantiomers. Where optical rotation information is not yet available, individual enantiomers of the products are individually identifiable by virtue of the chiral HPLC characteristics of the amine intermediate.

Where reactions are described as having been carried out in a similar manner to earlier, more completely described reactions, the general reaction conditions used were essentially the same. Work up conditions used were of the types standard in the art, but may have been adapted from one reaction to another.

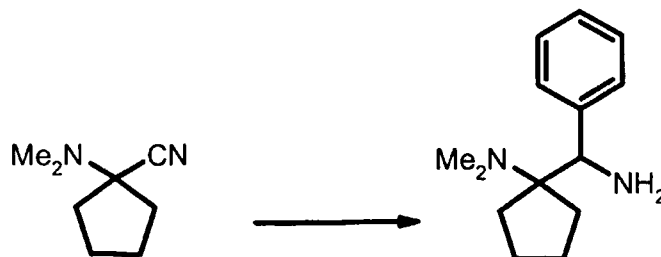
Description 1: 1-(Dimethylamino)cyclopentanecarbonitrile



To a suspension of dimethylamine hydrochloride (8.15g; 0.1mol) in cyclopentanone (8.4g; 0.1mol) cooled (ice bath) was added dropwise a solution of potassium cyanide (6.5g; 0.1mol) in water (50ml) over 10min. After vigorous stirring at room temperature for 18h, the crude reaction mixture was extracted three times with diethyl ether (3 x 200ml) and the combined extracts washed twice with water (2 x 50ml), dried (Na_2SO_4), and evaporated to afford the title product as a pale yellow oil (12.5g) which was used without further purification. ^1H NMR (CDCl_3) δ : 1.7 – 2.0 (6H, m), 2.15 – 2.3 (2H, m), 3.3 (6H, s). Mass Spectrum (Electrospray LC/MS): Found 112 ($\text{MH}^+ - \text{HCN}$). $\text{C}_8\text{H}_{14}\text{N}_2$ requires 138.

Alternative method:

To a stirred, ice cooled mixture of dimethylamine hydrochloride (26.32g; 0.323mol) and cyclopentanone (27.15g; 0.323mol) was added dropwise a solution of potassium cyanide (21.02g; 0.323mol) in water (170ml) over 10min. The mixture was stirred at room temperature overnight. Then, the mixture was extracted into diethylether (2 x 200ml) and the combined organics were washed with brine (200ml), dried (Na_2SO_4), and evaporated *in vacuo* to afford the title product as a colourless liquid (43g, 96.5%)

Description 2: (±){1-[Amino(phenyl)methyl]cyclopentyl}dimethylamine

To a solution of 1-(dimethylamino)cyclopentanecarbonitrile D1 (4g; 28.9mmol) in THF
5 (30ml) at -70°C under argon was added dropwise a solution of phenyllithium in
dibutylether (17.7ml of a 1.8M solution; 32mmol). The reaction mixture was allowed to
warm to room temperature over 3h., re-cooled to 0°C and methanol added (30ml) followed
by careful addition of sodium borohydride (3.3g; 87mmol). After stirring at room
temperature for 18h, the reaction mixture was cooled to 0°C and saturated aqueous
10 sodium bicarbonate added. The organic phase was evaporated and the resulting slurry
extracted three times with DCM (3 x 150ml). The combined extracts were dried (Na₂SO₄),
and evaporated to afford the crude product as a yellow oil (6.8g). Half of the crude
product was chromatographed on silica gel eluting with DCM-methanol (9/1) and DCM-2M
ammonia in methanol mixtures (95/5 to 9/1 to 8/2) to afford the title product as a
15 colourless oil (2.3g). This oil was dissolved in diethyl ether (20ml) and hydrogen chloride
in diethylether was added at 0°C. After 20min, the suspension was filtered to give the
dihydrochloride salt (2.8g) of the title product as a white solid. ¹H NMR (DMSO) δ: 1.25
(2H, bs), 1.36 (2H, bs), 1.66 – 2.13 (4H, m), 2.64 (3H, s), 2.79 (3H, s), 4.92 (1H, bs), 7.32
(3H, m), 7.54 (2H, m), 8.95 (3H, bs), 10.82 (1H, bs).

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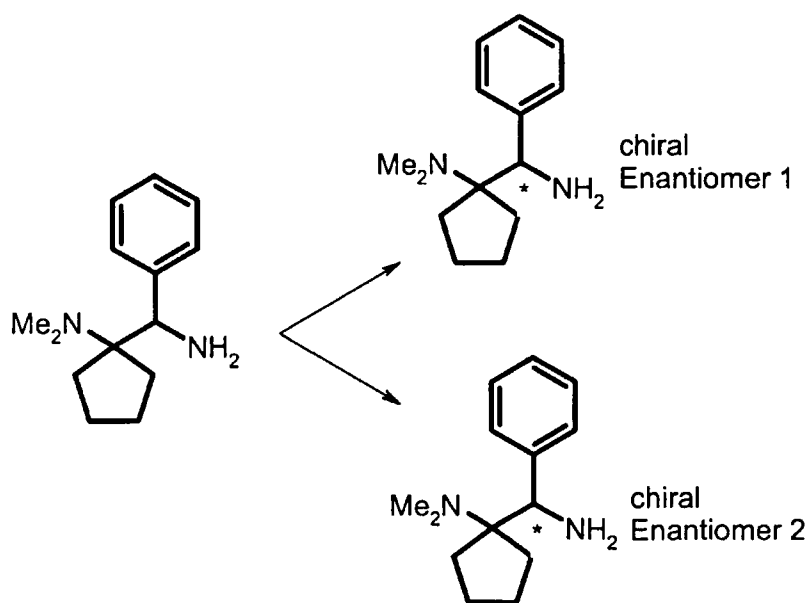
Alternative method:

To a solution of 1-(dimethylamino)cyclopentanecarbonitrile D1 (43g; 311mmol) in THF
(1L) at -70°C under argon was added dropwise a solution of phenyllithium in dibutylether
(346ml of a 1.8M solution; 622mmol) over 10 minutes. The reaction mixture was stirred at
25 -70°C for 2h, then allowed to warm to room temperature and it was stirred overnight. The
reaction mixture was cooled in ice and saturated aqueous sodium bicarbonate solution
was added. The mixture was stirred for 30 minutes, separated and the aqueous layer
extracted with diethyl ether. The combined organics were dried (Na₂SO₄) and
concentrated under reduced pressure to give an oil.

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The oil was dissolved in methanol (1.2L) and cooled in ice. Sodium borohydride (20g) was added in 4 portions over 5 minutes and the mixture was stirred for half an hour with ice cooling. The cooling was then removed and stirring was continued at room temperature for one and a half hours. The reaction mixture was then ice cooled and water was added. The resultant mixture was evaporated *in vacuo* and fractioned between 2N HCl and ethyl acetate. The organics were extracted with 2N HCl. The combined acid extracts were washed with ethyl acetate, basified with NaOH and extracted into DCM. The combined DCM extracts were dried (Na₂SO₄), and evaporated *in vacuo* to afford the product as a pale green liquid (64.66g, 95.4%).

Description 3: {1-[Amino(phenyl)methyl]cyclopentyl}dimethylamine Enantiomer 1 and Enantiomer 2



Method 1.

Racemic {1-[amino(phenyl)methyl]cyclopentyl}dimethylamine D2 (0.6g; 2.75mmol) was separated by semi-preparative chiral HPLC using the conditions described below to afford the title products, enantiomer 1, (0.27g); Chiral HPLC: 98% ee; ¹H NMR (CDCl₃) δ: 0.42 (1H, m), 1.32 (3H, m), 1.49 (1H, m), 1.63 (1H, m), 1.76 (1H, m), 1.95 (3H, m), 2.29 (6H, s), 4.39 (1H, s), 7.28 (3H, m), 7.50 (2H, d); Mass spectrum (Electrospray LC/MS): Found 219 (MH⁺). C₁₄H₂₂N₂ requires 218; and enantiomer 2 (0.28g); Chiral HPLC: 98% ee; ¹H

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NMR (CDCl₃) δ : 0.42 (1H, m), 1.32 (3H, m), 1.49 (1H, m), 1.63 (1H, m), 1.76 (1H, m), 1.95 (3H, m), 2.29 (6H, s), 4.39 (1H, s), 7.28 (3H, m), 7.50 (2H, d); Mass spectrum (Electrospray LC/MS): Found 219 (MH⁺). C₁₄H₂₂N₂ requires 218.

5 Semi-preparative HPLC conditions:

Column: Chiralpak AD-H 5 μ m, 250 x 21mm
Mobile phase: A: n-Hexane; B: Ethanol + 0.1% isopropylamine
Gradient: isocratic 5%B
Flow rate: 7ml/min
10 UV wavelength range: 225nm
Elution time: 30min

Analytical chromatography conditions:

Column: chiralpak AD-H 5 μ m, 250 x 4.6 mm
15 Mobile phase: A: n-Hexane; B: Ethanol + 0.1% isopropyl amine
Gradient: isocratic 5% B
Flow rate: 1 ml/min
UV wavelength range: 200-400 nm
Analysis time: 10 min
20 Ret. Time: 5.9min (Enantiomer 1); 7.6min (Enantiomer 2)

Method 2.

Salt formation:

To a solution of racemic {1-[amino(phenyl)methyl]cyclopentyl}dimethylamine D2 (16.9g; 25 77.5mmol) in isopropanol (170ml) at 50 °C, was added dropwise a solution of (R)-methoxy phenylacetic acid (12.84g; 77.5mmol) in isopropanol (75ml). After 20 min the mixture was cooled to room temperature and left stirring for a further 4h. The precipitated solid was collected by filtration (13.42g).

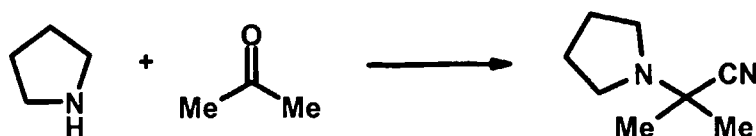
30 Regeneration of chiral free base:

The solid was then treated with 1M NaOH (50ml) and DCM (167ml). The phases were separated and the aqueous phase washed with DCM (4x167ml). The combined organic phases were washed with 1M NaOH (2x35ml), then brine (100ml), dried (Na₂SO₄), and concentrated to yield the title compound, enantiomer 2, as a colourless oil (7.6g). Chiral 35 HPLC: >96% ee; ¹H NMR (CDCl₃) δ : 0.42 (1H, m), 1.32 (3H, m), 1.49 (1H, m), 1.63 (1H,

5A

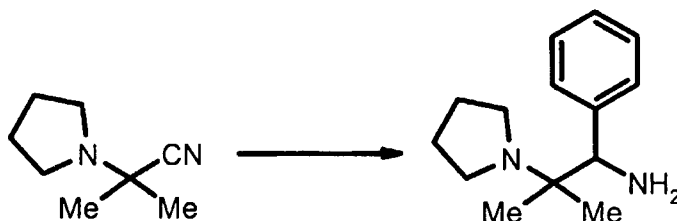
m), 1.76 (1H, m), 1.95 (3H, m), 2.29 (6H, s), 4.39 (1H, s), 7.28 (3H, m), 7.50 (2H, d); Mass spectrum (Electrospray LC/MS): Found 219 (MH⁺). C₁₄H₂₂N₂ requires 218.

Description 4: 2-Methyl-2-(1-pyrrolidinyl)propanenitrile



5 To a stirred, ice-cooled mixture of pyrrolidine (8.35ml; 0.1mol) and acetone (7.34ml; 0.1mol) was added a solution of potassium cyanide (6.51g; 0.1mol) in water (50ml) dropwise over 10min. After stirring at room temperature overnight, the crude reaction mixture was extracted with diethyl ether (2 x 250ml) and the combined extracts washed
10 with saturated brine (150ml), dried (MgSO₄), and evaporated under reduced pressure to afford the title product as a pale green liquid (10.7g; 78%) which was used without further purification. ¹H NMR (CDCl₃) δ: 1.51 (6H, s), 1.80 – 1.90 (4H, m), 2.70 – 2.80 (4H, m).

Description 5: (±)[2-Methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]amine



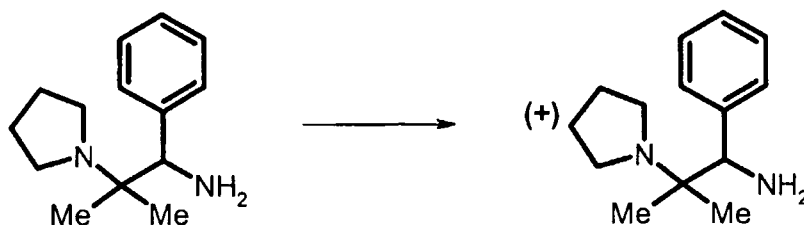
15 To a solution of 2-methyl-2-(1-pyrrolidinyl)propanenitrile D4 (10.7g; 77.54mmol) in THF (400ml) at -70°C under argon was added over 10 minutes a solution of phenyllithium in dibutylether (86.3ml of a 1.8M solution; 155mmol). The reaction mixture was stirred at -70°C for 2 hours then allowed to warm to room temperature and stirred overnight. The
20 reaction mixture was cooled in ice as saturated aqueous sodium hydrogen carbonate (400ml) was added. After stirring for a further 30 minutes the layers were separated, and the aqueous layer extracted with ether (200ml). Combined organics were dried (MgSO₄) and evaporated. The residual amber oil was dissolved in methanol (400ml), cooled in ice and sodium borohydride (5.2g; 137mmol) added in four portions over 5 minutes. The
25 reaction mixture was stirred with ice cooling for 30 minutes, the ice removed and stirred at room temperature for 1.5 hours. The mixture was cooled in ice as water (50ml) was added prior to concentration *in vacuo* to approx 70ml. The mixture was partitioned between 2N HCl (100ml) and ethyl acetate (400ml) and the organics extracted with 2N HCl (2 x 100ml). Combined acidic aqueous layers were washed with ethyl acetate (200ml),

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basified with 50% NaOH and extracted with DCM (3 x 150ml). Combined DCM organic extracts were dried (Na_2SO_4) and evaporated *in vacuo* to afford the title compound as a colourless solid (15g; 88%) ^1H NMR (CDCl_3), δ : 0.75 (3H, s), 0.99 (3H, s), 1.70 – 1.76 (4H, m), 1.80 (2H, bs), 2.65 – 2.70 (4H, m), 4.08 (1H, s), 7.20 – 7.42 (5H, m).

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Description 6: (+)- [2-Methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]amine



A solution of (R)-(-)- α -methoxyphenylacetic acid (8.08g; 49mmol) in 2-propanol (50ml) was added dropwise over 10 minutes to a stirred solution of [2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]amine D5 (10.64g; 49mmol) in 2-propanol (107ml) at 57°C. After complete addition heating was continued for a further 10 minutes. Heating was then removed and stirring continued for one and three quarter hours. Further 2-propanol (100ml) was added and the mixture filtered and the solid washed with 2-propanol (3 x 50ml), ether (100ml) and dried. The solid was recrystallised from boiling 2-propanol (1L) and the crystals filtered, washed with cold 2-propanol, ether and dried. A sample was partitioned between saturated aqueous sodium hydrogen carbonate and DCM and the organic layer passed through a phase separation cartridge and blown down with argon to afford the title compound as a colourless solid. ^1H NMR (CDCl_3), δ : 0.75 (3H, s), 0.99 (3H, s), 1.70 – 1.79 (4H, m), 1.85 (2H, bs), 2.65 – 2.70 (4H, m), 4.08 (1H, s), 7.20 – 7.42 (5H, m). Chiral HPLC: 97.5% ee, corresponding to the slower running enantiomer 2. $[\alpha]_D^{25} = +28.5^\circ$ ($c=1$, CHCl_3 at 27.5°C). The remaining free base was liberated in a similar manner (3.55g, 66%).

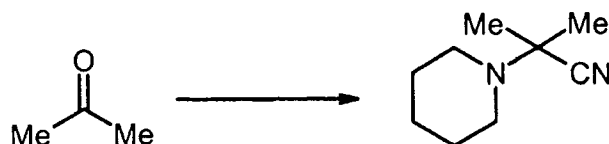
Conditions for resolution of racemate D5 were as follows:-

Analytical chromatography conditions:

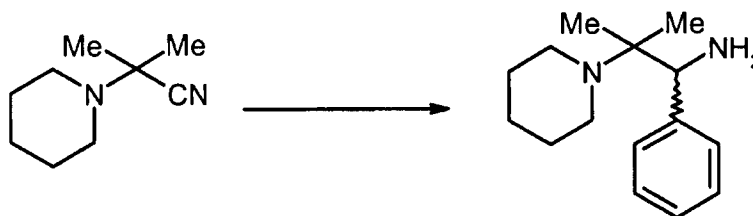
25	Column:	chiralcel OD-H 5 μm , 250 x 4.6 mm i.d. 10 micron particle size
	Mobile phase:	Heptane : Ethanol (90:10)
	Gradient:	isocratic
	Flow rate:	1 ml/min
30	UV wavelength range:	254 nm
	Analysis time:	10 min

56

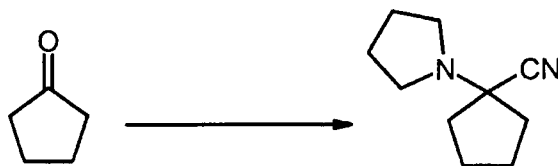
Ret. Time: 5.4min (Enantiomer 1); 7.0min (Enantiomer 2)

Description 7 : 2-Methyl-2-(1-piperidiny)propanenitrile

The title compound (2.33g, 77%) was prepared from piperidine hydrochloride (2.43g, 20mmol), acetone (1.16g, 20mmol) and potassium cyanide (1.30g, 20mmol) in water (10ml) in a similar manner to that described in D1. ¹H NMR (CDCl₃) δ: 1.46 (2H, m), 1.50 (6H, s), 1.63 (4H, m), 2.59 (4H, m).

Description 8 : (±)2-Methyl-1-phenyl-2-(1-piperidiny)-1-propanamine

The title compound (1.16g, 56%) was prepared from 2-methyl-2-(1-piperidiny)propanenitrile D7 (1.30g, 8.6mmol), and phenyllithium in dibutylether (5.2ml of a 1.8M solution; 9.4mmol) in THF (15ml), followed by reaction with sodium borohydride (0.975g, 25.7mmol) in methanol (20ml) in a similar manner to that described in D2. ¹H NMR (CDCl₃) δ: 0.76 (3H, s), 0.91 (3H, s), 1.44 (2H, m), 1.54 - 1.65 (4H, m), 1.95 (2H, m), 2.57 (4H, m), 4.19 (1H, s), 7.20 - 7.31 (3H, m), 7.40 (2H, m).

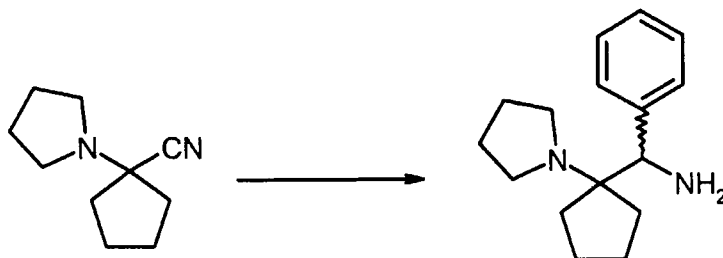
Description 9 : 1-(1-Pyrrolidiny)cyclopentanecarbonitrile

The title compound (2.50g, 76%) was prepared from pyrrolidine (1.42g, 20mmol), cyclopentanone (1.68g, 20mmol) and potassium cyanide (1.30g, 20mmol) in water (10ml)

57

in a similar manner to that described in D4. ^1H NMR (CDCl_3) δ : 1.80 – 1.90 (10H, m), 2.15 (2H, m), 2.71 (4H, m).

Description 10 : ($\pm$)-1-Phenyl-1-[1-(1-pyrrolidinyl)cyclopentyl]methanamine

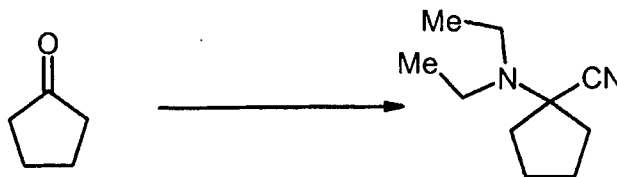


5

The title compound (0.55g, 56%) was prepared from 1-(1-pyrrolidinyl)cyclopentane carbonitrile D9 (0.66g, 4mmol), and phenyllithium in dibutylether (2.4ml of a 1.8M solution; 4.4mmol) in THF (4ml), followed by reaction with sodium borohydride (0.456g, 12mmol) in methanol (4ml) in a similar manner to that described in D2. ^1H NMR (CDCl_3) δ : 0.41 (1H, m), 1.17 (1H, m), 1.35 (2H, m), 1.60 (2H, m), 1.73 (5H, m), 1.84 – 2.02 (3H, m), 2.64 – 2.74 (4H, m), 4.27 (1H, s), 7.21 – 7.31 (3H, m), 7.48 (2H, m).

10

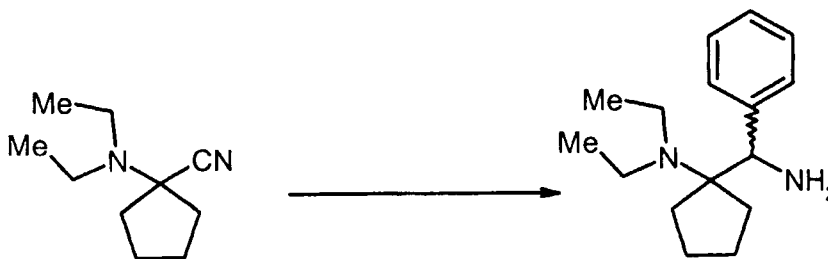
Description 11 : 1-(Diethylamino)cyclopentanecarbonitrile



The title compound (2.06g, 62%) was prepared from diethylamine hydrochloride (2.14g, 20mmol), cyclopentanone (1.68g, 20mmol) and potassium cyanide (1.30g, 20mmol) in water (10ml) in a similar manner to that described in D1. ^1H NMR (CDCl_3) δ : 1.11 (6H, t, J = 7Hz), 1.78 – 1.88 (6H, m), 2.22 (2H, m), 2.71 (4H, q, J = 7Hz).

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Description 12 : ($\pm$)-1-[Amino(phenyl)methyl]-*N,N*-diethylcyclopentanamine



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The title compound (0.45g, 47%) was prepared from 1-(diethylamino)cyclopentane carbonitrile D11 (0.65g, 3.9mmol), and phenyllithium in dibutylether (2.4ml of a 1.8M solution; 4.3mmol) in THF (4ml), followed by reaction with sodium borohydride (0.445g, 11.7mmol) in methanol (4ml) in a similar manner to that described in D2. ¹H NMR (CDCl₃)

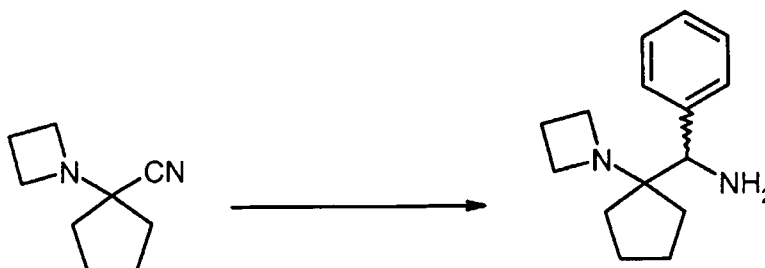
5 δ: 0.42 (1H, m), 1.10 (6H, m), 1.35 (3H, m), 1.55 (1H, m), 1.66 (2H, m), 1.80 – 2.08 (3H, m), 2.53 – 2.70 (4H, m), 4.22 (1H, s), 7.20 – 7.31 (3H, m), 7.47 (2H, m).

Description 13 : 1-(1-Azetidiny)cyclopentanecarbonitrile



- 10 The title compound (1.29g, 43%) was prepared from azetidine hydrochloride (1.85g, 20mmol), cyclopentanone (1.68g, 20mmol) and potassium cyanide (1.30g, 20mmol) in water (10ml) in a similar manner to that described in D1. ¹H NMR (CDCl₃) δ: 1.70 – 1.82 (6H, m), 1.86 (2H, m), 2.07 (2H, quin, J = 7Hz), 3.32 (4H, t, J = 7Hz).

15 **Description 14 : (±)1-[1-(1-Azetidiny)cyclopentyl]-1-phenylmethanamine**



- The title compound (0.45g, 47%) was prepared from 1-(1-azetidiny)cyclopentanecarbonitrile D13 (0.60g, 4.0mmol), and phenyllithium in ethers (2.6ml of a 1.7M solution; 4.4mmol) in THF (5ml), followed by reaction with sodium borohydride (0.456g, 12mmol) in methanol (5ml) in a similar manner to that described in D2. ¹H NMR (CDCl₃) δ: 0.67 (1H, m), 1.06 (1H, m), 1.32 (4H, m), 1.48 (2H, m), 1.91 – 2.03 (4H, m), 3.24 (4H, m), 3.83 (1H, s), 7.20 – 7.32 (3H, m), 7.44 (2H, m).
- 20

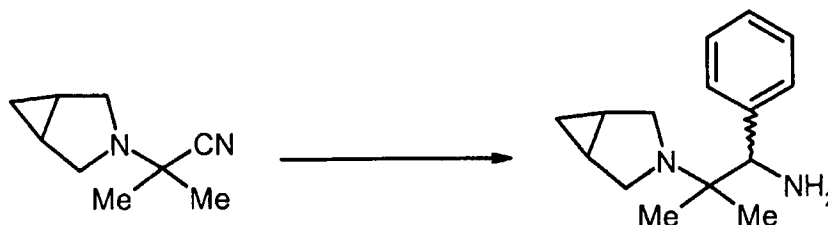
Description 15 : 2-(3-Azabicyclo[3.1.0]hex-3-yl)-2-methylpropanenitrile



59

The title compound (583mg, 84%) was prepared from 3-azabicyclo[3.1.0]hexane hydrochloride (550mg, 4.6mmol) [Pestic. Chem: Hum. Welfar Environ., Proc, Int, Congr. Pestic. Che., 5th, 1982, 1,159-64, 1983], acetone (267mg, 4.6mmol) and potassium cyanide (300mg, 4.6mmol) in water (2.5ml) in a similar manner to that described in D1. ¹H NMR (CDCl₃) δ: 0.40 (1H, m), 0.58 (1H, m), 1.43 (8H, m), 2.64 (2H, m), 3.10 (2H, d, J = 8Hz).

Description 16 : (±)2-(3-Azabicyclo[3.1.0]hex-3-yl)-2-methyl-1-phenyl-1-propanamine

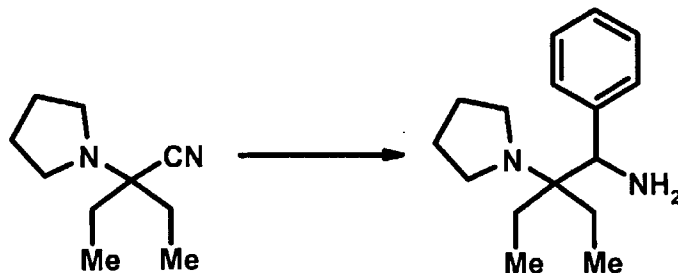


The title compound (393mg, 44%) was prepared from 2-(3-azabicyclo[3.1.0]hex-3-yl)-2-methylpropanenitrile D15 (583mg, 3.9mmol), and phenyllithium in dibutylether (2.15ml of a 2.0M solution; 4.3mmol) in THF (7ml), followed by reaction with sodium borohydride (445mg, 11.7mmol) in methanol (10ml) in a similar manner to that described in D2. ¹H NMR (CDCl₃) δ: 0.38 (1H, m), 0.66 (1H, m), 0.74 (3H, s), 0.93 (3H, s), 1.30 – 1.40 (2H, m), 1.74 (2H, bs), 2.67 (2H, m), 2.91 (2H, t, J = 8Hz), 4.03 (1H, s), 7.20 – 7.30 (3H, m), 7.38 (2H, m).

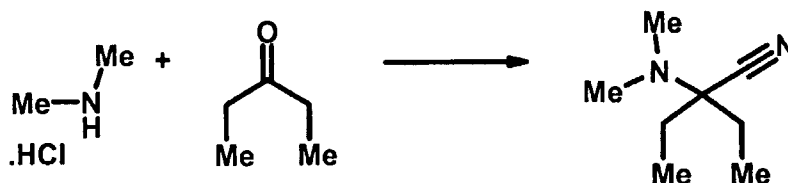
Description 17: 2-Ethyl-2-(1-pyrrolidinyl)butanenitrile



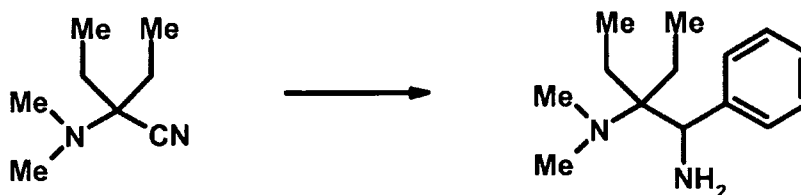
The title compound (8.8g, 100%) was prepared from pyrrolidine (8.96ml, 0.107mol), 3-pentanone (8.61g, 0.1mol) and potassium cyanide (6.51g, 0.1mol) in water (50ml) in a similar manner to that described in D4. ¹H NMR (CDCl₃) δ: 0.95 (6H, t, J = 7.6Hz), 1.67 – 1.90 (8H, m), 2.67 – 2.72 (4H, m).

Description 18: (±)[2-Ethyl-1-phenyl-2-(1-pyrrolidiny)butyl]amine

The title compound (11.5g, 88%) was prepared from 2-ethyl-2-(1-pyrrolidiny)butanenitrile D17 (8.8g, 0.053mol) and phenyllithium in dibutylether (59ml of a 1.8M solution; 0.106mol) in THF (350ml), followed by reaction with sodium borohydride (3.9g, 0.103mol) in methanol (300ml) in a similar manner to that described in D5. ¹H NMR (CDCl₃) δ: 0.75 (3H, t), 0.95 (3H, t, J = 7.6Hz), 1.50 – 1.90 (10H, m), 2.70 – 2.95 (4H, m), 4.01 (1H, s), 7.19 – 7.41 (5H, m).

10 Description 19: 2-(Dimethylamino)-2-ethylbutanenitrile

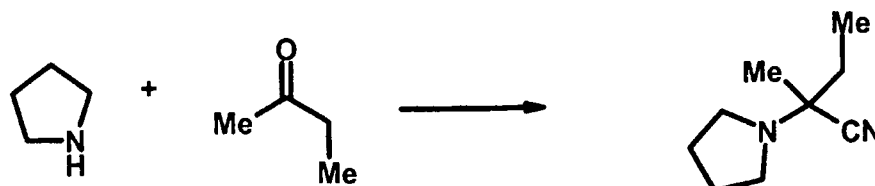
The title compound (8.05g, 57.5%) was prepared from dimethylamine hydrochloride (8.154g, 0.1mol), 3-pentanone (8.61g, 0.1mol) and potassium cyanide (6.51g, 0.1mol) in water (50ml) in a similar manner to that described in D1. ¹H NMR (CDCl₃) δ: 0.96 (6H, t, J = 7.6Hz), 1.67 – 1.90 (4H, m), 2.33 (6H, s).

Description 20: (±){1-[Amino(phenyl)methyl]-1-ethylpropyl}dimethylamine

The title compound (11.12g, 88%) was prepared from 2-(dimethylamino)-2-ethylbutanenitrile D19 (8.05g, 0.0575mol) and phenyllithium in dibutylether (64ml of a 1.8M solution; 0.115mol) in THF (350ml), followed by reaction with sodium borohydride (3.9g, 0.103mol) in methanol (300ml) in a similar manner to that described in D5. ¹H NMR

(CDCl₃) δ : 0.72 (3H, t, J = 7.6Hz), 0.97 (3H, t, J = 7.6Hz), 1.40 – 1.68 (4H, m), 1.70 (2H, br. m), 2.43 (6H, s), 4.09 (1H, s), 7.19 – 7.43 (5H, m).

Description 21: 2-Methyl-2-(1-pyrrolidiny)butanenitrile



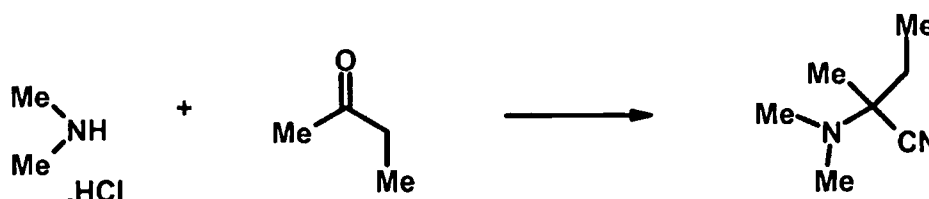
The title compound (9.6g, 63%) was prepared from pyrrolidine (8.35ml, 0.1mol), 2-butanone (8.96g, 0.1mol) and potassium cyanide (6.51g, 0.1mol) in water (50ml) in a similar manner to that described in D4. ¹H NMR (CDCl₃) δ : 1.06 (3H, t, J = 7.2Hz), 1.45 (3H, s), 1.66 – 1.93 (6H, m), 2.70 – 2.75 (4H, m).

Description 22: (±)[2-Methyl-1-phenyl-2-(1-pyrrolidiny)butyl]amine



The title compound (13.4g, 94%) was prepared from 2-methyl-2-(1-pyrrolidiny)butanenitrile D21 (9.6g, 0.063mol) and phenyllithium in dibutylether (63ml of a 2M solution; 0.126mol) in THF (200ml), followed by reaction with sodium borohydride (3.5g, 0.092mol) in methanol (200ml) in a similar manner to that described in D5, except that after addition of the sodium borohydride stirring was continued with ice cooling for 0.5 hours then at room temperature for 66 hours. Mass spectrum (Electrospray LC/MS), ES⁺: Found 233 (MH⁺). C₁₅H₂₄N₂ requires 232. Ret. times 0.78 and 1.06 min.

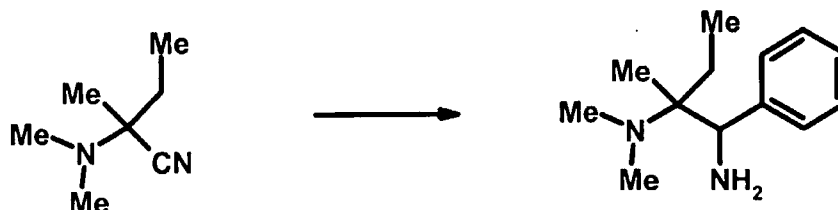
Description 23: 2-(Dimethylamino)-2-methylbutanenitrile



The title compound (9.95g, 78%) was prepared from dimethylamine hydrochloride (8.15g, 0.1mol), 2-butanone (8.96ml, 0.1mol) and potassium cyanide (6.51g, 0.1mol) in water (50ml) in a similar manner to that described in D1. ¹H NMR (CDCl₃) δ: 1.00 (3H, t, J = 7.2Hz), 1.43 (3H, s), 1.75 – 1.87 (2H, m), 2.33 (6H, s).

5

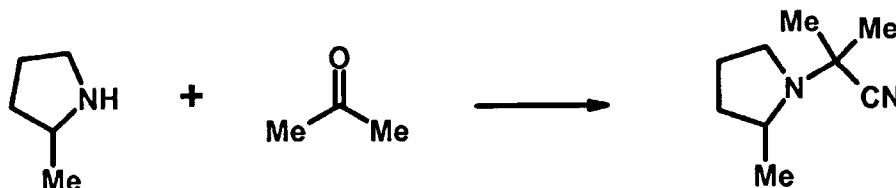
Description 24: (±){1-[Amino(phenyl)methyl]-1-methylpropyl}dimethylamine



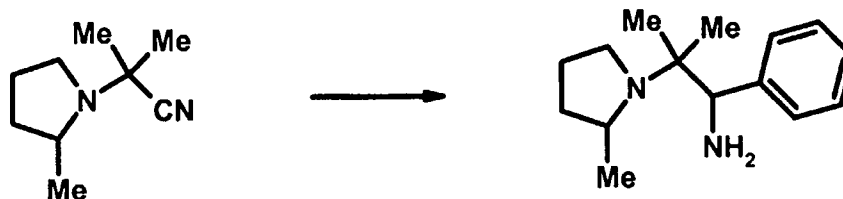
The title compound (15g, 93%) was prepared from 2-(dimethylamino)-2-methylbutanenitrile D23 (9.9g, 0.078mol) and phenyllithium in dibutylether (87.3ml of a 1.8M solution; 0.157mol) in THF (400ml), followed by reaction with sodium borohydride (5.25g, 0.138mol) in methanol (450ml) in a similar manner to that described in D5. Mass spectrum (Electrospray LC/MS), ES⁺: Found 207 (MH⁺). C₁₃H₂₂N₂ requires 206. Ret. times 0.83 and 1.10 min.

15

Description 25 : 2-Methyl-2-(2-methyl-1-pyrrolidinyl)propanenitrile

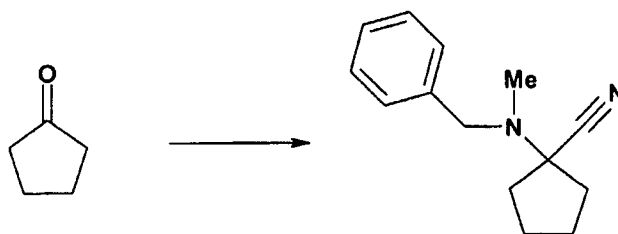


To a stirred, ice-cooled mixture of 2-(RS)-methylpyrrolidine (4.25g; 0.05mol) and acetone (3.67ml; 0.05mol) was added a solution of potassium cyanide (3.25g; 0.05mol) in water (25ml) dropwise over 10min. After stirring at room temperature overnight, the crude reaction mixture was extracted with diethyl ether (2 x 200ml) and the combined extracts washed with brine (200ml), dried (Na₂SO₄) and evaporated under reduced pressure to afford a pale yellow oil. This was dissolved in DCM and PS-Isocyanate (4.5g of resin loading 1.53mmol/g) added. The mixture was stirred for 3 hours, filtered and the filtrate evaporated to afford the title compound as a colourless semi-solid (2.82g; 37.5%). ¹H NMR (CDCl₃) δ(inter alia): 1.10 (3H, d), 1.45 (3H, s), 1.55 (3H, s), 1.75 – 2.00 (4H, m) 2.65 (1H, m) and 3.05 – 3.20 (2H, m).

Description 26: ($\pm$)[2-Methyl-2-(2-methyl-1-pyrrolidinyl)-1-phenylpropyl]amine

- 5 To a solution of 2-methyl-2-(2-methyl-1-pyrrolidinyl)propanenitrile D25 (2.82g; 18.56 mmol) in THF (100ml) at -70°C under argon was added over 15 minutes a solution of phenyllithium in dibutylether (20.6ml of a 1.8M solution; 37.11mmol). The reaction mixture was stirred at -70°C for 2 hours then allowed to warm to room temperature and stirred overnight. Saturated aqueous sodium hydrogen carbonate (100ml) was added and
- 10 stirring continued for a further 10 minutes. The mixture was extracted with diethyl ether (2 x 150ml). Combined organics were dried (Na_2SO_4) and evaporated *in vacuo*. The residual yellow oil was dissolved in methanol (100ml) and sodium borohydride (2.12g; 0.056mol) added portionwise over 5 minutes. The reaction mixture was stirred at room temperature for 4 hours, further sodium borohydride (1g; 0.026mol) added and the mixture heated at
- 15 60°C for 1.5 hours. The mixture was cooled and excess sodium borohydride decomposed by dropwise addition of water. The reaction mixture was evaporated *in vacuo* and the residue partitioned between saturated sodium hydrogen carbonate (150ml) and DCM (150ml). Solid potassium carbonate was added and the aqueous layer extracted with DCM (150ml) Combined organic extracts were dried (Na_2SO_4) and evaporated to give a
- 20 green oil. This was divided into 8 portions and each portion passed down a 10g SCX column. After washing each column with DCM, 50%DCM in methanol and methanol the product was eluted with 1M ammonia in methanol to yield the title compound as a pale yellow oil (3.46g; 80%). Mass spectrum (Electrospray LC/MS), ES^+ : Found 233 (MH^+). $\text{C}_{15}\text{H}_{24}\text{N}_2$ requires 232. Ret. times 0.96 and 1.07 min.

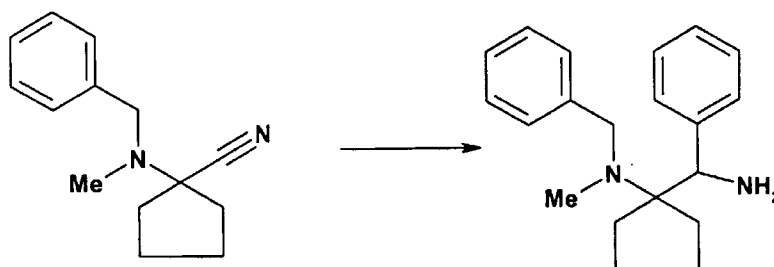
25

Description 27: 1-[Methyl(phenylmethyl)amino]cyclopentanecarbonitrile

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The title compound (15g; 84%) was prepared from N-methylbenzylamine (10.08g; 83mmol), cyclopentanone (7g; 83mmol) and potassium cyanide (5.41g; 83mmol) in water (45ml) in a similar manner to that described in D1. ¹H NMR (CDCl₃) δ: 1.90 (6H, m), 2.20 (3H, s), 2.3 (2H, m), 3.62 (2H, s), 7.25 (1H, m), 7.32 (4H, m); Mass Spectrum (Electrospray LC/MS): Found 188 (MH⁺-HCN). C₁₄H₁₈N₂ requires 214. Ret. time 1.21 min.

Description 28: (±)-{1-[Amino(phenyl)methyl]cyclopentyl}methyl (phenylmethyl) amine

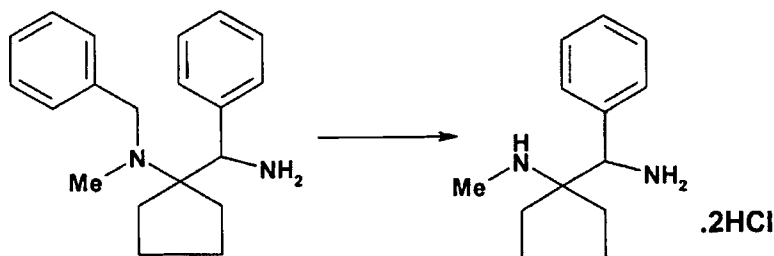


10

The title compound (3.90g; 47%) was prepared from 1-[methyl(phenylmethyl)amino]cyclopentanecarbonitrile D28 (6.0g; 28mmol) and phenyllithium in di-n-butylether (16.21ml of 1.9M solution; 30.8mmol) in THF (60ml), followed by reaction with sodium borohydride (3.2g; 84mmol) in methanol (60ml) in a similar manner to that described in D2. Mass Spectrum (Electrospray LC/MS), API⁺: Found 295 (MH⁺). C₂₀H₂₆N₂ requires 294. Ret. time 2.12 min.

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Description 29: (±)-{1-[Amino(phenyl)methyl]cyclopentyl}methylamine dihydrochloride

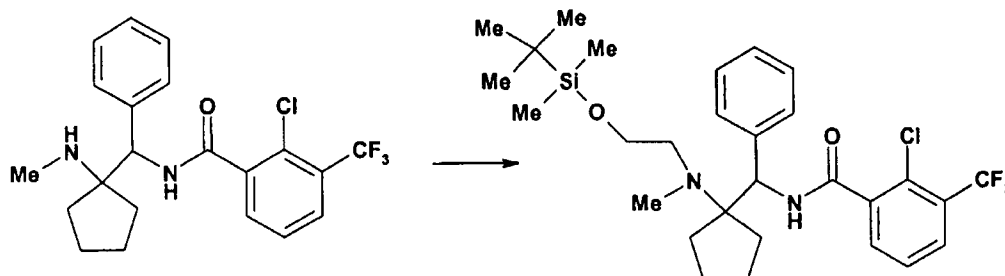


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To a solution of (±)-{1-[amino(phenyl)methyl]cyclopentyl}methyl(phenylmethyl)amine D28 (0.5g; 1.7mmol) in ethanol was added 3N HCl (1ml) and 10% palladium carbon (0.1g). The catalytic hydrogenation was carried out for 16h at room temperature and atmospheric pressure. The catalyst was filtered off through kieselguhr and the filtrate evaporated under

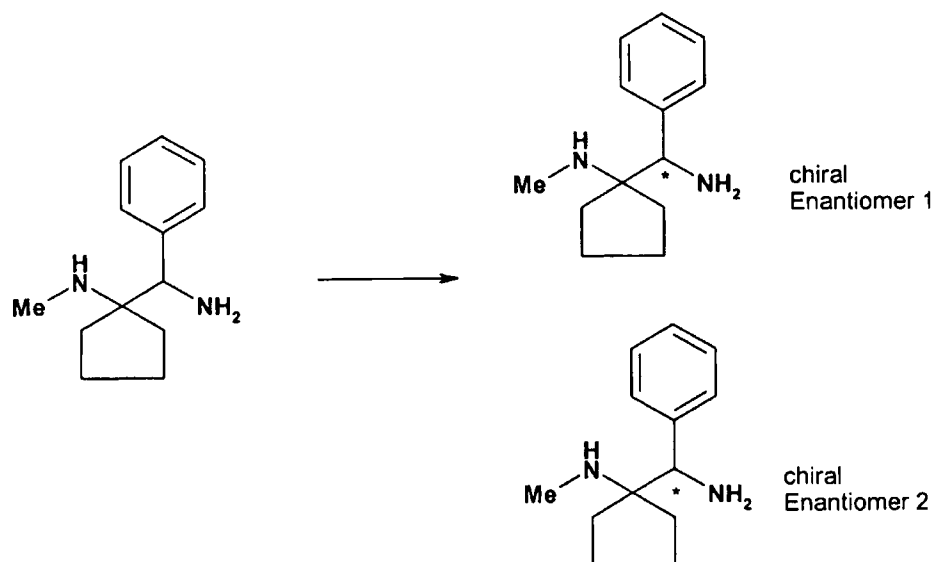
reduced pressure to give the title compound (0.32g; 69%). ^1H NMR (DMSO) δ : 1.3-2.2 (8H, m), 2.5 (3H, s), 4.6 (1H, s), 7.4 (3H, m), 7.6 (2H, m), 8.0 (2H, bs), 9.0 (1H, bs).

- Description 30:** ($\pm$)-2-Chloro-*N*-[1-[(2-[(1,1-dimethylethyl)(dimethyl)silyl]oxy)ethyl](methylamino)cyclopentyl](phenyl)methyl]-3-(trifluoromethyl)benzamide



- The title compound (0.390g, 99%) was prepared from ($\pm$)-2-chloro-*N*-[1-(methylamino)cyclopentyl](phenyl)methyl]-3-(trifluoromethyl)benzamide (0.282g; 0.686mmol), (tert-butyldimethylsilyloxy acetaldehyde (90%; 0.265g; 1.52mmol) and sodium triacetoxymethylborohydride (0.290g; 1.52mmol) in DCM (5ml) in a similar manner to that described in E30. Mass Spectrum (Electrospray LC/MS). Found 569(MH⁺). C₂₉H₄₀³⁵ClF₃N₂O₂Si requires 568. Ret. time: 3.04 min.

- Description 31:** {1-[Amino(phenyl)methyl]cyclopentyl}methylamine
Enantiomer 1 and Enantiomer 2



Racemic ($\pm$)-{1-[amino(phenyl)methyl]cyclopentyl}methylamine D29 (0.342g; 1.67mmol) was separated by preparative chiral HPLC to afford the title products enantiomer 1 (0.134g); Chiral HPLC: 99.8% ee; ^1H NMR (CDCl_3) δ : 1.30-1.78 (11H, m), 2.33 (3H, s), 4.08 (1H, s), 7.22 (1H, m), 7.28 (2H, m), 7.35 (2H, m), and enantiomer 2 (0.127g); Chiral HPLC: 99.8% ee; ^1H NMR (CDCl_3) δ : 1.30-1.78 (11H, m), 2.33 (3H, s), 4.08 (1H, s), 7.22 (1H, m), 7.28 (2H, m), 7.35 (2H, m).

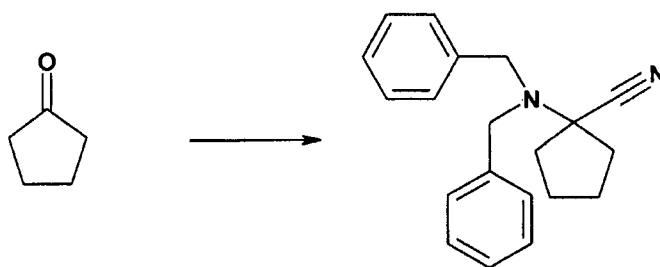
Analytical HPLC conditions:

Column: Chiral OD 10micron particle size 20mm i.d. x 250mm
10 Mobile phase: Heptane:Absolute Ethanol (90:10 v/v)
Gradient: Isocratic
UV Wavelength: 215nm
Flow rate: 1ml/min
Ret. Time: 7.5min (Enantiomer 1); 15.6min (Enantiomer 2)

15 Preparative HPLC conditions:

Column: Chiral OD 10micron particle size 20mm i.d. x 250mm
Mobile phase: Heptane:Absolute Ethanol (90:10 v/v)
Gradient: Isocratic
UV Wavelength: 215nm
20 Flow rate: 17ml/min

Description 32: 1-[Bis(phenylmethyl)amino]cyclopentanecarbonitrile



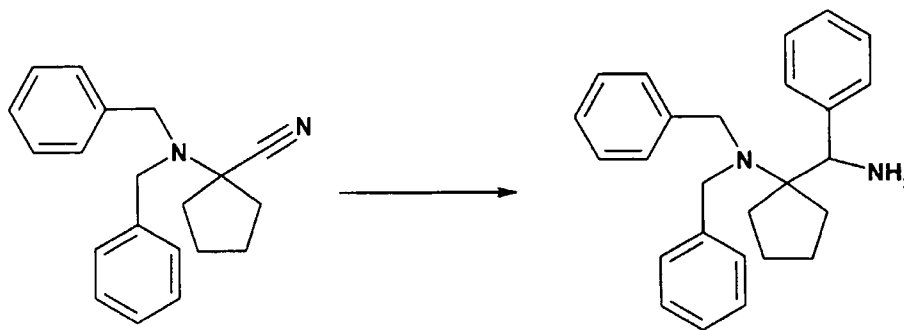
25

To an ice-cooled suspension of dibenzylamine hydrochloride (13.5g; 0.058mol) and cyclopentanone (4.86g; 0.058mol) in 25% ethanol in water (100ml) was added ethanol (60ml) and a solution of potassium cyanide (3.78g; 0.058mol) in water (35ml) dropwise over 20 minutes with stirring. After 6 days the reaction mixture was extracted with ethyl acetate, washed with sodium bicarbonate solution, dried (Na_2SO_4) and evaporated in

30

vacuo to afford the title compound as an off white solid (8.32g, 49%). ^1H NMR (CDCl_3) δ : 1.72 (6H, m), 2.12 (2H, m), 3.78 (4H, m), 7.1-7.3 (10H, m); Mass Spectrum (Electrospray LC/MS): Found 264 ($\text{MH}^+ - \text{HCN}$). $\text{C}_{20}\text{H}_{22}\text{N}_2$ requires 290. Ret. time 1.88min.

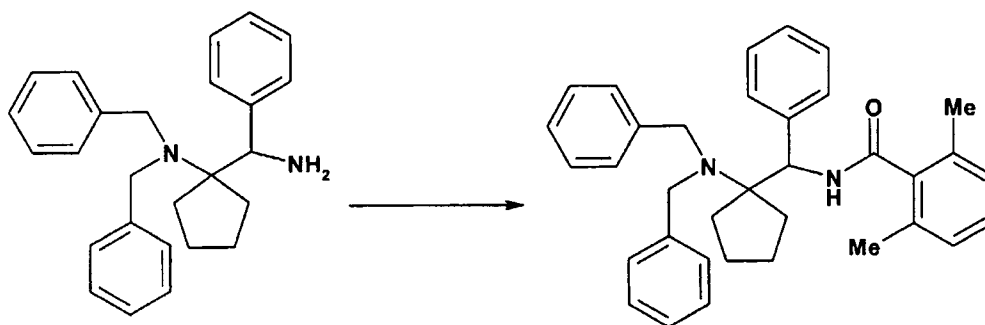
5 **Description 33: ($\pm$)-{1-[Amino(phenyl)methyl]cyclopentyl} bis(phenylmethyl)amine**



10 The title compound (2.31g; 38%) was prepared from 1-[bis(phenylmethyl)amino]cyclopentanecarbonitrile D32 (4.0g; 13.8mmol), and phenyllithium in di-n-butylether (8.4ml of 1.8M solution; 15.2mmol) in THF (80ml), followed by reaction with sodium borohydride (1.57g; 41.4mmol) in methanol (80ml) in a similar manner to that described in D2. Mass Spectrum (Electrospray LC/MS), API^+ : Found 371 (MH^+). $\text{C}_{26}\text{H}_{30}\text{N}_2$ requires 370. Ret. time 2.62 min.

15

Description 34: ($\pm$)-N-[[1-[bis(phenylmethyl)amino]cyclopentyl](phenyl)methyl]-2,6-dimethylbenzamide



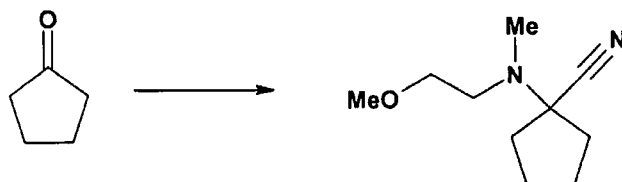
20 The title compound (2.51g; 80%) was prepared from ($\pm$)-{1-[amino(phenyl)methyl]cyclopentyl}bis(phenylmethyl)amine D33 (2.31g; 6.23mmol), 2,6-dimethyl benzoyl chloride (1.15g; 6.85mmol), triethylamine (1.73ml; 12.5mmol) in DCM (70ml) in a similar manner to

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that described in E13. ^1H NMR (CDCl_3) δ : 1.40-2.05 (8H, m), 2.28 (6H, s), 3.68 (4H, s), 5.37 (1H, d), 6.78 (1H, m), 6.95-7.36 (16H, m), 7.45 (2H, m); Mass Spectrum (Electrospray LC/MS), API^+ : Found 503 (MH^+). $\text{C}_{35}\text{H}_{38}\text{N}_2\text{O}$ requires 502. Ret. time 3.77 min.

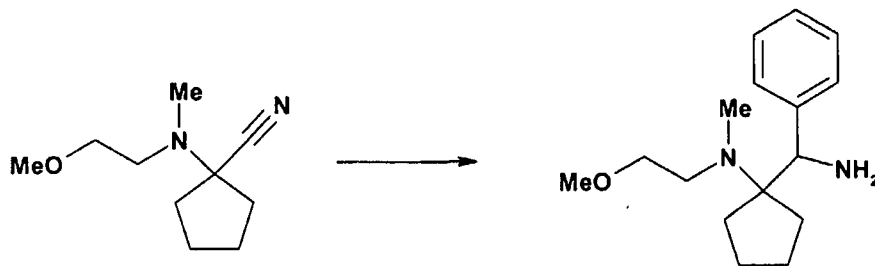
5

Description 35: 1-{Methyl[2-(methoxy)ethyl]amino}cyclopentanecarbonitrile



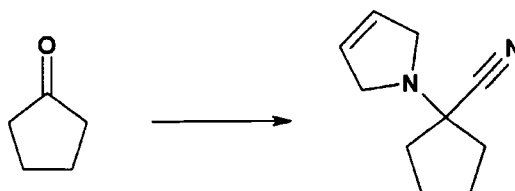
The title compound (3.39g; 82%) was prepared from N-(2-methoxyethyl) methylamine hydrochloride (2.84g; 22.6mmol), cyclopentanone (1.90g, 22.6mmol) and potassium cyanide (1.47g; 22.6mmol) in water (15ml) in a similar manner to that described in D1. ^1H NMR (CDCl_3) δ : 1.83 (6H, m), 2.20 (2H, m), 2.48 (3H, s), 2.68 (2H, t), 3.46 (3H, s), 3.5 (2H, t).

Description 36: ($\pm$)-{1-[Amino(phenyl)methyl]cyclopentyl} methyl[2-(methoxy)ethyl]amine

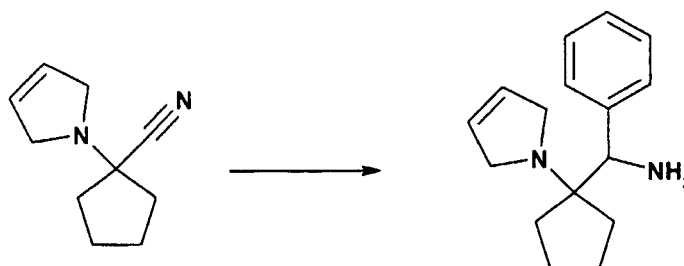


The title compound (1.22g; 42%) was prepared from 1-{methyl[2-(methoxy)ethyl]amino}cyclopentanecarbonitrile D35 (2.0g; 11mmol), and phenyllithium in di-n-butylether (6.7ml of 1.8M solution; 12mmol) in THF (25ml), followed by reaction with sodium borohydride (1.25g; 33mmol) in methanol (25ml) in a similar manner to that described in D2. Mass Spectrum (Electrospray LC/MS). Found 263 (MH^+). $\text{C}_{16}\text{H}_{26}\text{N}_2\text{O}$ requires 262. Ret. time 1.57min.

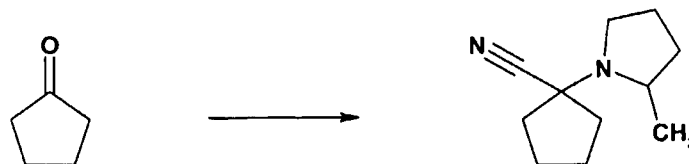
25

Description 37: 1-(2,5-Dihydro-1H-pyrrol-1-yl)cyclopentanecarbonitrile

The title compound (2.8g; 64%) was prepared from 3-pyrroline (1.86g; 27mmol),
5 cyclopentanone (2.26g; 27mmol) and potassium cyanide (1.75g; 27mmol) in water (15ml)
in a similar manner to that described in D1. ¹H NMR (CDCl₃) δ: 1.85 (6H, m), 2.08 (2H,
m), 3.61 (4H, s), 5.78 (2H, s).

**Description 38: (±)-[[1-(2,5-Dihydro-1H-pyrrol-1-yl)cyclopentyl] (phenyl)methyl]
10 amine**

The title compound (1.35g; 45%) was prepared from 1-(2,5-dihydro-1H-pyrrol-1-
yl)cyclopentanecarbonitrile D37 (2.0g; 12.3mmol), and phenyllithium in di-n-butylether
(7.5ml of 1.8M solution; 13.5mmol) in THF (20ml), followed by reaction with sodium
15 borohydride (1.402g; 36.9mmol) in methanol (20ml) in a similar manner to that described
in D2. Mass Spectrum (Electrospray LC/MS): Found 243 (MH⁺). C₁₆H₂₂N₂ requires 242.
Ret. time 1.02min.

Description 39: (±)-1-(2-Methyl-1-pyrrolidinyl)cyclopentanecarbonitrile

20

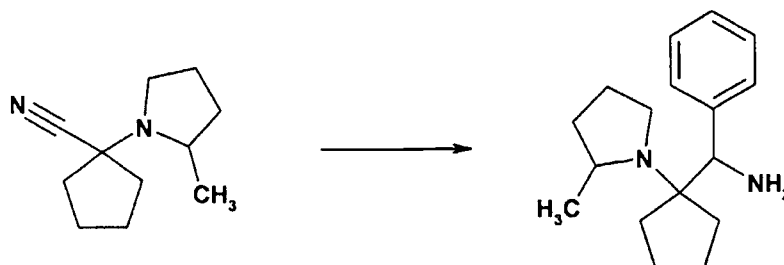
A mixture of cyclopentanone (1.34g, 16mmol) and 2-methylpyrrolidine (1.36g; 16mmol)
was cooled to 0°C (ice bath). A solution of potassium cyanide (1.04g, 16mmol) in water
(10ml) was added dropwise over 10min and the whole mixture stirred vigorously for 18 h

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at 20°C, and then partitioned between ethyl acetate and water. The organic layer was dried (Na₂SO₄) and evaporated in vacuo to afford the title compound (2.24g; 79%). ¹NMR (CDCl₃) δ: 1.1 (3H, d), 1.45 (1H, m), 1.75-2.05 (9H, m), 2.13 (2H, m), 2.65 (1H, m), 3.1 (2H, m).

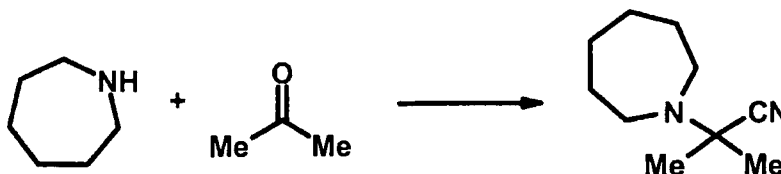
5

Description 40: (±)-[1-(2-methyl-1-pyrrolidinyl)cyclopentyl](phenyl) methyl]amine



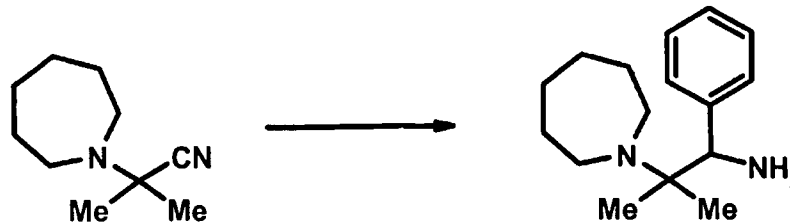
A solution of (±)-1-(2-methyl-1-pyrrolidinyl)cyclopentanecarbonitrile D39 (0.997g; 5.6mmol) in dry THF was cooled to -70°C. To this phenyllithium (1.7M in C₆H₁₄/ether, 1.1 equiv) was added slowly. The whole mixture was allowed to warm slowly to room temperature over 3 h with stirring under argon. Reaction cooled to 0°C and methanol added followed by sodium borohydride (portionwise) and allowed to react at 20°C overnight. The reaction was cooled to 0°C and quenched with saturated sodium bicarbonate, extracted with ethyl acetate, dried (Na₂SO₄) and evaporated. The product was purified by chromatography on a 5g SCX column eluting from 0-100% ethyl acetate in pet. ether, 0-10% methanol in ethyl acetate then 2% 0.880 ammonia in ethyl acetate to give the title compound as an oil (0.67g; 46%) was obtained. Mass Spectrum (Electrospray LC/MS): Found 259 (MH⁺). C₁₇H₂₆N₂ requires 258. Ret. time 1.19min.

Description 41: 2-(Hexahydro-1H-azepin-1-yl)-2-methylpropanenitrile



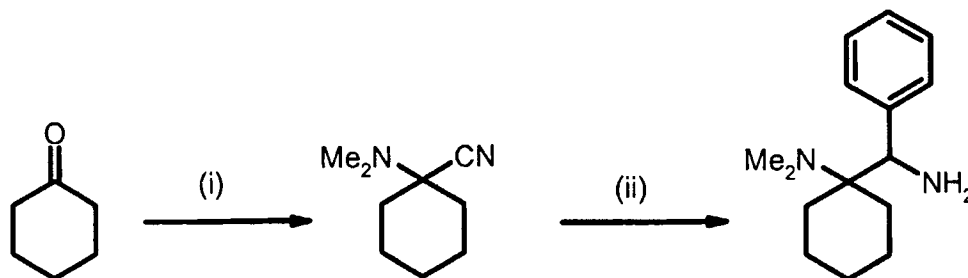
The title compound (6.6g; 80%) was prepared from homopiperidine hydrochloride (6.7g; 49mmol), acetone (3.67ml; 50mmol), and potassium cyanide (3.25g; 50mmol) in water (25ml) in a similar manner to that described in D1. ¹H NMR (CDCl₃) δ 1.43 (6H, s), 1.50 – 1.65 (8H, m), 2.66 (4H, m).

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Description 42: (±)[2-(Hexahydro-1H-azepin-1-yl)-2-methyl-1-phenylpropyl]amine

5 The title compound (3.7g; 83%) was prepared from 2-(hexahydro-1H-azepin-1-yl)-2-methylpropanenitrile D41 (3g; 18mmol) and phenyllithium in dibutylether (18ml of a 2M solution; 36mmol) in THF (100ml), followed by reaction with sodium borohydride (2.13g, 54mmol) in methanol (100ml) in a similar manner to that described in D5. ¹H NMR (CDCl₃) δ 0.78 (3H, s), 0.98 (3H, s), 1.55 – 1.70 (8H, m), 1.83 (2H, br s), 2.67 – 2.79 (4H, m), 4.18 (1H, s), 7.20 – 7.30 (3H, m), 7.40 – 7.42 (2H, m).

10

Description 43 : (±){1-[Amino(phenyl)methyl]cyclohexyl}dimethylamine

15 The title compound was prepared in two stages from (i) dimethylamine hydrochloride (3.26 g, 0.04 mol), cyclohexanone (3.9 g, 0.04 mol) and potassium cyanide (2.60 g, 0.04 mol) in water (25 ml) in a similar manner to that described in D1 to make 1-(dimethylamino)cyclohexanecarbonitrile (6.6 g, 100%). This was reacted directly in (ii) with phenyl lithium in dibutyl ether (10.5 ml of a 1.9M solution, 0.02 mol) in THF (30 ml)
 20 followed by sodium borohydride (1.51 g, 0.04 mol) in a similar manner to that described in D2 to afford the title compound (2.5 g, 36%). ¹H NMR (CDCl₃) δ: 0.85 (1H, m), 1.00 (1H, m), 1.25 (2H, m), 1.35-1.60 (6H, br m), 1.70 (1H, m), 2.10 (1H, m), 2.46 (6H, s), 4.15 (1H, s), 7.20-7.32 (5H, m).

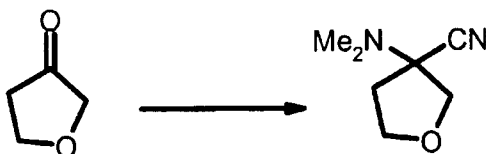
25

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Description 44 : Dihydro-3(2H)-furanone

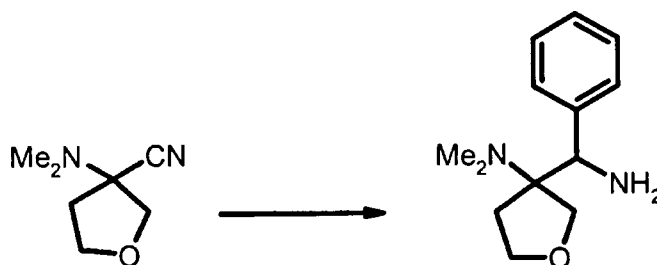
- 5 A mixture of 3-hydroxytetrahydrofuran (3.0 g, 0.034 mol) and pyridinium chlorochromate (14.7 g, 0.068 mol) in DCM (100 ml) was stirred at room temperature overnight. The title product was obtained by pouring the crude product through a silica pad using ethyl acetate as the eluent. The title product was obtained from 2 elutions (2.29 g; 79%). ¹H NMR (CDCl₃) δ: 2.50 (2H, t), 3.87 (2H, s), 4.26 (2H, t).

10 **Description 45 : (±)3-(Dimethylamino)tetrahydro-3-furancarbonitrile**



- The title compound (6.54 g, 88%) was prepared from dihydro-3(2H)-furanone D44 (4.54 g, 0.053 mol), dimethylamine hydrochloride (4.9 g, 0.06 mol) and potassium cyanide (3.5 g, 0.054 mol) in water (100 ml) in a similar manner to that described in D1. ¹H NMR (CDCl₃) δ: 2.15 (1H, m), 2.33 (6H, s), 2.44 (1H, m), 3.69 (1H, d), 4.02-4.13 (2H, m), 4.17 (1H, m).
- 15

Description 46: (±){3-[Amino(phenyl)methyl]tetrahydro-3-furanyl}dimethylamine diastereoisomers



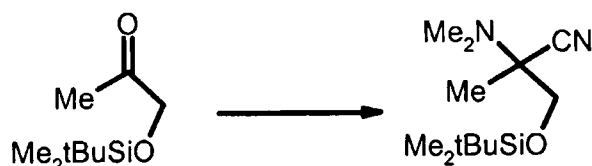
- 20 To a solution of 3-(dimethylamino)tetrahydro-3-furancarbonitrile D45 (4.55 g, 0.032 mol) in tetrahydrofuran (30ml) at -70°C under argon was added dropwise a solution of phenyllithium in dibutylether (36.1ml of a 1.8M solution; 0.064 mol). The reaction mixture was stirred and maintained at -50 to -70°C for 16 hours followed by careful addition of saturated aqueous sodium bicarbonate. The resulting slurry was extracted three times
- 25 with DCM. The combined extracts were dried (Na₂SO₄) and evaporated to afford the

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crude product as an orange oil which was chromatographed on silica gel eluting with 0 to 100% ethyl acetate / pentane to afford the imine intermediate as a yellow oil (5.18g). The oil was dissolved in methanol, sodium borohydride (1.8 g, 0.047 mol) added and the mixture stirred at room temperature overnight. The methanol was evaporated and the slurry partitioned between DCM and saturated aqueous sodium bicarbonate. The organics were dried by passage through a Phase-Sep column and evaporated to afford the title compound (3.47 g, 49%). ¹H NMR (CDCl₃) δ: 1.68 and 2.20 (1H, 2 x m), 1.75 (2H, br s), 1.90 and 2.05 (1H, 2 x m), 2.32 and 2.35 (6H, 2 x s), 2.70 and 3.42 (1H, 2 x m), 3.66-3.98 (3H, br m), 4.32 and 4.48 (1H, 2 x s), 7.20-7.51 (5H, m).

10

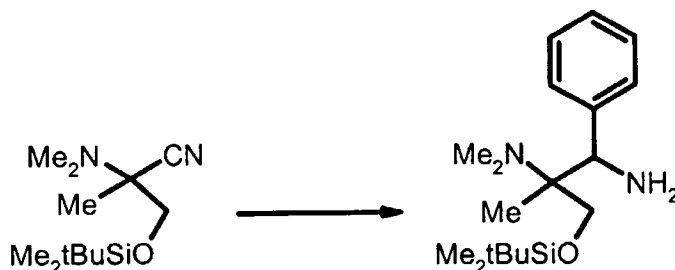
Description 47: (±)2-(Dimethylamino)-3-([(1,1-dimethylethyl)(dimethyl)silyl]oxy)-2-methylpropanenitrile



The title compound (2.16 g, 45%) was prepared from 1-(t-butyldimethylsilyloxy)-2-propanone (3.77 g, 0.02 mol), dimethylamine hydrochloride (1.71 g, 0.02 mol) and potassium cyanide (1.37 g, 0.02 mol) in water (50 ml) in a similar manner to that described in D1. An additional purification step was passage of the compound through SCX resin, elution with DCM to remove the starting material and then elution with 1M ammonia in methanol to elute the title compound. ¹H NMR (CDCl₃) δ: 0.00 (6H, d), 0.81 (9H, s), 1.38 (3H, s), 2.25 (6H, s), 3.36 (1H, d), 3.78 (1H, d).

20

Description 48: (±)[2-Amino-1-([(1,1-dimethylethyl)(dimethyl)silyl]oxy)methyl]-1-methyl-2-phenylethyl]dimethylamine diastereoisomers



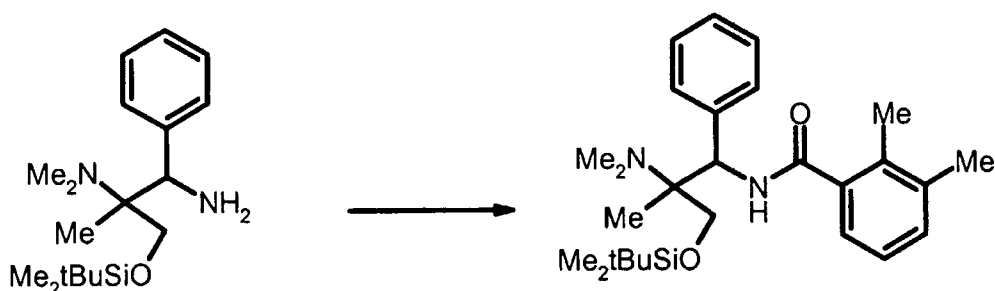
The title compound (930 mg, 33%) was prepared from 2-(dimethylamino)-3-([(1,1-dimethylethyl)(dimethyl)silyl]oxy)-2-methylpropanenitrile D47 (2.1 g, 8.67 mmol), phenyl lithium (10.0 ml of a 1.8M solution in dibutyl ether, 18.0 mmol) in THF (30 ml) followed by

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sodium borohydride (830 mg, 26.0 mmol) in methanol (50 ml) in a similar manner to that described in D2. Chromatography (Biotage Horizon) to isolate the title compound was carried out using (i) 0 to 100% ethyl acetate/ pentane, (ii) 100% ethyl acetate and (iii) 0 to 20% methanol/ ethyl acetate. The product containing fractions were combined and evaporated. Mass spectrum (Electrospray LC/MS), API⁺: Found 323 (MH⁺), 306 (M-16). C₁₈H₃₄N₂OSi requires 322. Ret. time 2.35-2.39 min. (broad peak).

Description 49 : (±)N-(2-(Dimethylamino)-3-(((1,1-dimethylethyl)(dimethyl)silyl)oxy))-2-methyl-1-phenylpropyl)-2,3-dimethylbenzamide
10 **diastereoisomers**

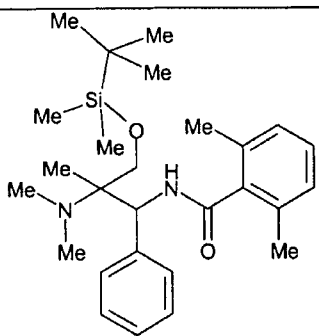
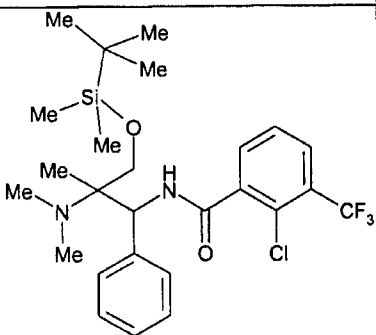


The title compound (64 mg; 30%) was prepared from [2-amino-1-(((1,1-dimethylethyl)(dimethyl)silyl)oxy)methyl]-1-methyl-2-phenylethyl] dimethylamine D48 (150 mg; 0.46mmol), 2,3-dimethylbenzoic acid (75 mg; 0.5mmol), PL-dicyclohexylcarbodiimide (385 mg; 0.5mmol; Polymer Labs 1.3 mmol/g), 1-hydroxybenzotriazole (77 mg; 0.5mmol) in DCM (5ml) in a similar manner to that described in E1. Mass spectrum (Electrospray LC/MS) : Found 455 (MH⁺), C₂₇H₄₂N₂O₂Si requires 454. Ret. time 2.57 and 2.61 min.

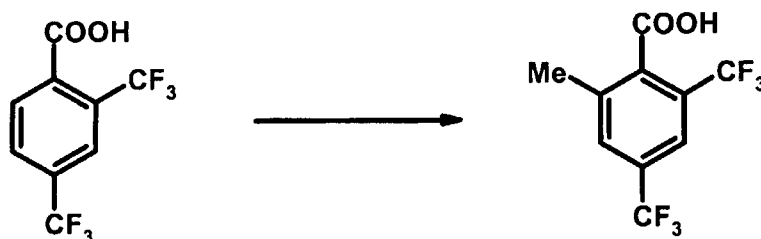
The compounds in Table 1 below were prepared in a manner similar to that described in description D49.

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Table 1

Description	Structure	Mass spectrum (Electrospray LC/MS), API ⁺ Ret.time (min)	Name
50		Found 455 (MH ⁺) C ₂₇ H ₄₂ N ₂ O ₂ Si requires 454; 2.60 and 2.62.	(±)-N-(2-(dimethylamino)-3- {[(1,1- dimethylethyl)(dimethyl)silyl] oxy}-2-methyl-1- phenylpropyl)-2,6- dimethylbenzamide diastereoisomers
51		Found 529 (MH ⁺) C ₂₆ H ₃₆ ³⁵ ClF ₃ N ₂ O ₂ Si requires 528; 2.72 and 2.79.	(±)-2-chloro-N-(2- (dimethylamino)-3- {[(1,1- dimethylethyl)(dimethyl)silyl] oxy}-2-methyl-1- phenylpropyl)-3- (trifluoromethyl)benzamide diastereoisomers

5 Description 52: 2-Methyl-4,6-bis(trifluoromethyl)benzoic acid



Dry THF (5ml) was stirred under argon at -80°C and treated with sec-butyl lithium (3.05ml of a 1.4M solution in cyclohexane, 4.27mmol) and N,N,N',N'-tetramethylethylenediamine (640ul, 4.27mmol). A solution of 2,4-bis(trifluoromethyl)benzoic acid (0.50g, 1.94mmol) in dry THF (2ml) was added dropwise over 30 minutes and allowed to stir for a further 30

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minutes at -80°C. Iodomethane (483ul, 7.76mmol) was added dropwise over 5 minutes and the reaction stirred at -70°C for a further 20 minutes and allowed to warm to room temperature. Water (1ml) was added dropwise and the mixture partitioned between ethyl acetate and water. The water layer was acidified with 2M hydrochloric acid and extracted
5 twice with ethyl acetate. The combined extracts were dried over magnesium sulphate and evaporated to afford a crude solid (416mg). NMR indicated this to be a mixture of 2-methyl-4,6-bis(trifluoromethyl)benzoic acid and recovered 2,4-bis(trifluoromethyl)benzoic acid. It was used without further purification.

10 **Description 52: 2-Methyl-4,6-bis(trifluoromethyl)benzoic acid - Alternative method.**

Dry THF (5ml) was stirred under argon at -80°C and treated with sec-butyl lithium (4.0ml of a 1.4M solution in cyclohexane, 5.60mmol) and N,N,N',N'-tetramethylethylenediamine (640ul, 4.27mmol). A solution of 2,4-bis(trifluoromethyl)benzoic acid (0.50g, 1.94mmol) in dry THF (2ml) was now added dropwise over 30 minutes and allowed to stir for a further
15 30 minutes at -80°C. Iodomethane (483ul, 7.76mmol) was now added dropwise over 5 minutes and the reaction stirred at -70°C for a further 20 minutes and allowed to warm to room temperature. Water (1ml) was added dropwise and the mixture partitioned between ethyl acetate and water. The water layer was acidified with 2M hydrochloric acid and extracted twice with ethyl acetate. The combined extracts were dried over magnesium
20 sulphate and evaporated to afford a crude solid (420mg). NMR indicated this to be a mixture of 2-methyl-4,6-bis(trifluoromethyl)benzoic acid (ca.80%), ¹H NMR (CDCl₃) δ: 2.54 (3H, s), 7.73 (1H, s), 7.81 (1H, s), and recovered 2,4-bis(trifluoromethyl)benzoic acid (ca.20%).

25 **Description: 53: 2-Methyl-4,6-bis(trifluoromethyl)benzoyl chloride**

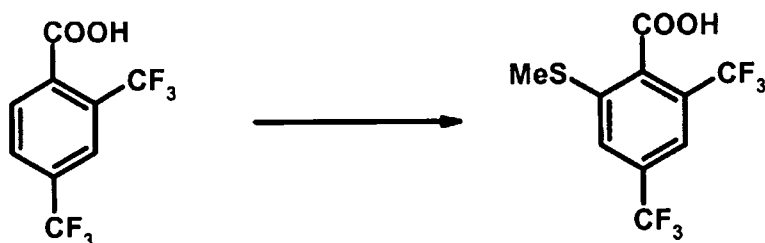


A solution of 2-methyl-4,6-bis(trifluoromethyl)benzoic acid D52 alternative method (400mg, approximately 1.47mmol) in DCM (5ml), containing DMF (1drop), was treated
30 with oxalyl chloride (166ul, 1.91mmol) and stirred under argon for 1 hour. The solvent was carefully removed under reduced pressure and the residue re-evaporated from

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further DCM. The mixture of acid chlorides was then treated with methanol (3ml) and kept at room temperature for 2 hours after which time the solvent was again carefully removed under reduced pressure. NMR data indicated this to be a mixture of the title product 2-methyl-4,6-bis(trifluoromethyl)benzoyl chloride and methyl 2,4-bis(trifluoromethyl)benzoate. The mixture was used without further purification.

Description: 54: 2-(Methylthio)-4,6-bis(trifluoromethyl)benzoic acid



- 10 Dry THF (5ml) was stirred under argon at -80°C and treated with N,N,N',N'-tetramethylethylenediamine (640ul, 4.27mmol) followed by sec-butyl lithium (3.05ml of a 1.4M solution in cyclohexane, 4.27mmol). A solution of 2,4-bis(trifluoromethyl)benzoic acid (0.50g, 1.94mmol) in dry THF (2ml) was now added dropwise over 15 minutes and allowed to stir for a further 60 minutes at -80°C . Dimethyldisulphide (687ul, 7.76mmol)
- 15 was now added dropwise over 2 minutes and the reaction stirred at -80°C for a further 40 minutes and allowed to warm to room temperature by cooling bath removal. Stirred at room temperature overnight. Water (1ml) was added dropwise and the mixture partitioned between ethyl acetate and water. The water layer was acidified with 2M hydrochloric acid and extracted twice with ethyl acetate. The combined extracts were
- 20 dried over magnesium sulphate and evaporated to afford a crude solid (400mg). NMR indicated this to be a mixture of the title product 2-(methylthio)-4,6-bis(trifluoromethyl)benzoic acid and recovered 2,4-bis(trifluoromethyl)benzoic acid which was used without further purification.

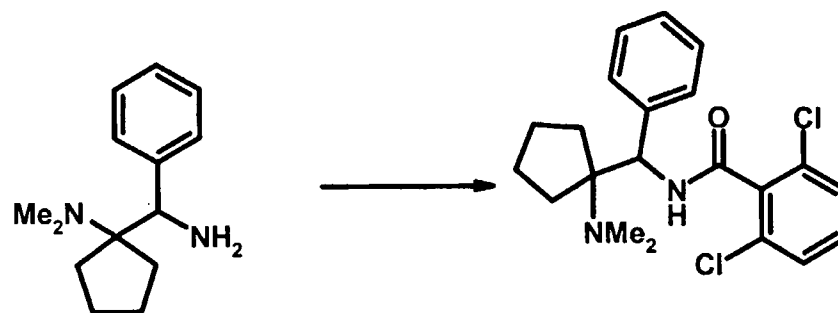
25 Description: 55: 2-(Methylthio)-4,6-bis(trifluoromethyl)benzoyl chloride



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A solution of the mixture containing 2-(methylthio)-4,6-bis(trifluoromethyl)benzoic acid D54 (225mg) in dry DCM (4ml), containing dry DMF (1drop), was treated with oxalyl chloride (87ul, 1.0mmol) and stirred at room temperature for 1 hour. The solvent was removed under reduced pressure to afford a crude product which was treated with dry methanol (2ml) and stirred at room temperature overnight. The solvent was then carefully removed under reduced pressure. The residue was chromatographed on silica gel, eluting with 0-10% ethyl acetate in pentane to afford the title product 2-(methylthio)-4,6-bis(trifluoromethyl)benzoyl chloride (60mg). ¹H NMR (CDCl₃) δ: 2.62 (3H, s), 7.77 (1H, s), 7.82 (1H, s). Further elution gave methyl 2,4-bis(trifluoromethyl)benzoate (100mg).

Example 1: (±)-2,6-Dichloro-N-[[1-(dimethylamino)cyclopentyl] (phenyl)methyl] benzamide



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To a solution of 2,6-dichlorobenzoic acid (20mg; 0.105mmol) in DCM (2ml) and N-methylpyrrolidinone (0.1-0.5ml) was added 1-hydroxybenzotriazole (18mg; 0.11mmol) and PL-dicyclohexylcarbodiimide (88mg; 0.14mmol; Polymer Labs 1.59mmol/g). The mixture was shaken at room temperature for 1 hour and then 1-[amino(phenyl)methyl]cyclopentyl]dimethylamine dihydrochloride D2 (20mg; 0.07mmol) and PS-diisopropylethylamine (82mg; 0.21mmol; Polymer Labs 2.59mmol/g) were then added and shaking continued overnight at room temperature. An excess of PS-Trisamine was then added and after shaking for a further 4h, the mixture was filtered and the resins washed well with DCM and methanol. The filtrate was reduced in volume by evaporation *in vacuo* and loaded onto an SCX cartridge (500mg). Washing with DCM, then methanol followed by elution with 1M ammonia in methanol afforded the title product (22.8mg). ¹H NMR (CDCl₃) δ: 0.98 (1H, m), 1.26 (1H, m), 1.40 (2H, m), 1.68 (2H, m), 1.85 (2H, m), 2.22 (6H, s), 5.08 (1H, bs), 7.27 (7H, m), and 7.47 (2H, m). Mass Spectrum (Electrospray LC/MS): Found 391 (MH⁺). C₂₁H₂₄³⁵Cl₂N₂O requires 390. Ret. time 1.88 min.

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The compounds in Table 2 below were prepared using similar methods to that described for Example 1. Coupling method: P = Polymer-supported DCC

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Table 2

Ex	Structure	Method	Mass spectrum (Electrospray LC/MS), API ⁺ Ret.time (min)	Name
2		P	Found 391 (MH ⁺) C ₂₁ H ₂₄ ³⁵ Cl ₂ N ₂ O requires 390; 2.03	(±)-2,4-Dichloro-N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]benzamide
3		P	Found 391 (MH ⁺) C ₂₁ H ₂₄ ³⁵ Cl ₂ N ₂ O requires 390; 2.01	(±)-2,5-Dichloro-N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]benzamide
4		P	Found 391 (MH ⁺) C ₂₁ H ₂₄ ³⁵ Cl ₂ N ₂ O requires 390; 2.02	(±)-2,3-Dichloro-N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]benzamide
5		P	Found 399 (MH ⁺) C ₂₇ H ₃₀ N ₂ O requires 398; 2.13	(±)-N-[[1-(Dimethylamino)cyclopentyl](phenyl)methyl]-2-biphenylcarboxamide
6		P	Found 351 (MH ⁺) C ₂₃ H ₃₀ N ₂ O requires 350; 1.96	(±)-N-[[1-(Dimethylamino)cyclopentyl](phenyl)methyl]-2,3-dimethylbenzamide
7		P	Found 351 (MH ⁺) C ₂₃ H ₃₀ N ₂ O requires 350; 1.87	(±)-N-[[1-(Dimethylamino)cyclopentyl](phenyl)methyl]-2,6-dimethylbenzamide

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8		P	Found 367 (MH ⁺) C ₂₃ H ₃₀ N ₂ O ₂ requires 366; 1.80	(±)-N-[[1-(Dimethylamino)cyclopentyl](phenyl)methyl]-2-methyl-6-(methoxy)benzamide
9		P	Found 425 (MH ⁺) C ₂₂ H ₂₄ ³⁵ ClF ₃ N ₂ O requires 424; 2.16 and 2.19.	(±)-2-Chloro-N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-3-(trifluoromethyl)benzamide

Example 10: 2-Chloro-N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-3-(trifluoromethyl)benzamide enantiomer 2

- 5 Racemic 2-chloro-N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-3-(trifluoromethyl)benzamide E9 (250mg; 0.59mmol) was separated by semi-preparative chiral HPLC to afford the title product enantiomer 1 (82mg); Chiral HPLC >99.8% ee; and the title product enantiomer 2 (86mg); Chiral HPLC >99.8% ee.

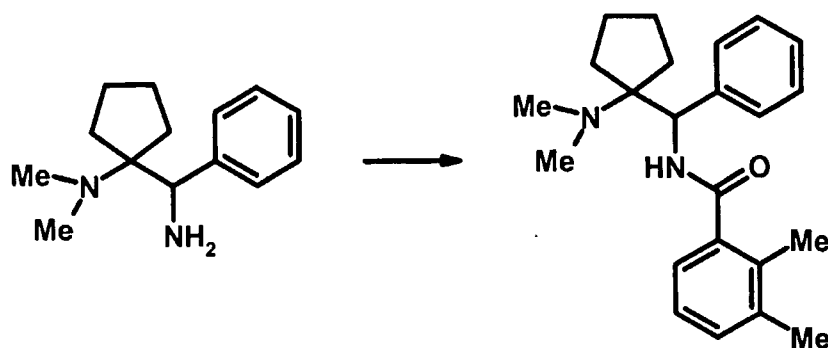
10 Semi-preparative chromatography conditions

- Column: chiralpak AD-H 5 μ m, 250 x 21 mm
 Mobile phase: A: n-Hexane; B: Isopropanol + 0.1% isopropylamine
 Gradient: isocratic 15% B
 Flow rate: 7 ml/min
 15 UV wavelength range: 225 nm
 Analysis time: 45 min

Analytical chromatography conditions

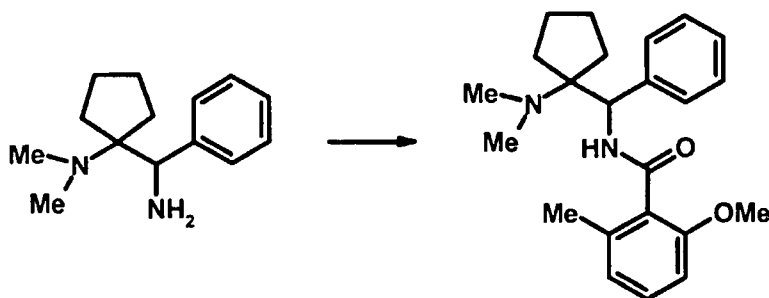
- Column: chiralpak AD-H 5 μ m, 250 x 4.6 mm
 20 Mobile phase: A: n-Hexane; B: Isopropanol
 Gradient: isocratic 15% B
 Flow rate: 1 ml/min
 UV wavelength range: 200-400 nm
 Analysis time: 25 min
 25 Ret. Time: 6.5min (Enantiomer 1); 10.1min (Enantiomer 2)

OR

Example 11: N-[[1-(Dimethylamino)cyclopentyl](phenyl)methyl]-2,3-dimethylbenzamide chiral

A mixture of {1-[amino(phenyl)methyl]cyclopentyl}dimethylamine D3 enantiomer 2
5 (0.102g, 0.47mmol), 2,3-dimethylbenzoic acid (0.100g, 0.67mmol), 1-hydroxybenzotriazole hydrate (0.092g, 0.6mmol) and PS-DCC (0.63g of 1.3mmol/g loading, 0.82mmol) in DCM (7ml) was shaken for 20h. The mixture was filtered and the resin washed with DCM (2 x 4ml). Combined organics were washed with saturated sodium hydrogen carbonate (20ml), the layers separated and the organic layer applied to
10 a 2g SCX cartridge. The cartridge was washed with DCM (2 volumes), 50% methanol in DCM (1 volume) and methanol (2 volumes). Elution with 1M ammonia in methanol (2 volumes) and evaporation of the solvent afforded a colourless gum. Chromatography on silica gel (10g) eluting with 0-100% ethyl acetate in pentane gradient afforded the title compound as a colourless solid (0.14g; 86%). ¹H NMR (CDCl₃) δ: 0.90 – 1.15 (1H, m),
15 1.20 – 1.38 (1H, m), 1.40 – 1.55 (2H, m), 1.60 – 1.75 (2H, m), 1.79 – 1.90 (2H, m), 2.22 (6H, s), 2.28 (6H, s), 5.15 (1H, d, J = 6Hz), 6.98 (1H, d, J = 6Hz), 7.10 – 7.15 (1H, m), 7.19 – 7.27 (3H, m), 7.29 – 7.35 (2H, m), 7.39 – 7.43 (2H, m). Mass spectrum (Electrospray LC/MS), ES⁺: Found 351 (MH⁺). C₂₃H₃₀N₂O requires 350. Ret. time 1.90 min. The title product was converted to the corresponding hydrochloride salt (0.150 g).

20

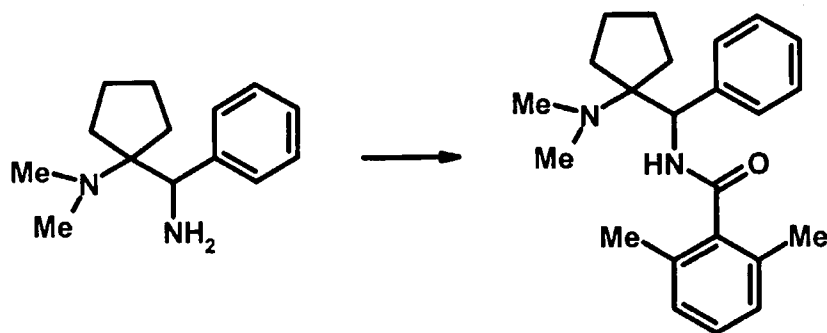
Example 12: N-[[1-(Dimethylamino)cyclopentyl](phenyl)methyl]-2-methyl-6-(methoxy)benzamide chiral

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A mixture of {1-[amino(phenyl)methyl]cyclopentyl}dimethylamine D3 enantiomer 2 (0.220 g, 1 mmol), 2-methoxy-6-methylbenzoic acid (0.200 g, 1.2 mmol), 1-hydroxybenzotriazole hydrate (0.183 g, 1.2 mmol) and PS-DCC (1 g of 1.3 mmol/g loading, 1.3 mmol) in DCM (10ml) was stirred vigorously overnight. The mixture was washed with saturated aqueous sodium hydrogen carbonate, the layers separated through a phase separation cartridge and the organic layer applied to an SCX cartridge. The cartridge was eluted with DCM (x2), and then methanol (x2) followed by 1M ammonia in methanol. Evaporation of the solvent afforded the title compound which was characterised. ¹H NMR (CDCl₃) δ: 1.00 – 1.10 (1H, m), 1.25 – 1.40 (1H, m), 1.40 – 1.60 (2H, m), 1.60 – 1.80 (2H, m), 1.80 – 2.00 (2H, m), 2.24 (6H, s), 2.28 (3H, s), 3.80 (3H, s), 5.17 (1H, d, J = 6Hz), 6.75 (1H, d, J = 8Hz), 6.79 (1H, d, J = 8Hz), 7.10 (1H, br s), 7.15 – 7.30 (4H, m), 7.44 (2H, m). Mass Spectrum (Electrospray LC/MS): Found 367 (MH⁺). C₂₃H₃₀N₂O₂ requires 366. Ret. time 1.92 min. The title product was converted to the corresponding hydrochloride salt (0.34 g, 85%).

15

Example 13: N-[[1-(Dimethylamino)cyclopentyl](phenyl)methyl]-2,6-dimethyl benzamide chiral



A solution of 2,6-dimethylbenzoyl chloride (1.7 g, 10.1 mmol) in DCM (10ml) was added dropwise to a mixture of {1-[amino(phenyl)methyl]cyclopentyl}dimethylamine D3 enantiomer 2 (2.0 g, 9.2 mmol), and triethylamine (1.4 ml, 10.0 mmol) in DCM (40ml) and stirred at room temperature for 2 h. The mixture was washed with saturated aqueous sodium hydrogen carbonate, the organic layer was separated through a phase separation cartridge and then evaporated to a white solid. Chromatography with eluent 50-100% ethyl acetate / pentane, then 0-10% methanol / ethyl acetate afforded the title product as a white solid (3.1 g, 97%). ¹H NMR (CDCl₃) δ: 0.85 – 1.00 (1H, m), 1.30 – 1.55 (3H, m), 1.60 – 1.75 (2H, m), 1.78 – 1.90 (2H, m), 2.21 (6H, s), 2.31 (6H, s), 5.19 (1H, d, J = 6Hz), 6.79 (1H, br d), 7.02 (2H, d, J = 8Hz), 7.16 (1H, t, J = 8Hz), 7.20 – 7.35 (3H, m), 7.43 (2H, m). Mass Spectrum (Electrospray LC/MS): Found 351 (MH⁺). C₂₃H₃₀N₂O requires 350.

Ret. time 2.0 min. The white solid product was converted to the HCl salt using 1M HCl/diethylether to afford the salt as a white solid on evaporation.

Example 13b: Succinate salt of N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-

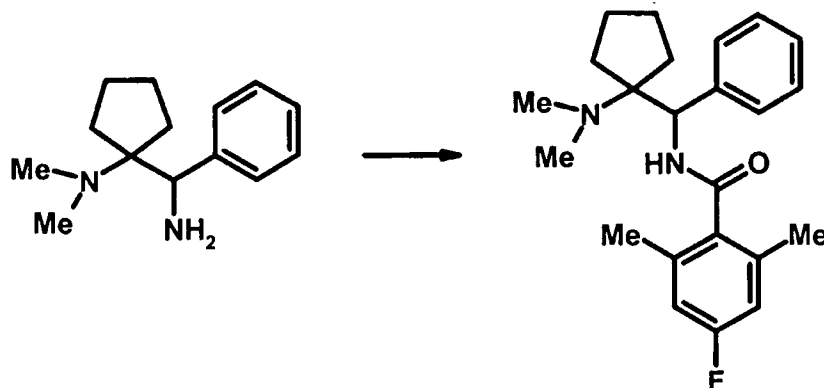
2,6-dimethyl benzamide chiral

To a mixture of 26.25g of the free base of the compound of Example 13 and 9.286g of succinic acid, was added 262ml of IPA (isopropyl alcohol) under nitrogen and the mixture was stirred at room temperature for 12 hours. Then the mixture was heated at 40°C for 1 hour, cooled at room temperature and chilled at 0°C for 1 hour. After further 30min at room temperature the solid is collected by filtration, dried overnight at 45°C under vacuum to get 31.92g of title material as a white solid.

Example 13c: Formulation of N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-2,6-dimethyl benzamide chiral

10.6mg of N-[[1-(Dimethylamino)cyclopentyl](phenyl)methyl]-2,6-dimethyl benzamide was dissolved in 7ml of Miglyol 812N. 217.1mg of Methocel K4M was added and the suspension was homogenised with a high shear mixer. The resulting concentrations were 1.5mg ml⁻¹ of active ingredient and 30mg ml⁻¹ of Methocel excipient.

Example 14: N-[[1-(Dimethylamino)cyclopentyl](phenyl)methyl]-4-fluoro-2,6-dimethylbenzamide chiral

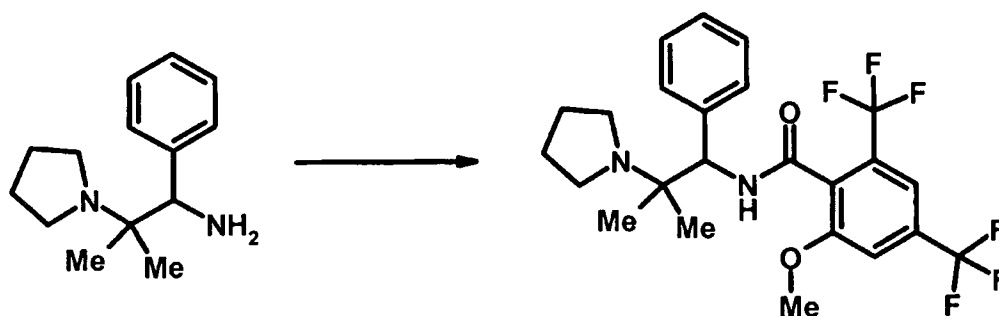


To {1-[amino(phenyl)methyl]cyclopentyl}dimethylamine D3 enantiomer 2 (0.904g; 4.147mmol) in DCM (45ml) under argon at room temperature was added triethylamine (0.573ml; 4.15mmol), followed by a solution of 4-fluoro-2,6-dimethylbenzoyl chloride (0.773g; 4.144mmol) in DCM (5ml). After 16h. the reaction was washed with water, dried with MgSO₄ and evaporated. The residue was chromatographed on silica gel eluting with an ethyl acetate – hexane 0 to 100% gradient to give the title compound (1.57g; 100%).

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¹H NMR (CDCl₃) δ: 0.85 – 1.00 (1H, m), 1.30 – 1.60 (3H, m), 1.60 – 1.75 (2H, m), 1.75 – 1.90 (2H, m), 2.22 (6H, s), 2.31 (6H, m), 5.18 (1H, d, J = 6Hz), 6.73 (2H, d, J = 9.6Hz overlaps 1H, br s), 7.20 – 7.35 (3H, m), 7.42 (2H, m). Mass Spectrum (Electrospray LC/MS): Found 369 (MH⁺). C₂₃H₂₉FN₂O requires 368. Ret. time 1.99min. The free base was dissolved in methanol. 1M HCl/diethylether was added to the stirred solution and stirring continued at room temperature for 5 minutes. The solution was then evaporated under reduced pressure, redissolved in DCM and evaporated at reduced pressure. The resulting foam was dried for 16 hours at reduced pressure. The hydrochloride salt was obtained as a white foam (1.45g).

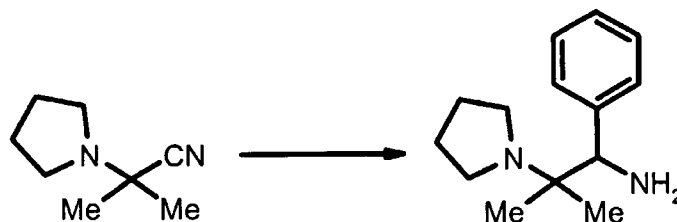
Example 15: 2-(Methoxy)-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]-4,6-bis(trifluoromethyl)benzamide chiral



To a solution of diisopropylethylamine (0.915ml; 5.37mmol), 2,4-difluoromethyl-6-methoxy-benzoic acid (0.511g; 1.78mmol) and (+)- [2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]amine D6 (0.501g; 1.74mmol) in DMF (50ml) under argon was added HATU (0.676g; 1.78mmol) portionwise. After stirring at room temperature for 3h., followed by standing for ca. 2 days the reaction mixture was purified using an SCX column and the resulting product partitioned between ethyl acetate and water. The solvent was removed in vacuo to afford the title product. ¹H NMR (CDCl₃) δ: 0.94 (6H, s), 1.60 – 1.80 (4H, m), 2.55 – 2.75 (4H, m), 3.89 (3H, s), 4.78 (1H, s), 7.20 – 7.40 (7H, m), 7.52 (1H, s). Mass Spectrum (Electrospray LC/MS): Found 489 (MH⁺). C₂₄H₂₆F₆N₂O₂ requires 488. Ret. time 2.06min. Conversion of the title product to the corresponding hydrochloride salt afforded an off-white solid (0.893g; 96%).

Example 15b: 2-(Methoxy)-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]-4,6-bis(trifluoromethyl)benzamide hydrochloride chiral alternative method

Step 1: (±)[2-Methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]amine (D5)



5 To a solution of 2-methyl-2-(1-pyrrolidinyl)propanenitrile D4 (40g; 289.85mmol) in dry THF (0.8L) under nitrogen, cooled at -78°C, was added dropwise a solution of phenyl lithium in dibutyl ether over 40 minutes (305.1mL of a 1.9M solution; 579.70mmol). After 2h the reaction was allowed to reach room temperature and then stirred overnight at this
10 temperature. The mixture was quenched at 0°C with a saturated solution of NaHCO₃ (0.8L) and stirred for 15 minutes and diluted with water (ca.0.6L). The phases were separated and the aqueous back extracted with diethylether (2x1L). The collected organics were dried over Na₂SO₄ and evaporated in vacuo to get 90g of crude material as a yellow oil that was dissolved in methanol (1L) at 0°C and treated portionwise with
15 sodium borohydride (21.93g; 579.70mmol). After 1 hour at 0°C and then overnight at room temperature the mixture was cooled and quenched with water (ca.0.5L). Methanol was evaporated in vacuo and the aqueous phase, diluted with water (200mL), was extracted with DCM (3x800mL). The collected organics were dried over Na₂SO₄ and evaporated in vacuo to get the title product (51g) as a yellow solid, used in step 2 without
20 further purification.

Step 2: [2-Methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]amine R(-)α methoxy phenyl acetic acid salt

25 [2-Methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]amine D5 from step 1 (51g; 234mmol) was dissolved in isopropanol (0.765L, 15 volumes, relative volumes being referred to the quantity of [2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]amine). To this stirred solution, heated at 50°C, was added a solution of R(-)α methoxy phenyl acetic acid (38.83g; 234mmol) in isopropanol (0.255L, 5 volumes, relative volumes being referred to the quantity of [2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]amine). After 1.5h the mixture was
30 cooled to room temperature and then left stirring at this temperature overnight. The solid was recovered by filtration and washed with cold isopropanol. This solid (40.5g) was

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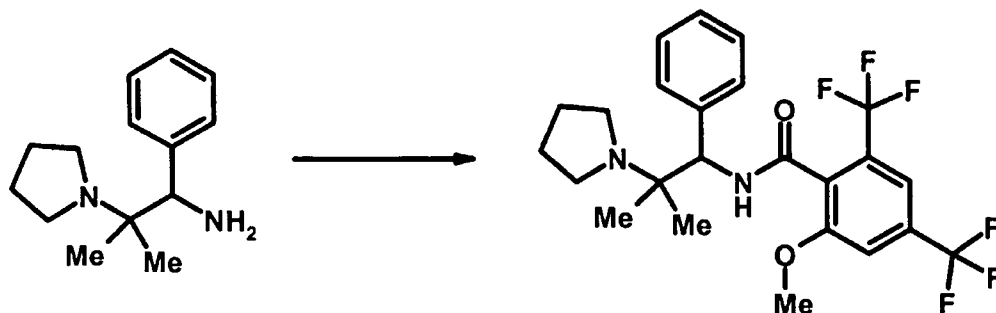
suspended in isopropanol (0.648L, 16 volumes, relative volumes being referred to the quantity of solid obtained in the last filtration step), and heated at 60°C for 2h, at room temperature overnight and recovered by filtration. This solid (38.5g) was suspended in isopropanol (0.616L, 16 volumes, relative volumes being referred to the quantity of solid obtained in the last filtration step), and heated at 60°C for 2h and at room temperature overnight, then recovered by filtration. This solid (37.8g) was suspended in isopropanol (0.756L, 20 volumes, relative volumes being referred to the quantity of solid obtained in the last filtration step), and heated at 60°C for 2h and at room temperature overnight, then recovered by filtration. This solid (36.5g) was suspended in isopropanol (0.912L, 25 volumes, relative volumes being referred to the quantity of solid obtained in the last filtration step), and heated at 60°C for 2h and then filtered at room temperature. This solid (34g) was suspended in isopropanol (0.850L, 25 volumes, relative volumes being referred to the quantity of solid obtained in the last filtration step), and heated at 60°C for 2h and filtered at room temperature. This solid (31.5g) was suspended in isopropanol (0.787L, 25 volumes, relative volumes being referred to the quantity of solid obtained in the last filtration step), and heated at 60°C for 2h, cooled down to 40°C and then filtered to get the title material (27g) as a white solid.

Step 3: 2-(Methoxy)-4,6-bis(trifluoromethyl)benzoyl chloride



To a solution of 2-(methoxy)-4,6-bis(trifluoromethyl)benzoic acid (20.2g; 70.14mmol) in dry DCM (400mL), at 0°C, was added dropwise oxalyl chloride (13.4mL; 154.31mmol) followed by dry DMF (5 drops). The reaction was allowed to reach room temperature. After overnight stirring the solvent was evaporated in vacuo to get the title product (23.5g) as a yellow slurry used without further purification.

Step 4: 2-(Methoxy)-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]-4,6-bis(trifluoromethyl)benzamide chiral (E15)

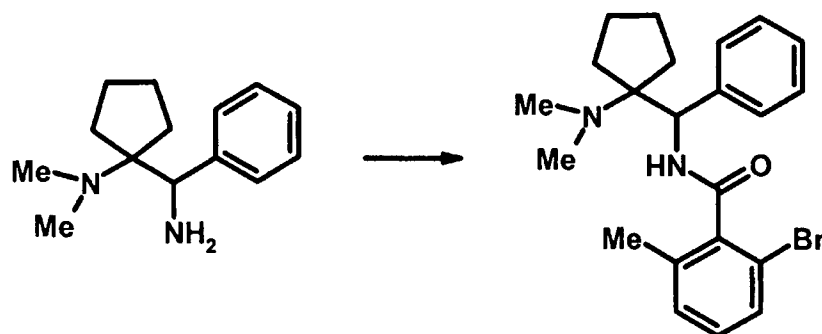


[2-Methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]amine R(-)- α methoxy phenyl acetic acid salt
 5 from step 2 (22g; 57.3mmol) was suspended in DCM at 0°C, treated with 1M NaOH solution (86mL) and stirred at room temperature for 20 minutes. To the mixture water (250mL) was added, the phases separated and the aqueous one extracted with DCM (2x300mL). The collected organics were dried over Na₂SO₄ and evaporated in vacuo to get 12.3g of white solid that was diluted with dry DCM (200mL) under nitrogen and cooled
 10 at 0°C. To this solution was added triethylamine (23.92mL; 172mmol) and a solution of 2-(methoxy)-4,6-bis(trifluoromethyl)benzoyl chloride from Step 3 in dry DCM (190ml of a 200mL solution in DCM of the step 3 material) over 30 minutes. The reaction was left stirring at room temperature for 2 hours and then quenched with a saturated solution of NaHCO₃ (ca.450mL). The phases were separated and the organic one washed with
 15 water (500mL), dried over Na₂SO₄ and evaporated in vacuo to get crude material that was purified by silica gel flash chromatography eluting with DCM/methanol 97/3. Evaporation of the solvent afforded the title material (26g) as a pale yellow solid.

Step 5: 2-(Methoxy)-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]-4,6-bis(trifluoromethyl)benzamide hydrochloride chiral

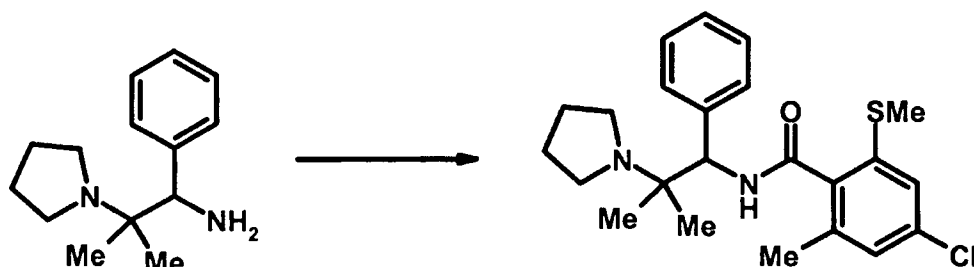
20 2-(Methoxy)-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]-4,6-bis(trifluoromethyl)benzamide E15 from step 4 (10g; 20.47mmol) was dissolved in dry ethyl ether (200mL), cooled to 0°C and treated with 1M solution of HCl in ethyl ether (21.5mL; 21.49mmol). After 0.5h the solid was collected by filtration, washed with diethyl ether and dried at 45°C
 25 overnight to get the title material (9.1g) as a pale yellow solid.

Example 16: 2-Bromo-N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-6-methylbenzamide chiral



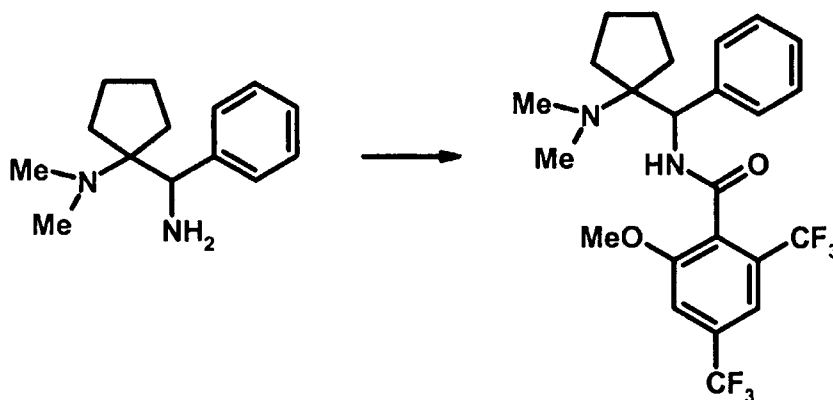
To {1-[amino(phenyl)methyl]cyclopentyl}dimethylamine D3 enantiomer 2 (50mg, 0.23 mmol) in DCM (5ml) was added 2-bromo-6-methylbenzoic acid (108mg; 0.5mmol), followed by 1-hydroxybenzotriazole (45mg; 0.3mmol) and PS-DCC (400mg of 1.3 mmol/g loading, 0.52mmol) and the mixture shaken at room temperature for ca.2 days. The reaction mixture was filtered through a phase-separation cartridge and the filtrate stirred with saturated aqueous sodium bicarbonate for 30min. The lower layer was removed, passed through another phase-separation cartridge and loaded onto an SCX cartridge which was eluted with 2 column volumes each of DCM, 50% methanol-DCM, methanol and 1M ammonia in methanol. The product containing fractions were evaporated to afford the title product (82mg; 82%). ¹H NMR (CDCl₃) δ: 0.95 -1.10 (2H, m), 1.40 -1.60 (2H, m), 1.60 - 1.80 (2H, m), 1.80 - 1.90 (2H, m), 2.23 (6H, s), 2.33 (3H, m), 5.13 (1H, d J = 6Hz), 6.97 (1H, br s), 7.10 - 7.15 (2H, m), 7.24 -7.34 (3H, m), 7.38 - 7.41 (1H, m), 7.46 - 7.48 (2H, m). Mass Spectrum (Electrospray LC/MS): Found 415 (MH⁺). C₂₂H₂₇⁷⁹BrN₂O requires 414. Ret. time 1.93 min.

Example 17: 4-Chloro-2-methyl-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]-6-(methylthio)benzamide chiral



A mixture of (+)- [2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]amine D6 (262mg; 1.2mmol), 4-chloro-2-methyl-6-(methylthio)benzoic acid (388mg; 1.8mmol), 1-hydroxybenzotriazole hydrate (276mg; 1.8mmol) and EDC (345mg; 1.8mmol) in DCM (16ml) was stirred for 16h. The reaction mixture was then partitioned between DCM and saturated aqueous sodium hydrogen carbonate and the organic layer separated, washed with brine, dried and evaporated. The residue was chromatographed on silica gel eluting with an ethyl acetate – hexane 0 to 100% gradient to give the title compound as a colourless oil (332mg; 66%). ¹H NMR (CDCl₃) δ: 0.90 (3H, s), 0.98 (3H, s), 1.66 – 1.75 (4H, m), 2.31 (3H, s), 2.44 (3H, s), 2.60 – 2.65 (2H, m), 2.69 – 2.74 (2H, m), 4.82 (1H, d J = 3Hz), 7.00 (1H, m), 7.09 (1H, m), 7.11 (1H, br s), 7.23 – 7.33 (3H, m), 7.41 – 7.43 (2H, m). Mass Spectrum (Electrospray LC/MS): Found 417 (MH⁺). C₂₃H₂₉³⁵ClN₂OS requires 416. Ret. time 2.08 min. The product was dissolved in methanol and 1M HCl/diethylether solution was added dropwise to the stirred solution. After stirring at room temperature for 5 minutes, the mixture was evaporated at reduced pressure. It was redissolved in DCM and evaporated again at reduced pressure to yield the hydrochloride salt as a white foam (320mg).

Example 18: N-[[1-(Dimethylamino)cyclopentyl](phenyl)methyl]-2-(methoxy)-4,6-bis(trifluoromethyl)benzamide chiral



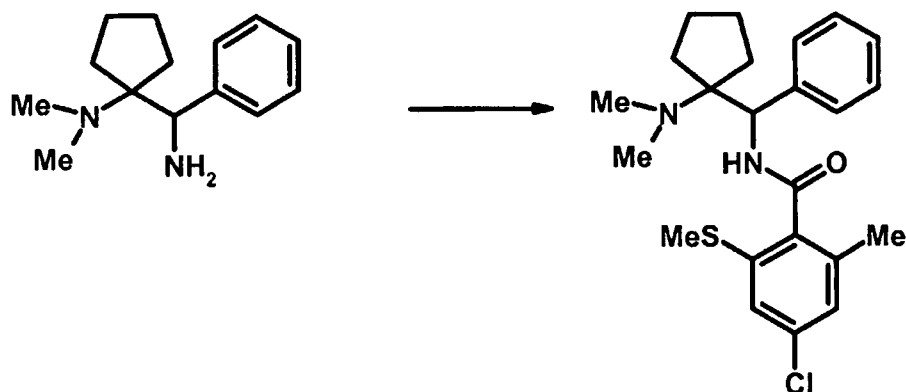
20

To a stirred solution of {1-[amino(phenyl)methyl]cyclopentyl}dimethylamine D3 enantiomer 2 (0.8g; 3.67mmol) and triethylamine (1.02ml; 7.34mmol) in DCM (35ml) was added 2,4-ditrifluoromethyl-6-methoxy-benzoyl chloride (1.12g; 3.67mmol) in DCM (5ml) dropwise over 5 min. The resulting solution was allowed to stand for 66h at room temperature and then saturated aqueous sodium bicarbonate solution (40ml) added. After stirring at room temperature for 0.5h. the reaction mixture was loaded onto a phase separation cartridge and the eluted organic phase evaporated under reduced pressure. The residue was

25

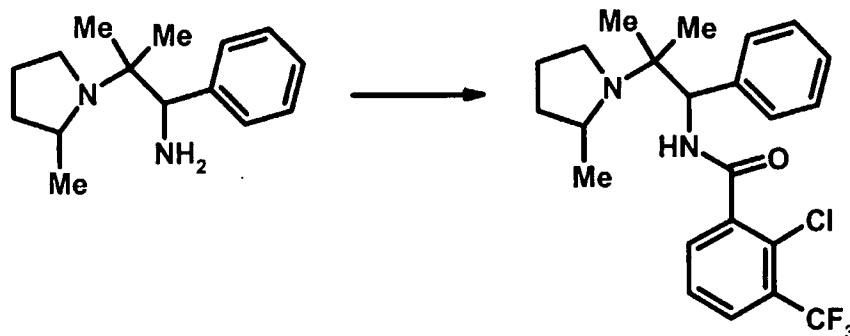
dissolved in a minimum of DCM and chromatographed on silica gel eluting with 0 to 95% ethyl acetate-pentane mixtures. After evaporating the collected fractions under reduced pressure, redissolving in DCM and evaporating under reduced pressure the title compound was obtained as a colourless solid (1.33g; 74%). ¹H NMR (CDCl₃) δ: 0.90 – 1.05 (1H, m), 1.25 – 1.60 (3H, m), 1.60 – 1.75 (2H, m), 1.80 – 1.90 (2H, m), 2.20 (6H, s), 3.93 (3H, s), 5.07 (1H, d, J = 5Hz), 7.14 (1H, br s), 7.20 – 7.35 (4H, m), 7.44 (2H, m), 7.53 (1H, s). Mass Spectrum (Electrospray LC/MS): Found 489 (MH⁺). C₂₄H₂₆F₆N₂O₂ requires 488. Ret. time 2.17min.

10 **Example 19: 4-Chloro-N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-2-methyl-6-(methylthio)benzamide chiral**



A mixture of {1-[amino(phenyl)methyl]cyclopentyl}dimethylamine D3 enantiomer 2 (203mg; 0.93mmol), 4-chloro-2-methyl-6-(methylthio)benzoic acid (obtainable as described in F.P. Doyle, J.H.C. Naylor, H.R.J. Waddington, J.C. Hanson and G.R. Thomas. J.Chem.Soc. 1963, 497) (202mg; 0.93mmol), EDC (178mg; 0.93mmol) and HOBt (143mg; 0.93mmol) in DCM (20ml) was stirred at room temperature for 4h and then stood at room temperature for 90h. The resulting reaction mixture was washed with saturated aqueous sodium bicarbonate (50ml) and the organic layer separated by passage through a phase separation cartridge. The organic layer was evaporated, the residue dissolved in a minimum of DCM and chromatographed on silica gel, eluting with 0 – 100% ethyl acetate – pentane. The fractions were combined and evaporated under reduced pressure to afford the title compound (200mg; 52%). ¹H NMR (CDCl₃) δ: 0.90 – 1.10 (1H, m), 1.38 – 1.55 (3H, m), 1.60 – 1.76 (2H, m), 1.80 – 1.90 (2H, m), 2.21 (6H, s), 2.26 (3H, s), 2.47 (3H, s), 5.11 (1H, d, J = 6Hz), 6.94 (1H, d, J = 5.2Hz), 7.00 (1H, m), 7.09 (1H, m), 7.20 – 7.35 (3H, m), 7.40 – 7.50 (2H, m). Mass spectrum (Electrospray LC/MS), ES⁺: Found 417 (MH⁺). C₂₃H₂₉³⁵ClN₂OS requires 416. Ret. time 2.03min. The title product was converted to its corresponding hydrochloride salt (210mg).

Example 20: ($\pm$)-2-Chloro-N-[2-methyl-2-(2-methyl-1-pyrrolidinyl)-1-phenylpropyl]-3-(trifluoromethyl)benzamide Diastereomers



5

A mixture of [2-methyl-2-(2-methyl-1-pyrrolidinyl)-1-phenylpropyl]amine D26 (0.150g; 0.647mmol), 2-chloro-3-(trifluoromethyl)benzoic acid (0.174g; 0.775mmol), EDC (0.149g; 0.777mmol) and HOBt (0.020g; 0.148mmol) in DCM (4ml) was shaken at room temperature for 66 hours. Saturated sodium hydrogen carbonate (8ml) was added and shaking continued for 0.5 hours. The organic layer was passed through a phase separation cartridge and applied to a 2g SCX column. The column was washed with DCM and methanol and the product eluted with 1M ammonia in methanol. The crude product was purified by chromatography on silica gel (20g) eluting with 0 – 100% ethyl acetate in pentane gradient to afford the title compound as two pairs of enantiomers.

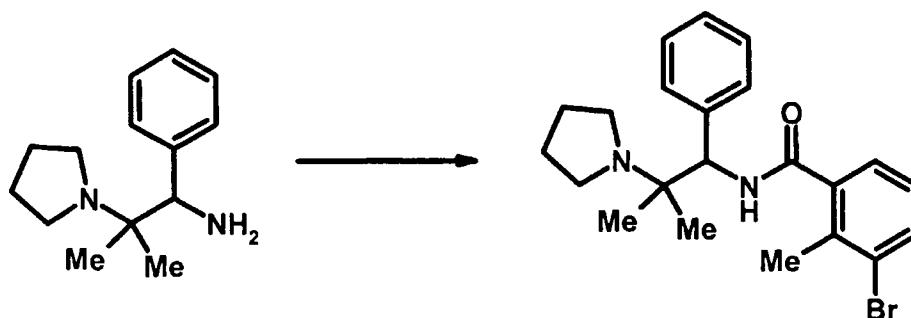
15 For the less polar pair of enantiomers (0.170g; 60%). ^1H NMR (CDCl_3) δ : 0.97 (6H, s), 1.05 (3H, d, $J = 6\text{Hz}$), 1.50 (1H, br m), 1.70 – 1.85 (3H, br m), 2.76 – 2.83 (1H, m), 2.90 – 2.97 (1H, m), 3.15 – 3.20 (1H, m), 4.73 (1H, d, $J = 2\text{Hz}$), 7.20 – 7.42 (5H, m), 7.43 (1H, t, $J = 8\text{Hz}$), 7.75 – 7.79 (2H, m), 7.84 (1H, br s). Mass spectrum (Electrospray LC/MS), ES^+ : Found 439 (MH^+). $\text{C}_{23}\text{H}_{26}^{35}\text{ClF}_3\text{N}_2\text{O}$ requires 438. Ret. time 2.17min. . The title product was converted to its corresponding hydrochloride salt.

20 For the more polar pair of enantiomers (0.100g; 35%). ^1H NMR (CDCl_3) δ : 0.95 – 1.10 (9H, m), 1.45 (1H, br m), 1.65 – 1.82 (3H, br m), 2.60 – 2.67 (1H, m), 2.85 – 2.93 (1H, m), 3.35 – 3.40 (1H, m), 4.76 (1H, d, $J = 3.2\text{Hz}$), 7.20 – 7.45 (5H, m), 7.60 (1H, br m), 7.70 – 7.80 (2H, m), 7.84 (1H, m). Mass spectrum (Electrospray LC/MS), ES^+ : Found 439 (MH^+). $\text{C}_{23}\text{H}_{26}^{35}\text{ClF}_3\text{N}_2\text{O}$ requires 438. Ret. time 2.17min. The title product was converted to its corresponding hydrochloride salt.

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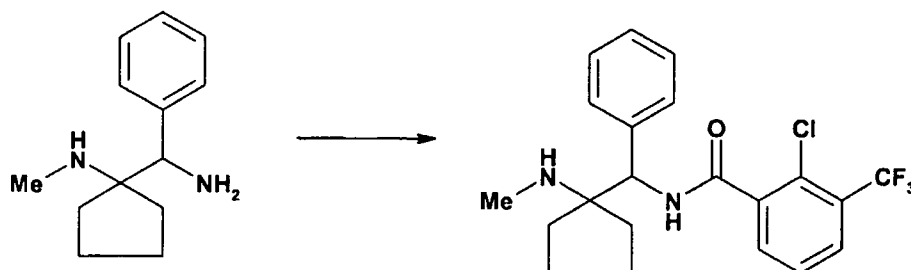
93

Example 21: (±)-3-Bromo-2-methyl-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]benzamide



To PS-EDC (0.068g; 0.1mmol; 1.42mmol/g) was added a solution of HOAt (0.01mmol in 5 0.8ml (THF:DCM, 1:1)) followed by the addition of 3-bromo-2-methyl-benzoic acid (0.011g; 0.05mmol) in 1:3 NMP:THF(0.25ml) and then [2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]amine D5 (0.011g 0.05mmol) in DCM (0.25ml). The reaction was allowed to mix for 60h. Following this PS-isocyanate (0.068g, 0.1mmol, 1.5mmol/g) and PS-CO₃ (0.068g, 0.1mmol, 1.5mmol/g) were added and allowed to mix for another 24h. 10 The reaction mixture was filtered and passed through an SCX block (500mg) (pre-wetted with DCM). The content of the Robbins block was washed with more solvent (DCM:THF, 1:1) and allowed to pass through the SCX which was then washed with DCM (2ml x2) and methanol (2ml x 2). The SCX was then eluted with 0.5M ammonia in methanol and the product containing eluent evaporated to afford the title product (17.4mg; 84%). Mass 15 Spectrum (Electrospray LC/MS): Found 414 (MH⁺). C₂₂H₂₇⁷⁹BrN₂O requires 415; Ret. time 2.64min*

Example 22: (±)-2-Chloro-N-[[1-(methylamino)cyclopentyl](phenyl)methyl]-3-(trifluoromethyl)benzamide



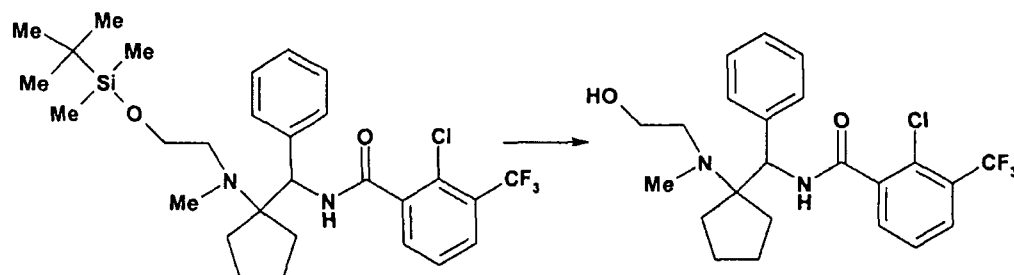
20

To a solution of 2-chloro-3-(trifluoromethyl)benzoic acid (0.728g; 3.24mmol) in DMF (20ml) and DIPEA (2.5ml) was added (±)-[[amino(phenyl)methyl]cyclopentyl] methylamine D29 (1.0g; 3.60mmol) and HATU (1.23g; 3.24mmol). The resulting mixture was allowed to stir at room temperature overnight and then DMF evaporated off in vacuo. Residual

94

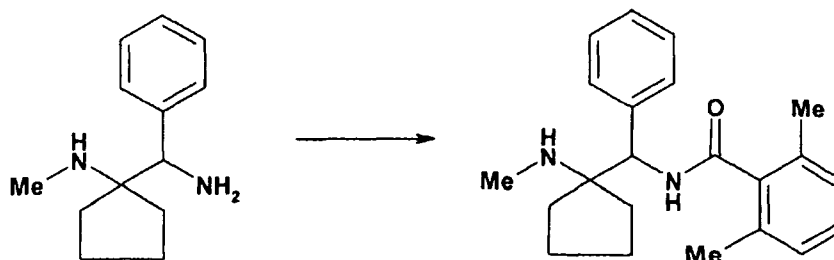
material was partitioned between ethyl acetate and water. The organic layer was dried (Na_2SO_4) and the filtrate evaporated in vacuo. The desired product was isolated by column chromatography on silica gel using 20% diethyl ether to 100% diethyl ether in n-pentane to afford the title compound as a white solid (0.908g; 61%). ^1H NMR (CDCl_3) δ : 1.47-1.83 (9H, m), 2.21 (3H, s), 5.1 (1H, m), 7.23-7.43 (6H, m), 7.58 (1H, m), 7.65 (1H, m), 7.73 (1H, m); Mass Spectrum (Electrospray LC/MS), API⁺: Found 411 (MH^+). $\text{C}_{21}\text{H}_{22}^{35}\text{ClF}_3\text{N}_2\text{O}$ requires 410. Ret. time 2.04min.

Example 23: ($\pm$)-2-Chloro-N-[[1-[(2-hydroxyethyl)(methyl)amino]cyclopentyl](phenyl)methyl]-3-(trifluoromethyl)benzamide



To a solution of ($\pm$)-2-chloro-N-[[1-[(2-[[1,1-dimethylethyl](dimethyl)silyl]oxy]ethyl)(methyl)amino]cyclopentyl](phenyl)methyl]-3-(trifluoromethyl)benzamide D30 (0.390g; 0.685mmol) in THF (10ml) was added tetrabutylammonium fluoride (1M solution in THF 1.6ml; 1.6mmol). The reaction mixture was allowed to stir at room temperature for 4 h. The desired product was isolated by column chromatography on silica using 20% to 50% ether in n-pentane, the solvent was reduced in volume by evaporation in vacuo and loaded onto an SCX cartridge. Washing with DCM, then methanol followed by elution with 1M ammonia in methanol afforded the title product (170mg, 73%). Mass Spectrum (Electrospray LC/MS). Found 455 (MH^+). $\text{C}_{23}\text{H}_{26}^{35}\text{ClF}_3\text{N}_2\text{O}_2$ requires 454. Ret. time: 2.09min.

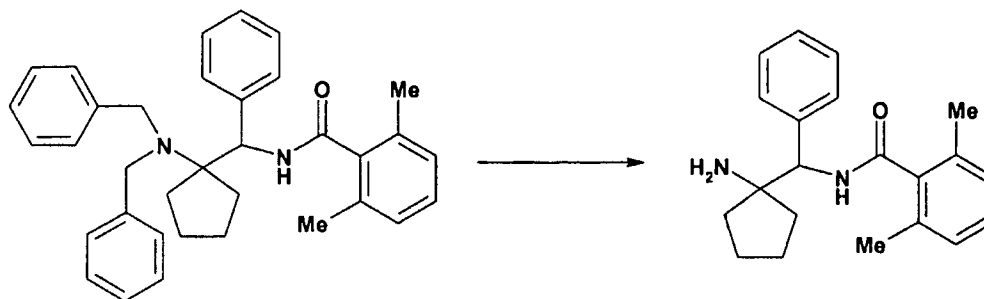
Example 24: 2,6-Dimethyl-N-[[1-(methylamino)cyclopentyl](phenyl)methyl]benzamide chiral



95

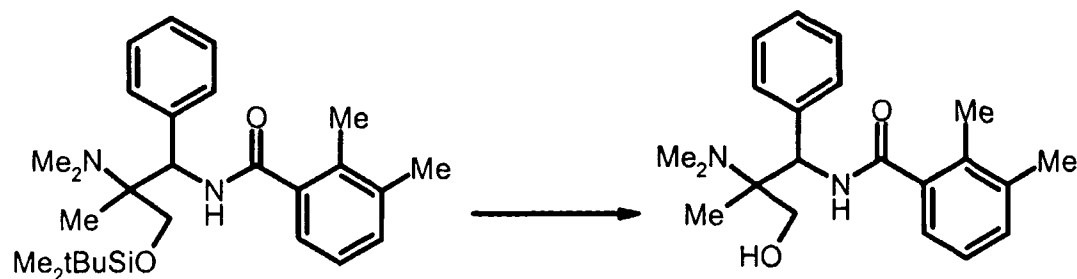
To a solution of 2,6-dimethylbenzoic acid (0.100g; 0.668mmol) in DMF (5ml) and DIPEA (0.12ml) was added {[amino(phenyl)methyl]cyclopentyl} methylamine D31 enantiomer 2 (0.124g; 0.608mmol) and HATU (0.254g; 0.668mmol). The resulting mixture was allowed to stir at room temperature for 3 days and then the DMF was evaporated off under reduced pressure. Residual material was partitioned between ethyl acetate and water, washed with water and the organic layer was dried (Na_2SO_4) and evaporated. The residual material was dissolved in DCM (2ml) and loaded onto an SCX cartridge. Washing with DCM, then methanol followed by elution with 1M ammonia in methanol afforded the title product (155mg; 76%). ^1H NMR (CDCl_3) δ : 1.3-1.8 (9H, m), 2.21 (3H, s), 2.28 (6H, s), 5.07 (1H, m), 7.0 (2H, m), 7.1-7.4 (7H, m). Mass Spectrum (Electrospray LC/MS). Found 337 (MH^+). $\text{C}_{22}\text{H}_{28}\text{N}_2\text{O}$ requires 336. Ret. time: 1.86min.

Example 25: ($\pm$)-N-[(1-aminocyclopentyl)(phenyl)methyl]-2,6-dimethylbenzamide



The title compound (1.14g; 71%) was prepared from the catalytic hydrogenation of ($\pm$)-N-[[1-[bis(phenylmethyl)amino]cyclopentyl](phenyl)methyl]-2,6-dimethylbenzamide D34 (2.51g; 5mmol) over 10% Pd/Carbon (0.4g) in 3M HCl (8ml) and ethanol (150ml) in a similar manner to that described in D29. The ethanol was evaporated off in vacuo and the residual material was partitioned between DCM and sodium bicarbonate solution and dried (Na_2SO_4). The filtrate was reduced in volume by evaporation in vacuo and loaded onto an SCX cartridge. Washing with DCM, then methanol followed by elution with 1M ammonia in methanol afforded the title product (90mg, 88%). ^1H NMR (CDCl_3) δ : 0.98-1.96 (10H, m), 2.23 (6H, s), 4.97 (1H, m), 7.0 (2H, m), 7.16 (1H, m), 7.22-7.41 (6H, m); Mass Spectrum (Electrospray LC/MS). Found 323 (MH^+). $\text{C}_{21}\text{H}_{26}\text{N}_2\text{O}$ requires 322. Ret. time 1.69min.

Example 26: ($\pm$)-*N*-[2-(Dimethylamino)-3-hydroxy-2-methyl-1-phenylpropyl]-2,3-dimethylbenzamide diastereomeric mixture



- 5 A solution of ($\pm$)-*N*-(2-(dimethylamino)-3-[(1,1-dimethylethyl)(dimethyl)silyloxy]-2-methyl-1-phenylpropyl)-2,3-dimethylbenzamide D49 (56 mg; 0.12mmol) in THF (5ml) was treated with a solution of tetrabutylammonium fluoride (1.0M solution in THF; 0.2ml, 0.2mmol) and the mixture stirred at room temperature overnight. The mixture was poured directly onto a chromatography column (Flashmaster II; eluent 0-100% ethyl acetate / pentane) to afford
- 10 the title compound (38mg; 63%). ^1H NMR (CDCl_3) δ : 0.73 and 1.14 (3H, 2 x s), 1.70-2.50 (1H, br s), 2.26 (6H, q), 2.38 and 2.48 (6H, 2 x s), 3.17, 3.39, and 3.55 (2H, 3 x d), 5.26 and 5.46 (1H, 2 x d), 6.83 and 7.89 (1H, 2 x br d), 7.07-7.46 (8H, br m). Mass spectrum (Electrospray LC/MS), API^+ : Found 341 (MH^+), $\text{C}_{21}\text{H}_{28}\text{N}_2\text{O}_2\text{Si}$ requires 340. Ret. time 1.71 and 1.76 min.

15

The examples in Table 3 were prepared in a manner similar to that described in example E26.

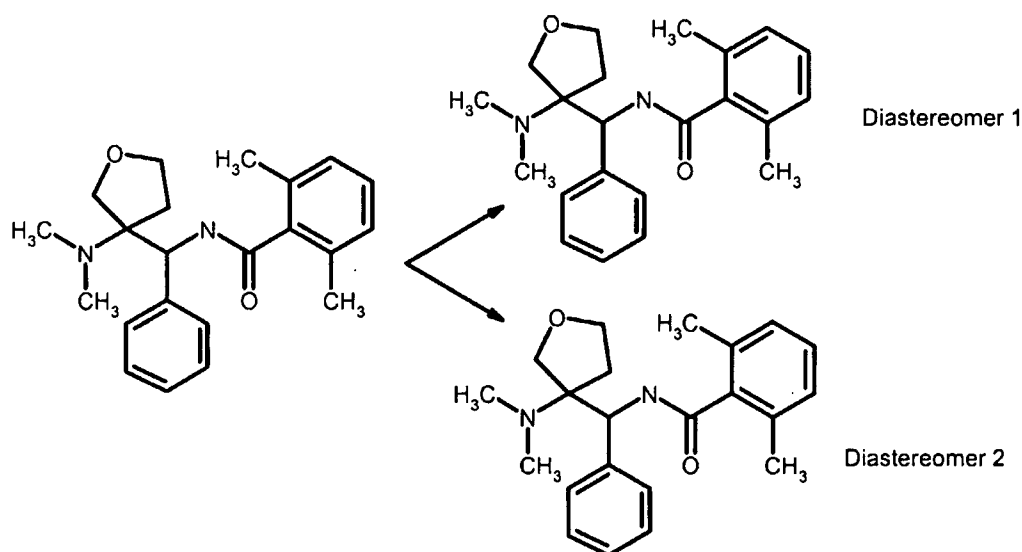
Table 3

Example	Structure	Mass spectrum (Electrospray LC/MS), API^+ Ret.time (min)	Name
27		Found 341 (MH^+) $\text{C}_{21}\text{H}_{28}\text{N}_2\text{O}_2$ requires 340; 1.78 and 1.83.	($\pm$)- <i>N</i> -[2-(dimethylamino)-3-hydroxy-2-methyl-1-phenylpropyl]-2,6-dimethylbenzamide

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28		Found 415 (MH ⁺) C ₂₀ H ₂₂ ³⁵ ClF ₃ N ₂ O ₂ requires 414; 1.91 and 1.94.	(±)-2-chloro- <i>N</i> -[2-(dimethylamino)-3-hydroxy-2-methyl-1-phenylpropyl]-3-(trifluoromethyl)benzamide
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Example 29: (±)-*N*-[[3-(Dimethylamino)tetrahydro-3-furanyl](phenyl)methyl]-2,6-dimethylbenzamide: Diastereomer 1 and Diastereomer 2



5

Racemic *N*-[[3-(dimethylamino)tetrahydro-3-furanyl](phenyl)methyl]-2,6-dimethyl benzamide E204 (40 mg, 0.11 mmol) was separated by preparative chiral HPLC to afford the title product diastereomer 1 (13 mg); Chiral HPLC: >95% de; Mass spectrum (Electrospray LC/MS): Found 353 (MH⁺). Ret. time 1.67 min. C₂₂H₂₈N₂O₂ requires 352 and diastereomer 2 (14 mg); Chiral HPLC: >95% de; Mass spectrum (Electrospray LC/MS): Found 353 (MH⁺) Ret. time 1.69 min. C₂₂H₂₈N₂O₂ requires 352.

Preparative HPLC conditions:

15 Column: S.F.C. Ethyl Pyridyl 150 mm x 21.1 mm i.d; 6 micron particle size

Mobile phase: Carbon Dioxide: Ethanol (95:5) v/v; pump-mixed isocratic

Flow rate: 50 ml/min

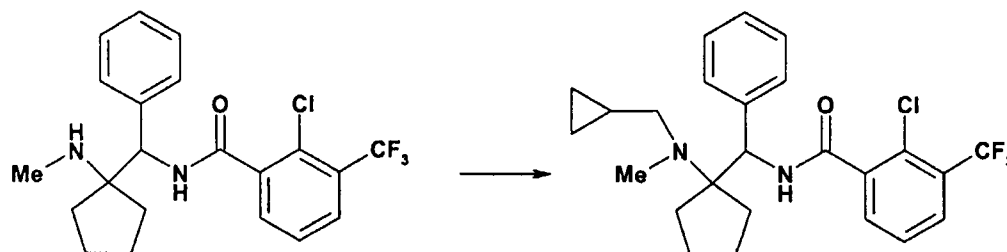
Pressure:	100 bar
Temperature:	40°C
UV wavelength range:	220nm
Elution time:	10 min
5 Ret. Time:	6.3 min (Diastereomer 1); 7.1 min (Diastereomer 2)

Analytical chromatography conditions:

Column:	S.F.C. Ethyl Pyridyl 150 mm x 4.6 mm i.d; 6 micron particle size
10 Mobile phase:	Carbon Dioxide: Ethanol (98:2) v/v; pump-mixed isocratic
Flow rate:	2.35 ml/min
Pressure:	100 bar
Temperature:	38°C
UV wavelength range:	254 nm
15 Elution time:	15 min
Ret. Time:	12.2 min (Diastereomer 1); 13.4 min (Diastereomer 2)

Example 30: (±)-2-Chloro-N-[[1-[(cyclopropylmethyl)(methyl)amino]cyclopentyl](phenyl)methyl]-3-(trifluoromethyl)benzamide hydrochloride

20



To a solution (±)-2-chloro-N-[[1-(methylamino)cyclopentyl](phenyl)methyl]-3-(trifluoromethyl)benzamide E22 (143g; 0.35mmol), cyclopropanecarboxaldehyde (0.026ml; 0.035mmol) and acetic acid (3 drops) in 1,2-dichloroethane (10ml) was added sodium triacetoxyborohydride (303mg; 1.4mmol). The resulting mixture was allowed to stir at room temperature under argon overnight. Then the reaction mixture was diluted with DCM (20ml), washed with saturated potassium carbonate solution and brine, dried (Na₂SO₄) and evaporated in vacuo. The mixture was separated by column chromatography on silica gel using 20% ether in n-pentane to 2% methanol in ether. The

oil obtained was treated with 1M HCl in ether to give the title product as an off white hydrochloride salt (0.054g; 33%). Mass Spectrum (Electrospray LC/MS). Found 465 (MH⁺). C₂₅H₂₈³⁵ClF₃N₂O requires 464. Ret. time: 2.30 min.

- 5 The compounds in Table 4 below were prepared using similar methods to those described for Example 30 above.

Table 4

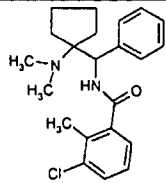
Example	Structure	Mass spectrum (Electrospray LC/MS), API ⁺ Ret.time (min)	Name
31		Found 365 (MH ⁺). C ₂₄ H ₃₂ N ₂ O requires 364; 1.96.	(±)-N-[(1-ethyl(methyl)amino)cyclopentyl](phenyl)methyl]-2,6-dimethylbenzamide
32		Found 377 (MH ⁺). C ₂₅ H ₃₂ N ₂ O requires 376; 2.07	(±)-N-[(1-(cyclopropylmethyl)amino)cyclopentyl](phenyl)methyl]-2,6-dimethylbenzamide
33		Found 439 (MH ⁺). C ₂₃ H ₂₆ ³⁵ ClF ₃ N ₂ O requires 438; 2.23.	(±)-2-chloro-N-[(1-ethyl(methyl)amino)cyclopentyl](phenyl)methyl]-3-(trifluoromethyl)benzamide
34		Found 351 (MH ⁺). C ₂₃ H ₃₀ N ₂ O requires 350; 1.82.	(±)-2-chloro-N-[(1-ethylamino)cyclopentyl](phenyl)methyl]-3-(trifluoromethyl)benzamide
35		Found 391 (MH ⁺). C ₂₆ H ₃₄ N ₂ O requires 390; 2.19	(±)-N-[(1-(cyclopropylmethyl)(methyl)amino)cyclopentyl](phenyl)methyl]-2,6-dimethylbenzamide

The compounds in Table 5 below were prepared using similar methods to those described for the Examples above. Coupling method: A = Acid chloride (using method similar to that in Example 13); E = EDC (using method similar to that in Example 17); H = HATU (using method similar to that in Example 15); P = Polymer-supported DCC (using method similar to that in Example 1); PE = Polymer-supported EDC (using method similar to that in Example 21). Work-up and purification was carried out using appropriate methods similar to those described in the examples above.

Benzoic acid starting materials were obtained commercially except for 2,6-dichloro-3-trifluoromethylbenzoic acid used for the examples indicated with a #, which was obtained by the method described in DE1924766. 4-chloro-2-methyl-6-(methylthio)benzoic acid is obtainable as described in F.P. Doyle, J.H.C. Naylor, H.R.J. Waddington, J.C. Hanson and G.R. Thomas. J.Chem.Soc. 1963, 497.

For the example compound names, those denoted by (±)- are derived from the corresponding racemic amine D2, D8, D10, D12, D14, D16, D18, D20, D22, D24, D26, D29, D36, D38, D40, D42, D43, D46, D48 and those without are from the corresponding chiral amines D3 enantiomer 2, D6, D31 enantiomer 2. LCMS retention times were generally measured using analytical LC/MS chromatography conditions method A. Compounds annotated with * are compounds prepared using array format described in Example 23 and they were analysed using analytical LC/MS chromatography conditions method B.

Table 5

Ex	Structure	Method	Mass spectrum (Electrospray LC/MS), API ⁺ Ret.time (min)	Name
36		P	Found 371 (MH ⁺) C ₂₂ H ₂₇ ³⁵ ClN ₂ O requires 370; 2.08	3-chloro-N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-2-methylbenzamide chiral

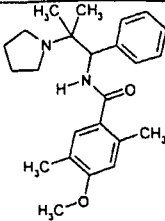
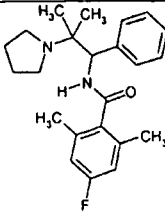
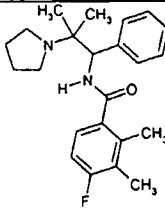
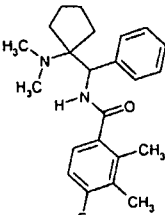
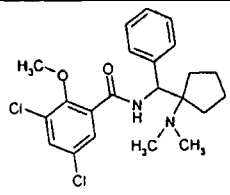
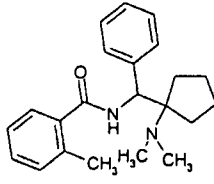
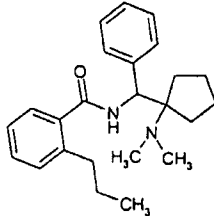
37		P	Found 415 (MH ⁺) C ₂₂ H ₂₇ ⁷⁹ BrN ₂ O requires 414; 2.09	3-bromo-N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-2-methylbenzamide chiral
38		P	Found 367 (MH ⁺) C ₂₃ H ₃₀ N ₂ O ₂ requires 366; 1.84	2-methyl-6-(methoxy)-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]benzamide chiral
39		P	Found 351 (MH ⁺) C ₂₃ H ₃₀ N ₂ O requires 350; 2.03	(±)-2,5-dimethyl-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]benzamide
40		P	Found 371 (MH ⁺) C ₂₂ H ₂₇ ³⁵ ClN ₂ O requires 370; 2.01	2-chloro-N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-3-methylbenzamide chiral
41		P	Found 405 (MH ⁺) C ₂₃ H ₂₇ F ₃ N ₂ O requires 404; 2.20	N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-2-methyl-5-(trifluoromethyl)benzamide chiral
42		P	Found 351 (MH ⁺) C ₂₃ H ₃₀ N ₂ O requires 350; 2.04	N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-2-methyl-5-(trifluoromethyl)benzamide chiral
43		PE	Found 429 (MH ⁺) C ₂₃ H ₂₉ ⁷⁹ BrN ₂ O requires 428; 2.68*	(±)-3-bromo-2-methyl-N-[2-methyl-2-(2-methyl-1-pyrrolidinyl)-1-phenylpropyl]benzamide
44		P	Found 371 (MH ⁺) C ₂₂ H ₂₇ ³⁵ ClN ₂ O requires 370; 1.98	(±)-2-chloro-3-methyl-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]benzamide

45		P	Found 371 (MH ⁺) C ₂₂ H ₂₇ ³⁵ ClN ₂ O requires 370; 1.90	(±)-2-chloro-6-methyl-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]benzamide
46		PE	Found 431 (MH ⁺) C ₂₄ H ₃₁ ³⁵ ClN ₂ OS requires 430; 2.57*	(±)-4-chloro-2-methyl-N-[2-methyl-2-(2-methyl-1-pyrrolidinyl)-1-phenylpropyl]-6-(methylthio)benzamide
47		P	Found 387 (MH ⁺) C ₂₂ H ₂₇ ³⁵ ClN ₂ O ₂ requires 386; 1.88	2-chloro-N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-6-(methoxy)benzamide chiral
48		P	Found 355 (MH ⁺) C ₂₂ H ₂₇ FN ₂ O requires 354; 1.96	(±)-3-fluoro-2-methyl-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]benzamide
49		P	Found 415 (MH ⁺) C ₂₂ H ₂₇ ⁷⁹ BrN ₂ O requires 414; 1.92	(±)-2-bromo-6-methyl-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]benzamide
50		P	Found 371 (MH ⁺) C ₂₂ H ₂₇ ³⁵ ClN ₂ O requires 370; 2.08	(±)-3-chloro-2-methyl-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]benzamide
51		P	Found 355 (MH ⁺) C ₂₂ H ₂₇ FN ₂ O requires 354; 1.97	N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-3-fluoro-2-methylbenzamide chiral

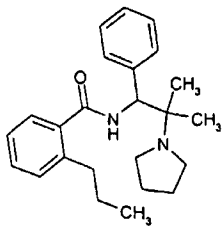
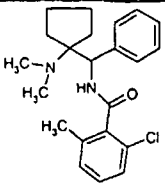
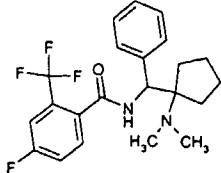
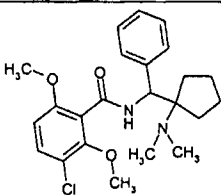
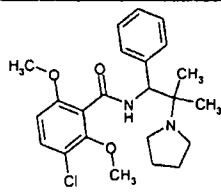
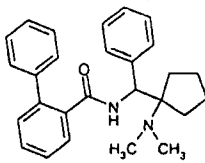
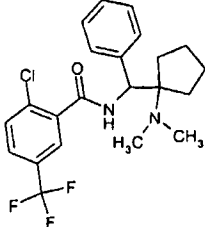
103

52		PE	Found 383 (MH ⁺) C ₂₃ H ₃₀ N ₂ OS requires 382; 2.62*	(±)-N-[2-methyl-2-(2-methyl-1-pyrrolidinyl)-1-phenylpropyl]-2-(methylthio)benzamide
53		PE	Found 429 (MH ⁺) C ₂₃ H ₂₉ ⁷⁹ BrN ₂ O requires 428; 2.44*	(±)-2-bromo-6-methyl-N-[2-methyl-2-(2-methyl-1-pyrrolidinyl)-1-phenylpropyl]benzamide
54		P	Found 367 (MH ⁺) C ₂₃ H ₃₀ N ₂ O ₂ requires 366; 1.84	(±)-2-methyl-6-(methoxy)-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]benzamide
55		PE	Found 385 (MH ⁺) C ₂₃ H ₂₉ ³⁵ ClN ₂ O requires 384; 2.65*	(±)-2-chloro-3-methyl-N-[2-methyl-2-(2-methyl-1-pyrrolidinyl)-1-phenylpropyl]benzamide
56		P	Found 425 (MH ⁺) C ₂₁ H ₂₃ ³⁵ Cl ₃ N ₂ O requires 424; 2.08	2,4,6-trichloro-N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]benzamide chiral
57		P	Found 405 (MH ⁺) C ₂₃ H ₂₇ F ₃ N ₂ O requires 404; 2.18	(±)-2-methyl-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]-5-(trifluoromethyl)benzamide
58		P	Found 381 (MH ⁺) C ₂₄ H ₃₂ N ₂ O ₂ requires 380; 2.10	2,3-Dimethyl-4-(methoxy)-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]benzamide chiral

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59		P	Found 381 (MH ⁺) C ₂₄ H ₃₂ N ₂ O ₂ requires 380; 2.14	2,5-Dimethyl-4-(methyloxy)- N-[2-methyl-1-phenyl-2-(1- pyrrolidinyl)propyl]benzamid e chiral
60		A	Found 369 (MH ⁺) C ₂₃ H ₂₉ FN ₂ O requires 368; 2.00	4-Fluoro-2,6-dimethyl-N-[2- methyl-1-phenyl-2-(1- pyrrolidinyl)propyl]benzamid e chiral
61		P	Found 369 (MH ⁺) C ₂₃ H ₂₉ FN ₂ O requires 368; 2.02	4-Fluoro-2,3-dimethyl-N-[2- methyl-1-phenyl-2-(1- pyrrolidinyl)propyl]benzamid e chiral
62		P	Found 369 (MH ⁺) C ₂₃ H ₂₉ FN ₂ O requires 368; 2.05	N-[[1- (Dimethylamino)cyclopentyl](phenyl)methyl]-4-fluoro-2,3- dimethylbenzamide chiral
63		PE	Found 421 (MH ⁺) C ₂₂ H ₂₆ ³⁵ Cl ₂ N ₂ O ₂ requires 420; 2.55*	3,5-dichloro-N-[[1- (dimethylamino)cyclopentyl](phenyl)methyl]-2- (methyloxy)benzamide chiral
64		PE	Found 337 (MH ⁺) C ₂₂ H ₂₈ N ₂ O requires 336; 2.34*	N-[[1- (dimethylamino)cyclopentyl](phenyl)methyl]-2- methylbenzamide chiral
65		PE	Found 365 (MH ⁺) C ₂₄ H ₃₂ N ₂ O requires 364; 2.48*	N-[[1- (dimethylamino)cyclopentyl](phenyl)methyl]-2- propylbenzamide chiral

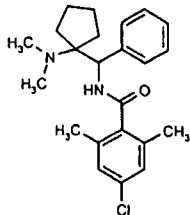
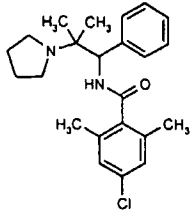
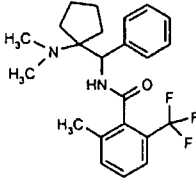
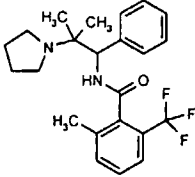
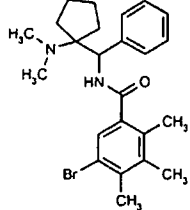
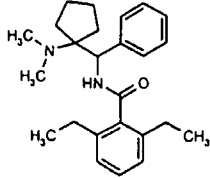
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66		PE	Found 365 (MH ⁺) C ₂₄ H ₃₂ N ₂ O requires 364; 2.45*	(±)-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]-2-propylbenzamide
67		P	Found 371 (MH ⁺) C ₂₂ H ₂₇ ³⁵ ClN ₂ O requires 370; 1.93	2-chloro-N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-6-methylbenzamide chiral
68		PE	Found 409 (MH ⁺) C ₂₂ H ₂₄ F ₄ N ₂ O requires 408; 2.44*	N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-4-fluoro-2-(trifluoromethyl)benzamide chiral
69		PE	Found 417 (MH ⁺) C ₂₃ H ₂₉ ³⁵ ClN ₂ O ₃ requires 416; 2.43*	3-chloro-N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-2,6-bis(methoxy)benzamide chiral
70		PE	Found 417 (MH ⁺) C ₂₃ H ₂₉ ³⁵ ClN ₂ O ₃ requires 416; 2.4*	(±)-3-chloro-2,6-bis(methoxy)-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]benzamide
71		PE	Found 399 (MH ⁺) C ₂₇ H ₃₀ N ₂ O requires 398; 2.51*	N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-2-biphenylcarboxamide chiral
72		PE	Found 425 (MH ⁺) C ₂₂ H ₂₄ ³⁵ ClF ₃ N ₂ O requires 424; 2.48*	2-chloro-N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-5-(trifluoromethyl)benzamide chiral

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73		PE	Found 369 (MH ⁺) C ₂₂ H ₂₈ N ₂ OS requires 368; 2.58*	N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-2-(methylthio)benzamide chiral
74		PE	Found 425 (MH ⁺) C ₂₁ H ₂₃ ³⁵ Cl ₃ N ₂ O requires 424; 2.93*	(±)-2,4,6-trichloro-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]benzamide
75		PE	Found 383 (MH ⁺) C ₂₃ H ₃₀ N ₂ O ₃ requires 382; 2.88*	N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-2,6-bis(methoxy)benzamide chiral
76		PE	Found 387 (MH ⁺) C ₂₂ H ₂₇ ³⁵ ClN ₂ O ₂ requires 386; 2.56*	2-chloro-N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-5-(methoxy)benzamide chiral
77		PE	Found 365 (MH ⁺) C ₂₄ H ₃₂ N ₂ O requires 364; 2.46*	(±)-2,4,6-trimethyl-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]benzamide
78		PE	Found 375 (MH ⁺) C ₂₁ H ₂₄ ³⁵ ClFN ₂ O requires 374; 2.99*	2-chloro-N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-3-fluorobenzamide chiral
79		PE	Found 351 (MH ⁺) C ₂₃ H ₃₀ N ₂ O requires 350; 2.96*	N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-2,4-dimethylbenzamide chiral

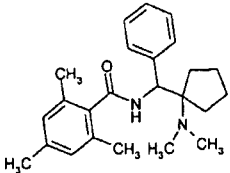
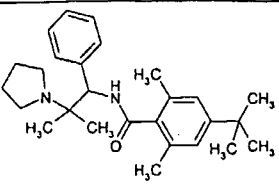
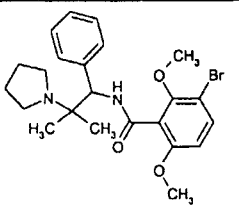
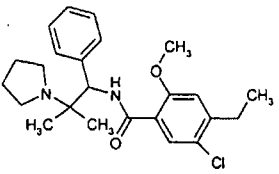
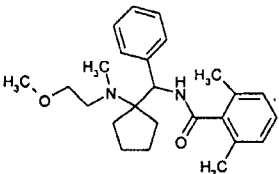
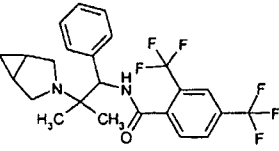
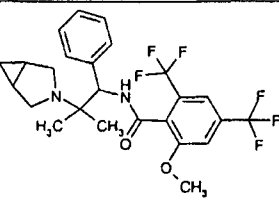
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80		E	Found 385 (MH ⁺) C ₂₃ H ₂₉ ³⁵ ClN ₂ O requires 384; 2.19	4-chloro-N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-2,6-dimethylbenzamide chiral
81		E	Found 385 (MH ⁺) C ₂₃ H ₂₉ ³⁵ ClN ₂ O requires 384; 2.07	4-chloro-2,6-dimethyl-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]benzamide chiral
82		E	Found 405 (MH ⁺) C ₂₃ H ₂₇ F ₃ N ₂ O requires 404; 1.91	N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-2-methyl-6-(trifluoromethyl)benzamide chiral
83		E	Found 405 (MH ⁺) C ₂₃ H ₂₇ F ₃ N ₂ O requires 404; 1.91	2-methyl-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]-6-(trifluoromethyl)benzamide chiral
84		A	Found 443 (MH ⁺) C ₂₄ H ₃₁ ⁷⁹ BrN ₂ O requires 442; 2.27	5-bromo-N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-2,3,4-trimethylbenzamide chiral
85		E	Found 379 (MH ⁺) C ₂₅ H ₃₄ N ₂ O requires 378; 2.07	N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-2,6-diethylbenzamide chiral

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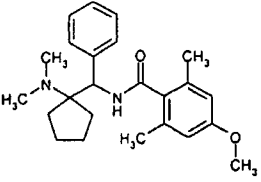
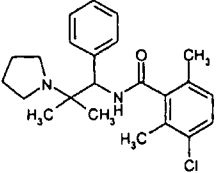
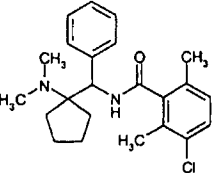
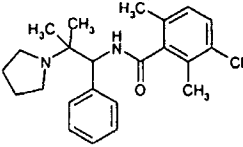
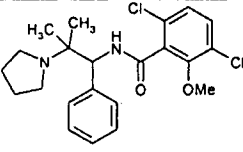
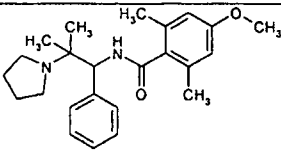
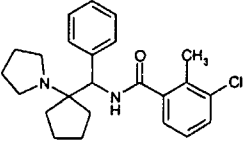
86		E	Found 365 (MH ⁺) C ₂₄ H ₃₂ N ₂ O requires 364; 2.06	N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-2,3,4-trimethylbenzamide chiral
87		E	Found 381 (MH ⁺) C ₂₄ H ₃₂ N ₂ O ₂ requires 380; 2.00	N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-2,5-dimethyl-4-(methyloxy)benzamide chiral
88		E	Found 381 (MH ⁺) C ₂₄ H ₃₂ N ₂ O ₂ requires 380; 1.96	N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-2,3-dimethyl-4-(methyloxy)benzamide chiral
89		E	Found 365 (MH ⁺) C ₂₄ H ₃₂ N ₂ O requires 364; 2.02	N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-2-(1-methylethyl)benzamide chiral
90		P	Found 413 (MH ⁺) C ₂₈ H ₃₂ N ₂ O requires 412;	(±)-N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-2-methyl-3-biphenylcarboxamide
91		P#	Found 459 (MH ⁺) C ₂₂ H ₂₃ ³⁵ Cl ₂ F ₃ N ₂ O requires 458; 2.11	2,6-dichloro-N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-3-(trifluoromethyl)benzamide chiral
92		H	Found 337 (MH ⁺) C ₂₂ H ₂₈ N ₂ O requires 336; 1.88	(±)-2,6-dimethyl-N-[[1-(methylamino)cyclopentyl](phenyl)methyl]benzamide

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93		P	Found 365 (MH ⁺) C ₂₄ H ₃₂ N ₂ O requires 364; 1.97	N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-2,4,6-trimethylbenzamide chiral
94		P	Found 407 (MH ⁺) C ₂₇ H ₃₈ N ₂ O requires 406; 2.34	(±)-4-(1,1-dimethylethyl)-2,6-dimethyl-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]benzamide
95		P	Found 461 (MH ⁺) C ₂₃ H ₂₉ ⁷⁹ BrN ₂ O ₃ requires 460; 1.98	(±)-3-bromo-2,6-bis(methoxy)-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]benzamide
96		P	Found 415 (MH ⁺) C ₂₄ H ₃₁ ³⁵ ClN ₂ O ₂ requires 414; 2.36	(±)-5-chloro-4-ethyl-2-(methoxy)-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]benzamide
97		A	Found 395 (MH ⁺) C ₂₅ H ₃₄ N ₂ O ₂ requires 394; 2.14	(±)-2,6-dimethyl-N-[(1-{methyl[2-(methoxy)ethyl]amino}cyclopentyl)(phenyl)methyl]benzamide
98		A	Found 471 (MH ⁺) C ₂₄ H ₂₄ F ₆ N ₂ O requires 470; 2.29	(±)-N-[2-(3-azabicyclo[3.1.0]hex-3-yl)-2-methyl-1-phenylpropyl]-2,4-bis(trifluoromethyl)benzamide
99		H	Found 501 (MH ⁺) C ₂₅ H ₂₆ F ₆ N ₂ O ₂ requires 500; 2.30	(±)-N-[2-(3-azabicyclo[3.1.0]hex-3-yl)-2-methyl-1-phenylpropyl]-2-(methoxy)-4,6-bis(trifluoromethyl)benzamide

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100		A	Found 363 (MH ⁺) C ₂₄ H ₃₀ N ₂ O requires 362; 1.94	(±)-N-[2-(3-azabicyclo[3.1.0]hex-3-yl)-2-methyl-1-phenylpropyl]-2,6-dimethylbenzamide
101		H	Found 375 (MH ⁺) C ₂₅ H ₃₀ N ₂ O requires 374; 1.94	(±)-N-[[1-(2,5-dihydro-1H-pyrrol-1-yl)cyclopentyl](phenyl)methyl]-2,6-dimethylbenzamide
102		H	Found 513 (MH ⁺) C ₂₆ H ₂₆ F ₆ N ₂ O ₂ requires 512; 2.35	(±)-N-[[1-(2,5-dihydro-1H-pyrrol-1-yl)cyclopentyl](phenyl)methyl]-2-(methoxy)-4,6-bis(trifluoromethyl)benzamide
103		H	Found 429 (MH ⁺) C ₂₃ H ₂₉ ⁷⁹ BrN ₂ O requires 428; 2.02	(±)-2-bromo-6-methyl-N-[2-methyl-1-phenyl-2-(1-piperidinyl)propyl]benzamide
104		H	Found 473 (MH ⁺) C ₂₄ H ₂₆ F ₆ N ₂ O requires 472; 2.18	(±)-N-[2-methyl-1-phenyl-2-(1-piperidinyl)propyl]-2,4-bis(trifluoromethyl)benzamide
105		H	Found 503 (MH ⁺) C ₂₅ H ₂₈ F ₆ N ₂ O ₂ requires 502; 2.28	(±)-2-(methoxy)-N-[2-methyl-1-phenyl-2-(1-piperidinyl)propyl]-4,6-bis(trifluoromethyl)benzamide
106		H	Found 365 (MH ⁺) C ₂₄ H ₃₂ N ₂ O requires 364; 1.88	(±)-2,6-dimethyl-N-[2-methyl-1-phenyl-2-(1-piperidinyl)propyl]benzamide
107		H	Found 405 (MH ⁺) C ₂₂ H ₂₆ ³⁵ Cl ₂ N ₂ O requires 404;	2,4-dichloro-6-methyl-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]benzamide

			2.10	e chiral
108		H	Found 381 (MH ⁺) C ₂₄ H ₃₂ N ₂ O ₂ requires 380; 1.89	<i>N</i> -[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-2,6-dimethyl-4-(methoxy)benzamide chiral
109		P	Found 385 (MH ⁺) C ₂₃ H ₂₉ ³⁵ ClN ₂ O requires 384; 2.11	3-chloro-2,6-dimethyl- <i>N</i> -[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]benzamide chiral
110		P	Found 385 (MH ⁺) C ₂₃ H ₂₉ ³⁵ ClN ₂ O requires 384; 2.12	3-chloro- <i>N</i> -[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-2,6-dimethylbenzamide chiral
111		H	Found 385 (MH ⁺) C ₂₃ H ₂₉ ³⁵ ClN ₂ O requires 384; 2.02	(±)-3-chloro-2,6-dimethyl- <i>N</i> -[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]benzamide
112		H	Found 421 (MH ⁺) C ₂₂ H ₂₆ ³⁵ Cl ₂ N ₂ O ₂ requires 420; 2.02	(±)-3,6-dichloro-2-(methoxy)- <i>N</i> -[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]benzamide
113		H	Found 381 (MH ⁺) C ₂₄ H ₃₂ N ₂ O ₂ requires 380; 1.86	(±)-2,6-dimethyl-4-(methoxy)- <i>N</i> -[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]benzamide
114		H	Found 397 (MH ⁺) C ₂₄ H ₂₉ ³⁵ ClN ₂ O requires 396; 2.13	(±)-3-chloro-2-methyl- <i>N</i> -{phenyl[1-(1-pyrrolidinyl)cyclopentyl]methyl}benzamide

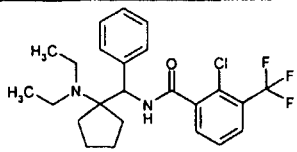
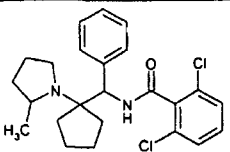
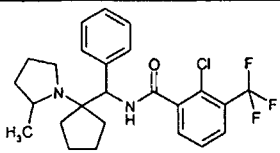
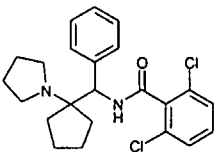
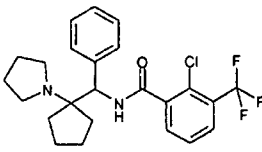
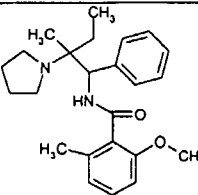
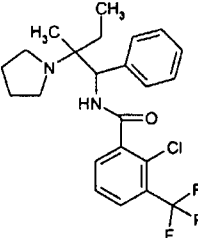
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115		H	Found 441 (MH ⁺) C ₂₄ H ₂₉ ⁷⁹ BrN ₂ O requires 440; 2.15	(±)-3-bromo-2-methyl-N- {phenyl[1-(1- pyrrolidinyl)cyclopentyl]meth yl}benzamide
116		H	Found 451 (MH ⁺) C ₂₃ H ₂₅ ³⁵ Cl ₃ N ₂ O requires 450; 2.14	(±)-2,4,6-trichloro-N- {phenyl[1-(1- pyrrolidinyl)cyclopentyl]meth yl}benzamide
117		H	Found 377 (MH ⁺) C ₂₅ H ₃₂ N ₂ O requires 376; 2.02	(±)-2,3-dimethyl-N-{phenyl[1- (1- pyrrolidinyl)cyclopentyl]meth yl}benzamide
118		H	Found 393 (MH ⁺) C ₂₅ H ₃₂ N ₂ O ₂ requires 392; 1.95	(±)-2-methyl-6-(methoxy)- N-{phenyl[1-(1- pyrrolidinyl)cyclopentyl]meth yl}benzamide
119		H	Found 391 (MH ⁺) C ₂₆ H ₃₄ N ₂ O requires 390; 2.08	(±)-2,4,6-trimethyl-N- {phenyl[1-(1- pyrrolidinyl)cyclopentyl]meth yl}benzamide
120		H	Found 443 (MH ⁺) C ₂₅ H ₃₁ ³⁵ ClN ₂ OS requires 442; 2.18	(±)-4-chloro-2-methyl-6- (methylthio)-N-{phenyl[1-(1- pyrrolidinyl)cyclopentyl]meth yl}benzamide
121		H	Found 397 (MH ⁺) C ₂₄ H ₂₉ ³⁵ ClN ₂ O requires 396; 2.08	(±)-2-chloro-6-methyl-N- {phenyl[1-(1- pyrrolidinyl)cyclopentyl]meth yl}benzamide
122		H	Found 413 (MH ⁺) C ₂₄ H ₂₉ ³⁵ ClN ₂ O ₂ requires 412; 1.92	(±)-2-chloro-6-(methoxy)- N-{phenyl[1-(1- pyrrolidinyl)cyclopentyl]meth yl}benzamide

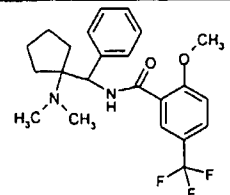
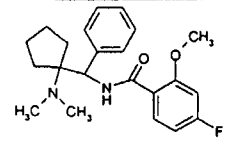
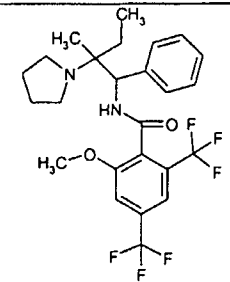
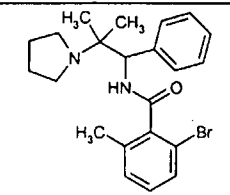
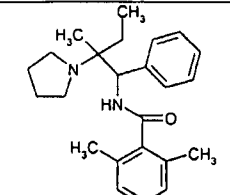
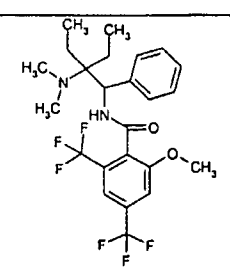
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123		H	Found 441 (MH ⁺) C ₂₄ H ₂₉ ⁷⁹ BrN ₂ O requires 440; 1.97	(±)-2-bromo-6-methyl-N-{phenyl[1-(1-pyrrolidinyl)cyclopentyl]methyl}benzamide
124		H	Found 379 (MH ⁺) C ₂₄ H ₃₀ N ₂ O ₂ requires 378; 1.97	(±)-N-[[1-(1-azetidiny)cyclopentyl](phenyl)methyl]-2-methyl-6-(methoxy)benzamide
125		A	Found 363 (MH ⁺) C ₂₄ H ₃₀ N ₂ O requires 362; 1.99	(±)-N-[[1-(1-azetidiny)cyclopentyl](phenyl)methyl]-2,3-dimethylbenzamide
126		A	Found 363 (MH ⁺) C ₂₄ H ₃₀ N ₂ O requires 362; 1.90	(±)-N-[[1-(1-azetidiny)cyclopentyl](phenyl)methyl]-2,6-dimethylbenzamide
127		A	Found 391 (MH ⁺) C ₂₆ H ₃₄ N ₂ O requires 390; 2.06	(±)-2,6-dimethyl-N-[[1-(2-methyl-1-pyrrolidinyl)cyclopentyl](phenyl)methyl]benzamide
128		A	Found 379 (MH ⁺) C ₂₅ H ₃₄ N ₂ O requires 378; 2.04	(±)-N-[[1-(diethylamino)cyclopentyl](phenyl)methyl]-2,6-dimethylbenzamide
129		A	Found 377 (MH ⁺) C ₂₅ H ₃₂ N ₂ O requires 376; 1.90	(±)-2,6-dimethyl-N-{phenyl[1-(1-pyrrolidinyl)cyclopentyl]methyl}benzamide
130		H	Found 419 (MH ⁺) C ₂₃ H ₂₈ ³⁵ Cl ₂ N ₂ O requires 418; 2.15	(±)-2,6-dichloro-N-[[1-(diethylamino)cyclopentyl](phenyl)methyl]benzamide

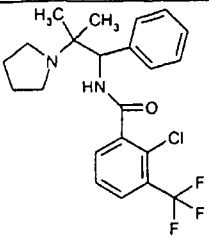
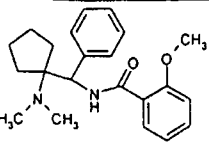
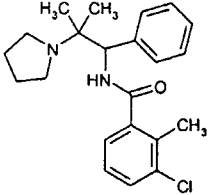
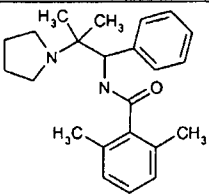
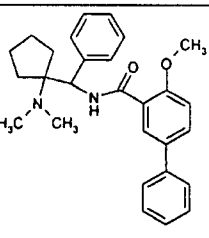
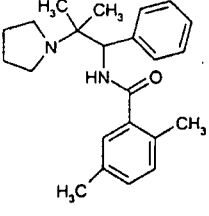
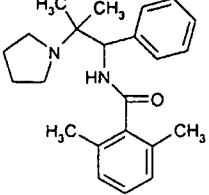
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131		H	Found 453 (MH ⁺) C ₂₄ H ₂₈ ³⁵ ClF ₃ N ₂ O requires 452; 2.25	(±)-2-chloro-N-[[1-(diethylamino)cyclopentyl](phenyl)methyl]-3-(trifluoromethyl)benzamide
132		H	Found 431 (MH ⁺) C ₂₄ H ₂₈ ³⁵ Cl ₂ N ₂ O requires 430; 1.93	(±)-2,6-dichloro-N-[[1-(2-methyl-1-pyrrolidinyl)cyclopentyl](phenyl)methyl]benzamide
133		H	Found 465 (MH ⁺) C ₂₅ H ₂₈ ³⁵ ClF ₃ N ₂ O requires 464; 2.15	(±)-2-chloro-N-[[1-(2-methyl-1-pyrrolidinyl)cyclopentyl](phenyl)methyl]-3-(trifluoromethyl)benzamide
134		H	Found 417 (MH ⁺) C ₂₃ H ₂₆ ³⁵ Cl ₂ N ₂ O requires 416; 1.99	(±)-2,6-dichloro-N-{phenyl[1-(1-pyrrolidinyl)cyclopentyl]methyl}benzamide
135		H	Found 451 (MH ⁺) C ₂₄ H ₂₆ ³⁵ ClF ₃ N ₂ O requires 450	(±)-2-chloro-N-{phenyl[1-(1-pyrrolidinyl)cyclopentyl]methyl}-3-(trifluoromethyl)benzamide
136		E	Found 381 (MH ⁺) C ₂₄ H ₃₂ N ₂ O ₂ requires 380; 1.83 & 1.87	(±)-2-methyl-6-(methoxy)-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)butyl]benzamide
137		A	Found 439 (MH ⁺) C ₂₃ H ₂₆ ³⁵ ClF ₃ N ₂ O requires 438; 2.11 & 2.17.	(±)-2-chloro-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)butyl]-3-(trifluoromethyl)benzamide

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138		P	Found 421 (MH ⁺) C ₂₃ H ₂₇ F ₃ N ₂ O ₂ requires 420; 2.19.	(±)-N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-2-(methoxy)-5-(trifluoromethyl)benzamide
139		P	Found 371 (MH ⁺) C ₂₂ H ₂₇ FN ₂ O ₂ requires 370; 1.99.	(±)-N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-4-fluoro-2-(methoxy)benzamide
140		E	Found 503 (MH ⁺) C ₂₅ H ₂₈ F ₆ N ₂ O ₂ requires 502; 2.23 & 2.27.	(±)-2-(methoxy)-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)butyl]-4,6-bis(trifluoromethyl)benzamide
141		E	Found 415 (MH ⁺) C ₂₂ H ₂₇ ⁷⁹ BrN ₂ O requires 414; 1.84.	2-bromo-6-methyl-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]benzamide chiral
142		A	Found 365 (MH ⁺) C ₂₄ H ₃₂ N ₂ O requires 364; 1.86 & 1.94.	(±)-2,6-dimethyl-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)butyl]benzamide
143		E	Found 491 (MH ⁺) C ₂₄ H ₂₈ F ₆ N ₂ O ₂ requires 490; 2.26.	(±)-N-[2-(dimethylamino)-2-ethyl-1-phenylbutyl]-2-(methoxy)-4,6-bis(trifluoromethyl)benzamide

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144		P	Found 425 (MH ⁺) C ₂₂ H ₂₄ ³⁵ ClF ₃ N ₂ O requires 424; 2.0.	(±)-2-chloro-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]-3-(trifluoromethyl)benzamide
145		P	Found 353 (MH ⁺) C ₂₂ H ₂₈ N ₂ O ₂ requires 352; 1.93 .	(±)-N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-2-(methoxy)benzamide
146		E	Found 371 (MH ⁺) C ₂₂ H ₂₇ ³⁵ ClN ₂ O requires 370; 1.98 .	3-chloro-2-methyl-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]benzamide chiral
147		E	Found 351 (MH ⁺) C ₂₃ H ₃₀ N ₂ O requires 350; 1.89 .	2,6-dimethyl-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]benzamide chiral
148		P	Found 429 (MH ⁺) C ₂₈ H ₃₂ N ₂ O ₂ requires 428; 2.32 .	(±)-N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-4-(methoxy)-3-biphenylcarboxamide
149		E	Found 351 (MH ⁺) C ₂₃ H ₃₀ N ₂ O requires 350; 1.94 .	2,5-dimethyl-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]benzamide chiral
150		P	Found 351 (MH ⁺) C ₂₃ H ₃₀ N ₂ O requires 350 1.80 .	(±)-2,6-dimethyl-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]benzamide

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151		E	Found 365 (MH ⁺) C ₂₄ H ₃₂ N ₂ O requires 364; 1.88 .	2,4,6-trimethyl-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]benzamide chiral
152		E	Found 387 (MH ⁺) C ₂₂ H ₂₇ ³⁵ ClN ₂ O ₂ requires 386; 1.84 .	2-chloro-6-(methoxy)-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]benzamide chiral
153		E	Found 499 (MH ⁺) C ₂₃ H ₂₆ ⁷⁹ BrF ₃ N ₂ O ₂ requires 498; 2.28 .	3-bromo-2-(methoxy)-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]-5-(trifluoromethyl)benzamide chiral
154		E	Found 365 (MH ⁺) C ₂₄ H ₃₂ N ₂ O requires 364; 2.00 .	(±)-2,6-dimethyl-N-[2-methyl-2-(2-methyl-1-pyrrolidinyl)-1-phenylpropyl]benzamide
155		E	Found 405 (MH ⁺) C ₂₃ H ₂₇ F ₃ N ₂ O requires 404; 2.19 .	2-methyl-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]-5-(trifluoromethyl)benzamide chiral
156		E	Found 415 (MH ⁺) C ₂₂ H ₂₇ ⁷⁹ BrN ₂ O requires 414; 2.12	3-bromo-2-methyl-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]benzamide chiral
157		E	Found 355 (MH ⁺) C ₂₂ H ₂₇ FN ₂ O requires 354; 1.96 .	3-fluoro-2-methyl-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]benzamide chiral

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158		E	Found 425 (MH ⁺) C ₂₁ H ₂₃ ³⁵ Cl ₃ N ₂ O requires 424; 2.11 .	2,4,6-trichloro- <i>N</i> -[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]benzamide chiral
159		E	Found 517 (MH ⁺) C ₂₆ H ₃₀ F ₆ N ₂ O ₂ requires 516; 2.32 .	(±)- <i>N</i> -[2-ethyl-1-phenyl-2-(1-pyrrolidinyl)butyl]-2-(methoxy)-4,6-bis(trifluoromethyl)benzamide
160		E	Found 365 (MH ⁺) C ₂₄ H ₃₂ N ₂ O requires 364; 1.96 .	(±)-2,6-dimethyl- <i>N</i> -[2-methyl-2-(2-methyl-1-pyrrolidinyl)-1-phenylpropyl]benzamide
161		E	Found 371 (MH ⁺) C ₂₂ H ₂₇ ³⁵ ClN ₂ O requires 370; 1.89 .	2-chloro-3-methyl- <i>N</i> -[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]benzamide chiral
162		E	Found 445 (MH ⁺) C ₂₃ H ₂₉ ⁷⁹ BrN ₂ O ₂ requires 444; 2.15	5-bromo-3-methyl-2-(methoxy)- <i>N</i> -[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]benzamide chiral
163		P	Found 407 (MH ⁺) C ₂₂ H ₂₅ F ₃ N ₂ O ₂ requires 406; 2.05 .	(±)- <i>N</i> -[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-2-[(trifluoromethyl)oxy]benzamide
164		P	Found 387 (MH ⁺) C ₂₂ H ₂₇ ³⁵ ClN ₂ O ₂ requires 386; 2.10 .	(±)-4-chloro- <i>N</i> -[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-2-(methoxy)benzamide

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165		E	Found 503 (MH ⁺) C ₂₅ H ₂₈ F ₆ N ₂ O ₂ requires 502; 2.21 .	2-(ethoxy)-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]-4,6-bis(trifluoromethyl)benzamide e chiral
166		A	Found 339 (MH ⁺) C ₂₂ H ₃₀ N ₂ O requires 338; 1.75 .	(±)-N-[2-(dimethylamino)-2-methyl-1-phenylbutyl]-2,6-dimethylbenzamide
167		PE	Found 463 (MH ⁺) C ₂₃ H ₂₈ ⁷⁹ BrFN ₂ O ₂ requires 462; 2.44* .	(±)-6-bromo-2-fluoro-N-[2-methyl-2-(2-methyl-1-pyrrolidinyl)-1-phenylpropyl]-3-(methoxy)benzamide
168		P	Found 339 (MH ⁺) C ₂₂ H ₃₀ N ₂ O requires 338; 1.71 & 1.76 .	(±)-N-[2-(dimethylamino)-2-methyl-1-phenylbutyl]-2,6-dimethylbenzamide
169		E	Found 367 (MH ⁺) C ₂₄ H ₃₄ N ₂ O requires 366; 1.87 .	(±)-N-[2-(dimethylamino)-2-ethyl-1-phenylbutyl]-2,4,6-trimethylbenzamide
170		E	Found 373 (MH ⁺) C ₂₂ H ₂₉ ³⁵ ClN ₂ O requires 372; 1.85 .	(±)-3-chloro-N-[2-(dimethylamino)-2-ethyl-1-phenylbutyl]-2-methylbenzamide
171		E	Found 393 (MH ⁺) C ₂₆ H ₃₆ N ₂ O requires 392; 2.02 .	(±)-N-[2-ethyl-1-phenyl-2-(1-pyrrolidinyl)butyl]-2,4,6-trimethylbenzamide
172		E	Found 425 (MH ⁺) C ₂₁ H ₂₃ ³⁵ Cl ₃ N ₂ O requires 424; 2.25 .	(±)-2,3,6-trichloro-N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]benzamide

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173		E	Found 503 (MH ⁺) C ₂₅ H ₂₈ F ₆ N ₂ O ₂ requires 502; 2.18 .	N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-2-(ethoxy)-4,6-bis(trifluoromethyl)benzamide chiral
174		E	Found 399 (MH ⁺) C ₂₄ H ₃₁ ³⁵ ClN ₂ O requires 398; 2.12 .	(±)-3-chloro-N-[2-ethyl-1-(pyrrolidinyl)butyl]-2-phenyl-2-methylbenzamide
175		E	Found 417 (MH ⁺) C ₂₂ H ₂₉ ⁷⁹ BrN ₂ O requires 416; 1.81 .	(±)-2-bromo-N-[2-(dimethylamino)-2-ethyl-1-phenylbutyl]-6-methylbenzamide
176		A	Found 339 (MH ⁺) C ₂₂ H ₃₀ N ₂ O requires 338; 1.63 .	(±)-N-[2-(dimethylamino)-2-methyl-1-phenylbutyl]-2,6-dimethylbenzamide
177		P	Found 393 (MH ⁺) C ₂₂ H ₂₇ F ₃ N ₂ O requires 392; 1.95 & 2.03 .	(±)-N-[2-(dimethylamino)-2-methyl-1-phenylbutyl]-2-methyl-5-(trifluoromethyl)benzamide
178		E	Found 395 (MH ⁺) C ₂₅ H ₃₄ N ₂ O ₂ requires 394; 1.86 .	(±)-N-[2-ethyl-1-phenyl-2-(1-pyrrolidinyl)butyl]-2-methyl-6-(methoxy)benzamide
179		A	Found 379 (MH ⁺) C ₂₅ H ₃₄ N ₂ O requires 378; 1.89 .	(±)-N-[2-ethyl-1-phenyl-2-(1-pyrrolidinyl)butyl]-2,6-dimethylbenzamide
180		P	Found 339 (MH ⁺) C ₂₂ H ₃₀ N ₂ O requires 388; 1.90 .	N-[2-(dimethylamino)-2-methyl-1-phenylbutyl]-2,3-dimethylbenzamide chiral

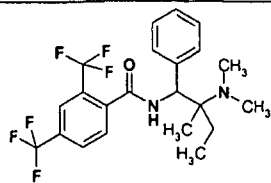
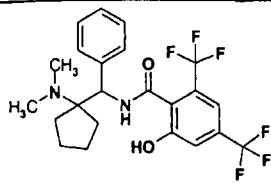
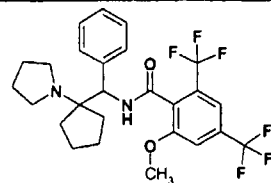
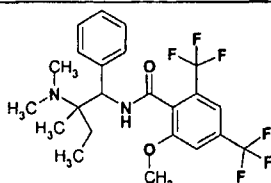
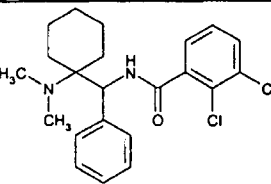
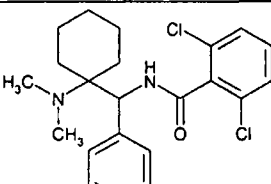
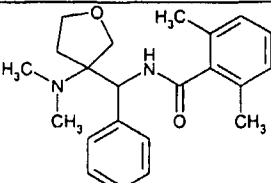
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181		E	Found 443 (MH ⁺) C ₂₄ H ₃₁ ⁷⁹ BrN ₂ O requires 442; 2.00 .	(±)-2-bromo-N-[2-ethyl-1-phenyl-2-(1-pyrrolidinyl)butyl]-6-methylbenzamide
182		A	Found 353 (MH ⁺) C ₂₃ H ₃₂ N ₂ O requires 352; 1.82 .	(±)-N-[2-(dimethylamino)-2-ethyl-1-phenylbutyl]-2,6-dimethylbenzamide
183		P	Found 359 (MH ⁺) C ₂₁ H ₂₇ ³⁵ ClN ₂ O requires 358; 1.88 & 1.91.	(±)-2-chloro-N-[2-(dimethylamino)-2-methyl-1-phenylbutyl]-6-methylbenzamide
184		P	Found 413 (MH ⁺) C ₂₁ H ₂₄ ³⁵ ClF ₃ N ₂ O requires 412; 2.09 & 2.21.	(±)-2-chloro-N-[2-(dimethylamino)-2-methyl-1-phenylbutyl]-3-(trifluoromethyl)benzamide
185		E	Found 433 (MH ⁺) C ₂₅ H ₃₁ F ₃ N ₂ O requires 432; 2.20 .	(±)-N-[2-ethyl-1-phenyl-2-(1-pyrrolidinyl)butyl]-2-methyl-5-(trifluoromethyl)benzamide
186		E	Found 369 (MH ⁺) C ₂₃ H ₃₂ N ₂ O ₂ requires 368; 1.74 .	(±)-N-[2-(dimethylamino)-2-ethyl-1-phenylbutyl]-2-methyl-6-(methoxy)benzamide
187		P	Found 467 (MH ⁺) C ₂₇ H ₂₈ ³⁵ Cl ₂ N ₂ O requires 466; 2.3	(±)-3',5-dichloro-N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-2-biphenylcarboxamide
188		E	Found 407 (MH ⁺) C ₂₃ H ₂₉ F ₃ N ₂ O requires 406; 2.08 .	(±)-N-[2-(dimethylamino)-2-ethyl-1-phenylbutyl]-2-methyl-5-(trifluoromethyl)benzamide

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189		P	Found 433 (MH ⁺) C ₂₇ H ₂₉ ³⁵ ClN ₂ O requires 432; 2.0	(±)-3'-chloro-N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-2-biphenylcarboxamide
190		P	Found 421 (MH ⁺) C ₂₂ H ₂₆ ³⁵ Cl ₂ N ₂ O ₂ requires 420; 2.12	(±)-3,5-dichloro-N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-2-(methoxy)benzamide
191		P	Found 468 (MH ⁺) C ₂₇ H ₂₈ ³⁵ Cl ₂ N ₂ O requires 467; 2.3	(±)-3',4-dichloro-N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-2-biphenylcarboxamide
192		A	Found 473 (MH ⁺) C ₂₄ H ₂₈ F ₆ N ₂ O requires 472; 1.97 .	(±)-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)butyl]-2,6-bis(trifluoromethyl)benzamide
193		A	Found 459(MH ⁺) C ₂₃ H ₂₄ F ₆ N ₂ O Requires 458; 2.20	N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-2,4-bis(trifluoromethyl)benzamide chiral
194		A	Found 459(MH ⁺) C ₂₃ H ₂₄ F ₆ N ₂ O Requires 458; 2.21	N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]-2,4-bis(trifluoromethyl)benzamide chiral
195		A	Found 471(MH ⁺) C ₂₄ H ₂₄ F ₆ N ₂ O Requires 470; 2.24	(±)-N-[[1-(1-azetidiny)cyclopentyl](phenyl)methyl]-2,4-bis(trifluoromethyl)benzamide
196		A	Found 485(MH ⁺) C ₂₅ H ₂₆ F ₆ N ₂ O Requires 484; 2.28	(±)-N-{phenyl[1-(1-pyrrolidinyl)cyclopentyl]methyl}-2,4-bis(trifluoromethyl)benzamide

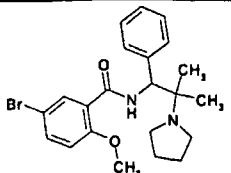
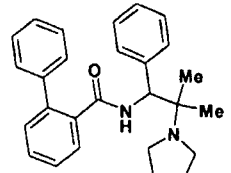
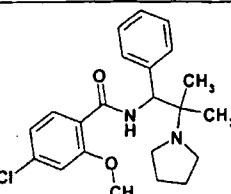
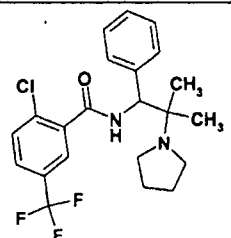
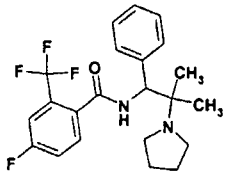
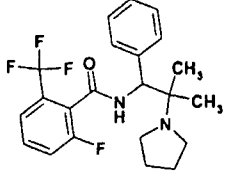
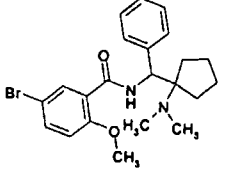
123

197		A	Found 447(MH ⁺) C ₂₂ H ₂₄ F ₆ N ₂ O Requires 446; 2.16	(±)-N-[2-(dimethylamino)-2-methyl-1-phenylbutyl]-2,4-bis(trifluoromethyl)benzamide
198		A	Found 475(MH ⁺) C ₂₃ H ₂₄ F ₆ N ₂ O ₂ Requires 475; 1.97	N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-2-hydroxy-4,6-bis(trifluoromethyl)benzamide chiral
199		P	Found 515(MH ⁺) C ₂₆ H ₂₈ F ₆ N ₂ O ₂ Requires 514; 2.33	(±)-2-(methoxy)-N-{phenyl[1-(1-pyrrolidinyl)cyclopentyl]methyl}-4,6-bis(trifluoromethyl)benzamide
200		P	Found 477(MH ⁺) C ₂₃ H ₂₆ F ₆ N ₂ O ₂ Requires 476; 2.21	(±)-N-[2-(dimethylamino)-2-methyl-1-phenylbutyl]-2-(methoxy)-4,6-bis(trifluoromethyl)benzamide
201		P	Found 439 (MH ⁺) C ₂₃ H ₂₆ ³⁵ ClF ₃ N ₂ O requires 438; 2.16.	(±)-2-chloro-N-[[1-(dimethylamino)cyclohexyl](p-phenyl)methyl]-3-(trifluoromethyl)benzamide
202		P	Found 405 (MH ⁺) C ₂₂ H ₂₆ ³⁵ Cl ₂ N ₂ O requires 404; 1.90.	(±)-2,6-dichloro-N-[[1-(dimethylamino)cyclohexyl](p-phenyl)methyl]benzamide
203		P	Found 353 (MH ⁺) C ₂₂ H ₂₈ N ₂ O ₂ requires 352; 1.70 and 1.72.	(±)-N-[[3-(dimethylamino)tetrahydro-3-furanyl](phenyl)methyl]-2,6-dimethylbenzamide

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204		P	Found 369 (MH ⁺) C ₂₂ H ₂₈ N ₂ O ₃ requires 368; 1.75 and 1.77.	(±)-N-[[3-(dimethylamino)tetrahydro-3-furanyl](phenyl)methyl]-2-methoxybenzamide
205		P	Found 427 (MH ⁺) C ₂₁ H ₂₂ ³⁵ ClF ₃ N ₂ O ₂ requires 426; 1.94 and 1.96.	(±)-2-chloro-N-[[3-(dimethylamino)tetrahydro-3-furanyl](phenyl)methyl]-3-(trifluoromethyl)benzamide
206		P	Found 353 (MH ⁺) C ₂₂ H ₂₈ N ₂ O ₂ requires 352; 1.74 and 1.76.	(±)-N-[[3-(dimethylamino)tetrahydro-3-furanyl](phenyl)methyl]-2,3-dimethylbenzamide
207		A	Found 459 (MH ⁺) C ₂₃ H ₂₄ F ₆ N ₂ O requires 458; 1.97.	N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-2,6-bis(trifluoromethyl)benzamide chiral
208		A	Found 459 (MH ⁺) C ₂₃ H ₂₄ F ₆ N ₂ O requires 458; 1.92.	N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]-2,6-bis(trifluoromethyl)benzamide chiral
209		A	Found 473 (MH ⁺) C ₂₄ H ₂₆ F ₆ N ₂ O requires 472; 2.05 & 2.09.	(±)-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)butyl]-2,6-bis(trifluoromethyl)benzamide
210		PE	Found 421 (MH ⁺) C ₂₂ H ₂₆ ³⁵ Cl ₂ N ₂ O ₂ requires 420; 2.53*.	(±)-3,5-dichloro-2-(methoxy)-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]benzamide

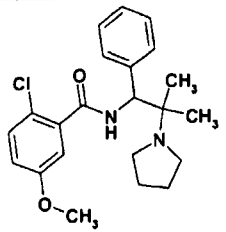
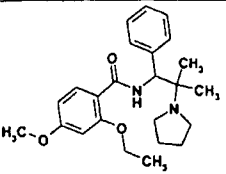
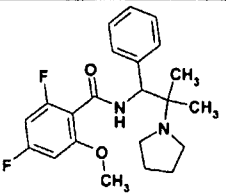
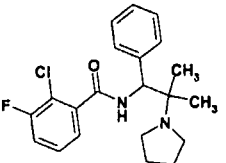
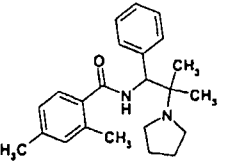
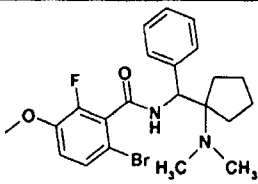
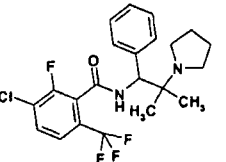
125

211		PE	Found 431 (MH ⁺) C ₂₂ H ₂₇ ⁷⁹ BrN ₂ O ₂ requires 430; 2.57*.	(±)-5-bromo-2-(methoxy)- N-[2-methyl-1-phenyl-2-(1- pyrrolidinyl)propyl]benzamid e
212		PE	Found 399 (MH ⁺) C ₂₇ H ₃₀ N ₂ O requires 398; 2.47*.	(±)-N-[2-methyl-1-phenyl-2- (1-pyrrolidinyl)propyl]-2- biphenylcarboxamide
213		PE	Found 387 (MH ⁺) C ₂₂ H ₂₇ ³⁵ ClN ₂ O ₂ requires 386; 2.49*.	(±)-4-chloro-2-(methoxy)- N-[2-methyl-1-phenyl-2-(1- pyrrolidinyl)propyl]benzamid e
214		PE	Found 425 (MH ⁺) C ₂₂ H ₂₄ ³⁵ ClF ₃ N ₂ O requires 424; 2.45*.	(±)-2-chloro-N-[2-methyl-1- phenyl-2-(1- pyrrolidinyl)propyl]-5- (trifluoromethyl)benzamide
215		PE	Found 409 (MH ⁺) C ₂₂ H ₂₄ F ₄ N ₂ O requires 408; 2.39*.	(±)-4-fluoro-N-[2-methyl-1- phenyl-2-(1- pyrrolidinyl)propyl]-2- (trifluoromethyl)benzamide
216		PE	Found 409 (MH ⁺) C ₂₂ H ₂₄ F ₄ N ₂ O requires 408; 2.56*.	(±)-2-fluoro-N-[2-methyl-1- phenyl-2-(1- pyrrolidinyl)propyl]-6- (trifluoromethyl)benzamide
217		PE	Found 431 (MH ⁺) C ₂₂ H ₂₇ ⁷⁹ BrN ₂ O ₂ requires 430; 2.54*.	5-bromo-N-[[1- (dimethylamino)cyclopentyl](phenyl)methyl]-2- (methoxy)benzamide chiral

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218		PE	Found 387 (MH ⁺) C ₂₂ H ₂₇ ³⁵ ClN ₂ O ₂ requires 386; 2.54*.	4-chloro- <i>N</i> -[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-2-(methoxy)benzamide chiral
219		PE	Found 409 (MH ⁺) C ₂₂ H ₂₄ F ₄ N ₂ O requires 408; 2.47*.	<i>N</i> -[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-2-fluoro-6-(trifluoromethyl)benzamide chiral
220		PE	Found 459 (MH ⁺) C ₂₄ H ₃₁ ⁷⁹ BrN ₂ O ₂ requires 458; 2.81*.	(±)-5-bromo-4-ethyl-2-(methoxy)- <i>N</i> -[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]benzamide
221		PE	Found 421 (MH ⁺) C ₂₃ H ₂₇ F ₃ N ₂ O ₂ requires 420; 2.63*.	(±)-2-(methoxy)- <i>N</i> -[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]-3-(trifluoromethyl)benzamide
222		PE	Found 381 (MH ⁺) C ₂₄ H ₃₂ N ₂ O ₂ requires 380; 2.52*.	(±)-3,5-dimethyl-2-(methoxy)- <i>N</i> -[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]benzamide
223		PE	Found 383 (MH ⁺) C ₂₃ H ₃₀ N ₂ O ₃ requires 382; 2.77*.	(±)-2,6-bis(methoxy)- <i>N</i> -[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]benzamide
224		PE	Found 415 (MH ⁺) C ₂₄ H ₃₁ ³⁵ ClN ₂ O ₂ requires 414; 3.05*.	(±)-4-chloro- <i>N</i> -[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]-2-(propyloxy)benzamide

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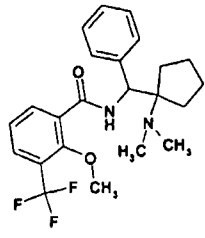
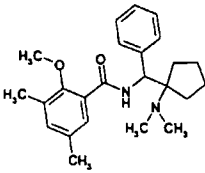
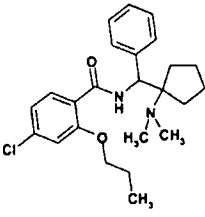
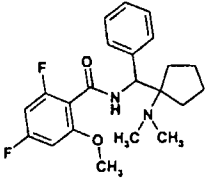
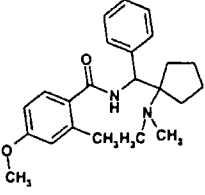
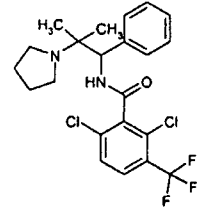
225		PE	Found 387 (MH ⁺) C ₂₂ H ₂₇ ³⁵ ClN ₂ O ₂ requires 386; 2.53*.	(±)-2-chloro-5-(methoxy)- <i>N</i> -[2-methyl-1-phenyl-2-(1- pyrrolidinyl)propyl]benzamid e
226		PE	Found 397 (MH ⁺) C ₂₄ H ₃₂ N ₂ O ₃ requires 396; 2.58*.	(±)-2-(ethoxy)-4- (methoxy)- <i>N</i> -[2-methyl-1- phenyl-2-(1- pyrrolidinyl)propyl]benzamid e
227		PE	Found 389 (MH ⁺) C ₂₂ H ₂₆ F ₂ N ₂ O ₂ requires 388; 2.47*.	(±)-2,4-difluoro-6- (methoxy)- <i>N</i> -[2-methyl-1- phenyl-2-(1- pyrrolidinyl)propyl]benzamid e
228		PE	Found 375 (MH ⁺) C ₂₁ H ₂₄ ³⁵ ClFN ₂ O requires 374; 2.86*.	(±)-2-chloro-3-fluoro- <i>N</i> -[2- methyl-1-phenyl-2-(1- pyrrolidinyl)propyl]benzamid e
229		PE	Found 351 (MH ⁺) C ₂₃ H ₃₀ N ₂ O requires 350; 2.84*.	(±)-2,4-dimethyl- <i>N</i> -[2-methyl- 1-phenyl-2-(1- pyrrolidinyl)propyl]benzamid e
230		PE	Found 449 (MH ⁺) C ₂₂ H ₂₆ ⁷⁹ BrFN ₂ O ₂ requires 448; 2.45*	6-bromo- <i>N</i> -[[1- (dimethylamino)cyclopentyl](phenyl)methyl]-2-fluoro-3- (methoxy)benzamide chiral
231		PE	Found 443 (MH ⁺) C ₂₂ H ₂₃ ³⁵ ClF ₄ N ₂ O requires 442; 2.94*.	(±)-3-chloro-2-fluoro- <i>N</i> -[2- methyl-1-phenyl-2-(1- pyrrolidinyl)propyl]-6- (trifluoromethyl)benzamide

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232		P	Found 337 (MH ⁺) C ₂₂ H ₂₈ N ₂ O requires 336; 1.86.	(±)-N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-2-methylbenzamide
233		A	Found 517 (MH ⁺) C ₂₆ H ₃₀ F ₆ N ₂ O ₂ requires 516; 2.32.	(±)-N-[2-(hexahydro-1H-azepin-1-yl)-2-methyl-1-phenylpropyl]-2-(methoxy)-4,6-bis(trifluoromethyl)benzamide
234		A	Found 453 (MH ⁺) C ₂₄ H ₂₈ ³⁵ ClF ₃ N ₂ O requires 452; 2.21.	(±)-2-chloro-N-[2-(hexahydro-1H-azepin-1-yl)-2-methyl-1-phenylpropyl]-3-(trifluoromethyl)benzamide
235		PE	Found 401 (MH ⁺) C ₂₃ H ₂₉ ³⁵ ClN ₂ O ₂ requires 400; 2.48*.	(±)-2-chloro-N-[2-methyl-2-(2-methyl-1-pyrrolidinyl)-1-phenylpropyl]-6-(methoxy)benzamide
236		PE	Found 397 (MH ⁺) C ₂₄ H ₃₂ N ₂ O ₃ requires 396; 2.79*.	(±)-N-[2-methyl-2-(2-methyl-1-pyrrolidinyl)-1-phenylpropyl]-2,6-bis(methoxy)benzamide
237		PE	Found 401 (MH ⁺) C ₂₃ H ₂₉ ³⁵ ClN ₂ O ₂ requires 400; 2.53*.	(±)-2-chloro-N-[2-methyl-2-(2-methyl-1-pyrrolidinyl)-1-phenylpropyl]-5-(methoxy)benzamide
238		PE	Found 403 (MH ⁺) C ₂₃ H ₂₈ F ₂ N ₂ O ₂ requires 402; 2.52*.	(±)-2,4-difluoro-N-[2-methyl-2-(2-methyl-1-pyrrolidinyl)-1-phenylpropyl]-6-(methoxy)benzamide

239		PE	Found 389 (MH ⁺) C ₂₂ H ₂₆ ³⁵ ClFN ₂ O requires 388; 2.89*.	(±)-2-chloro-3-fluoro-N-[2-methyl-2-(2-methyl-1-pyrrolidinyl)-1-phenylpropyl]benzamide
240		PE	Found 365 (MH ⁺) C ₂₄ H ₃₂ N ₂ O requires 364; 2.66*.	(±)-2,5-dimethyl-N-[2-methyl-2-(2-methyl-1-pyrrolidinyl)-1-phenylpropyl]benzamide
241		PE	Found 365 (MH ⁺) C ₂₄ H ₃₂ N ₂ O requires 364; 2.94*.	(±)-2,4-dimethyl-N-[2-methyl-2-(2-methyl-1-pyrrolidinyl)-1-phenylpropyl]benzamide
242		PE	Found 379 (MH ⁺) C ₂₅ H ₃₄ N ₂ O requires 378; 2.5*.	(±)-2,4,6-trimethyl-N-[2-methyl-2-(2-methyl-1-pyrrolidinyl)-1-phenylpropyl]benzamide
243		PE	Found 439 (MH ⁺) C ₂₂ H ₂₅ ³⁵ Cl ₃ N ₂ O requires 438; 2.91*.	(±)-2,4,6-trichloro-N-[2-methyl-2-(2-methyl-1-pyrrolidinyl)-1-phenylpropyl]benzamide
244		PE	Found 381 (MH ⁺) C ₂₄ H ₃₂ N ₂ O ₂ requires 380; 2.84*.	(±)-2-methyl-N-[2-methyl-2-(2-methyl-1-pyrrolidinyl)-1-phenylpropyl]-4-(methoxy)benzamide
245		PE	Found 457 (MH ⁺) C ₂₃ H ₂₅ ³⁵ ClF ₄ N ₂ O requires 456; 2.97*.	(±)-3-chloro-2-fluoro-N-[2-methyl-2-(2-methyl-1-pyrrolidinyl)-1-phenylpropyl]-6-(trifluoromethyl)benzamide
246		PE	Found 459 (MH ⁺) C ₂₄ H ₃₁ ⁷⁹ BrN ₂ O ₂ requires 458; 2.84*.	5-bromo-N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-4-ethyl-2-(methoxy)benzamide chiral

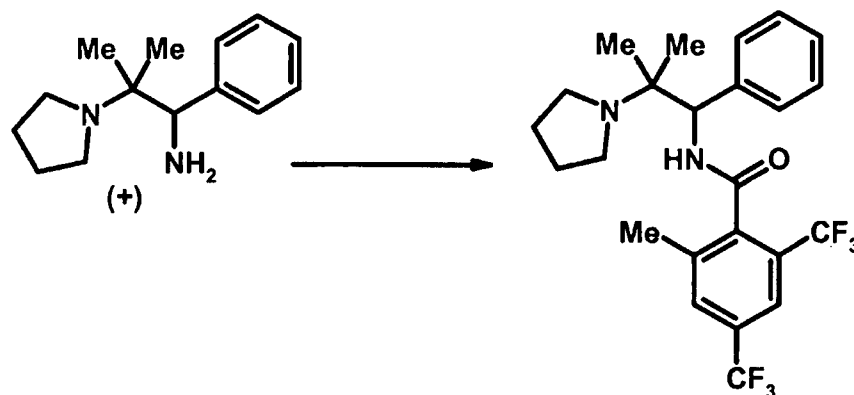
130

247		PE	Found 421 (MH ⁺) C ₂₃ H ₂₇ F ₃ N ₂ O ₂ requires 420; 2.67*.	<i>N</i> -[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-2-(methoxy)-3-(trifluoromethyl)benzamide chiral
248		PE	Found 381 (MH ⁺) C ₂₄ H ₃₂ N ₂ O ₂ requires 380; 2.54*.	<i>N</i> -[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-3,5-dimethyl-2-(methoxy)benzamide chiral
249		PE	Found 415 (MH ⁺) C ₂₄ H ₃₁ ³⁵ ClN ₂ O ₂ requires 414; 3.21*.	4-chloro- <i>N</i> -[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-2-(propyloxy)benzamide chiral
250		PE	Found 389 (MH ⁺) C ₂₂ H ₂₆ F ₂ N ₂ O ₂ requires 388; 2.51*.	<i>N</i> -[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-2,4-difluoro-6-(methoxy)benzamide chiral
251		PE	Found 367 (MH ⁺) C ₂₃ H ₃₀ N ₂ O ₂ requires 366; 2.98*.	<i>N</i> -[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-2-methyl-4-(methoxy)benzamide chiral
252		P#	Found 459 (MH ⁺) C ₂₂ H ₂₃ ³⁵ Cl ₂ F ₃ N ₂ O requires 458; 2.07	2,6-dichloro- <i>N</i> -[2-methyl-1-(pyrrolidinyl)propyl]-3-(trifluoromethyl)benzamide chiral

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253		A	Found 473 (MH ⁺) C ₂₄ H ₂₆ F ₆ N ₂ O requires 472; 2.22.	2-methyl-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]-4,6-bis(trifluoromethyl)benzamide chiral
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Example 253: 2-Methyl-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]-4,6-bis(trifluoromethyl)benzamide chiral – alternative method

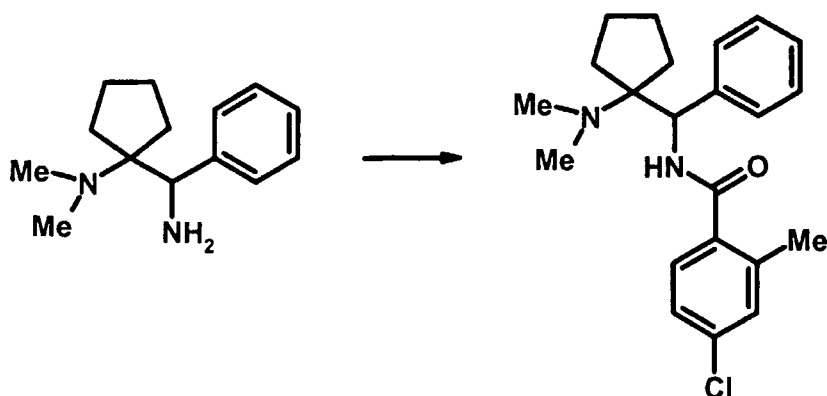


- 5 A mixture of 2-methyl-4,6-bis(trifluoromethyl)benzoyl chloride and methyl 2,4-bis(trifluoromethyl)benzoate (approximately 0.5mmol) prepared as described in D53 was dissolved in dry DCM (3ml) and treated with (+)-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]amine D6 (109mg, 0.50mmol) and triethylamine (140ul, 1.00 mmol) and left overnight at room temperature. The volatile components were removed under
- 10 reduced pressure and the residue chromatographed on silica gel. Elution with 0-80% ethyl acetate in pentane gave the title product as an gum (127mg, ca.54%). ¹H NMR (CDCl₃) δ: 0.90 (3H, s), 1.01 (3H, s), 1.70 (4H, overlapping m), 2.47 (3H, s), 2.63 (4H, overlapping m), 4.84 (1H, d, J = 2.8 Hz), 7.16 (1H, br s), 7.26 – 7.38 (5H, overlapping m) 7.67 (1H, s), 7.77 (1H, s). Mass Spectrum (Electrospray LC/MS): Found 473 (MH⁺)
- 15 C₂₄H₂₆F₆N₂O requires 472. Ret time 2.24 min.

This was converted to the hydrochloride salt (white solid, 140mg) by addition of excess 1M HCl in ether to a chloroform solution of the amine and removal of the solvent under reduced pressure.

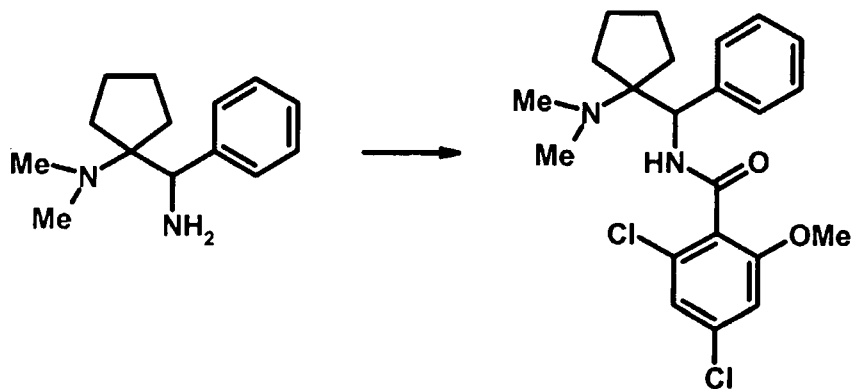
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Example 254: 4-Chloro-N-[[1-(dimethylamino)cyclopentyl](phenyl) methyl] -2-methylbenzamide chiral



- 5 A mixture of {1-[amino(phenyl)methyl]cyclopentyl}dimethylamine D3 enantiomer 2 (80mg, 0.37 mmol), 4-chloro-2-methylbenzoic acid (68mg; 0.40mmol), HOBT (61mg; 0.40mmol) and PS-DCC (310mg of 1.3 mmol/g loading, 0.40mmol) in DCM (4ml) was shaken overnight. Saturated aqueous sodium bicarbonate was added and the mixture separated with a phase-sep cartridge and the organics applied directly to SCX resin. Elution with
- 10 DCM, methanol and then 1M ammonia in methanol, followed by chromatography eluting with 12 – 100% ethyl acetate – pentane (SP4 Biotage) afforded the title product (64mg; 43%). ¹H NMR (CDCl₃) δ: 0.9 – 1.0 (1H, m), 1.25 – 1.40 (1H, m), 1.4 – 1.6 (2H, m), 1.6 – 1.75 (2H, m), 1.8 – 1.9 (2H, m), 2.22 (6H, s), 2.41 (3H, s), 5.09 (1H, d, J = 5Hz), 7.07 (1H, d, J = 5Hz), 7.2 – 7.4 (8H, m). Mass Spectrum (Electrospray LC/MS): Found 371 (MH⁺).
- 15 C₂₂H₂₇³⁵ClN₂O requires 370. Ret. time 2.26 min. The title product was converted to the corresponding hydrochloride salt.

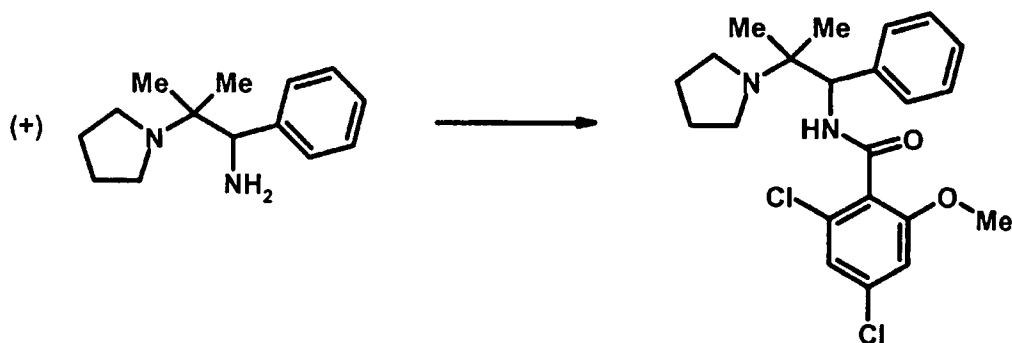
Example 255: 2,4-Dichloro-N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-6-(methoxy)benzamide chiral



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A mixture of {1-[amino(phenyl)methyl]cyclopentyl}dimethylamine D3 enantiomer 2 (80mg, 0.37 mmol), 2,4-dichloro-6-(methyloxy)benzoic acid (88mg; 0.40mmol), HOBt (61mg; 0.40mmol) and PS-DCC (310mg of 1.3 mmol/g loading, 0.40mmol) in DCM (4ml) was shaken overnight. Saturated aqueous sodium bicarbonate was added and the mixture separated with a phase-sep cartridge and the organics applied directly to SCX resin. Elution with DCM, methanol and then 1M ammonia in methanol, followed by chromatography eluting with 12 – 100% ethyl acetate – pentane (SP4 Biotage) afforded the title product (133mg; 79%). ¹H NMR (CDCl₃) δ: 0.95 – 1.10 (1H, m), 1.25 – 1.35 (1H, m), 1.40 – 1.60 (2H, m), 1.60 – 1.75 (2H, m), 1.80 – 1.90 (2H, m), 2.22 (6H, s), 3.82 (3H, s), 5.08 (1H, d, J = 5Hz), 6.82 (1H, d, J = 2Hz), 7.02 (1H, d, J = 2Hz), 7.07 (1H, m), 7.22 – 7.33 (3H, m), 7.44 – 7.46 (2H, m). Mass Spectrum (Electrospray LC/MS): Found 421 (MH⁺). C₂₂H₂₆³⁵Cl₂N₂O₂ requires 420. Ret. time 2.34 min. The title product was converted to the corresponding hydrochloride salt. 2,4-Dichloro-6-(methyloxy)benzoic acid can be prepared as described by G. E. Stokker, A. W. Alberts, P. S. Anderson, E. J. Cragoe Jr., A. A. Deana, J. L. Gilfillan, J. Hirshfield, W. J. Holtz, W. F. Hoffman, J.W. Huff, T.J. Lee, F.C. Novello, J.D. Prugh, C.S. Rooney, R.L. Smith, A.K. Willard J Med Chem, 1986, 29(2), 170.

Example 256: 2,4-Dichloro-6-(methyloxy)-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]benzamide chiral



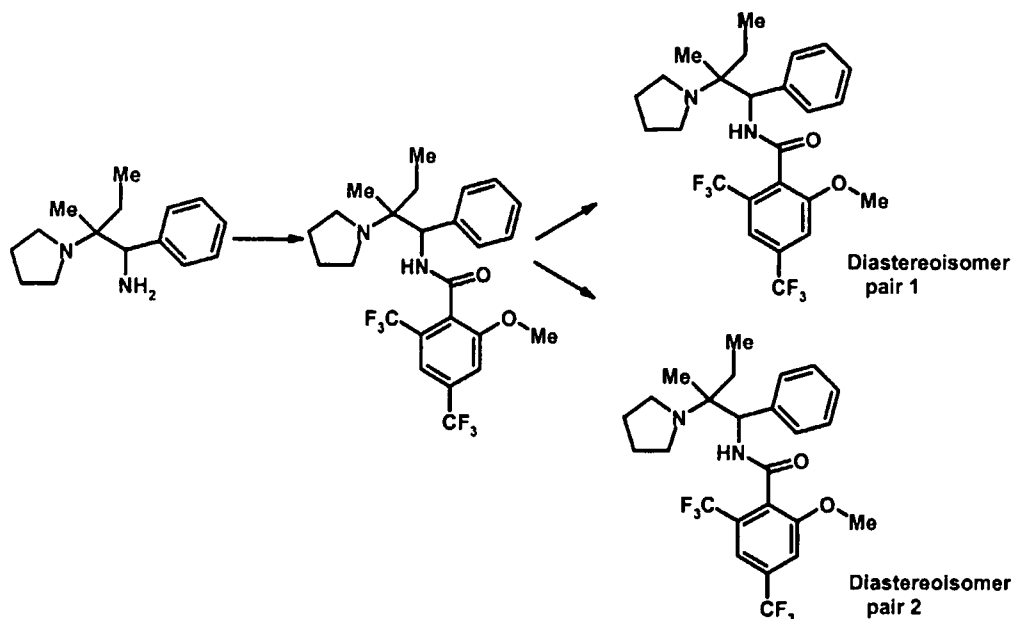
To a solution of (+)-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]amine D6 (0.10g; 0.459mmol) and triethylamine (0.15ml; 1mmol) in DCM (3ml) was added a solution of 2,4-dichloro-6-methoxybenzoyl chloride (0.13g; 0.540mmol) in DCM (2ml). After 1 h. saturated aqueous sodium hydrogen carbonate (8ml) was added and the mixture shaken for 2 minutes. The organic layer was passed through a phase separation cartridge and the solvent removed under reduced pressure. The residue was dissolved in the minimum of DCM and applied to a 10g silica gel column. Elution with 0 – 100% ethyl acetate in pentane gradient and removal of solvent under reduced pressure afforded the title

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compound as a colourless gum (0.14g; 72%). ^1H NMR (CDCl_3) δ : 0.91 (3H, s), 0.96 (3H, s), 1.60-1.80 (4H, m), 2.55-2.75 (4H, m), 3.82 (3H, s), 4.76 (1H, d, $J = 2.4\text{Hz}$), 6.81 (1H, d, $J = 1.6\text{Hz}$), 7.02 (1H, d, $J = 1.6\text{Hz}$), 7.20-7.50 (6H, m). Mass spectrum (Electrospray LC/MS). Found 421 (MH^+). $\text{C}_{22}\text{H}_{28}^{35}\text{Cl}_2\text{N}_2\text{O}_2$ requires 420. Ret. Time: 1.97min.

5

Examples 257: ($\pm$)-2-(Methoxy)-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)butyl]-4,6-bis(trifluoromethyl)benzamide Diastereoisomer Pair 1 and Diastereoisomer Pair 2



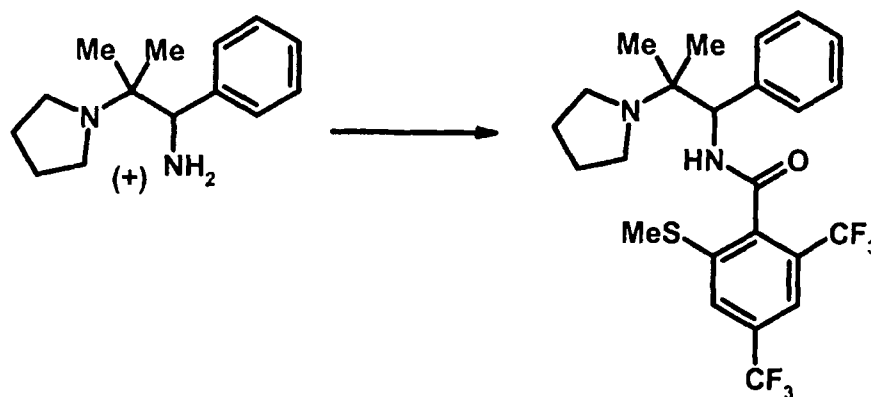
To a stirred solution of ($\pm$)-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)butyl]amine D22 (2.32g; 10mmol) and triethylamine (2.78ml; 20mmol) in DCM (75ml) at room temperature was added a solution of 2-(methoxy)-4,6-bis(trifluoromethyl)benzoyl chloride (3.10g; 10mmol) in DCM (25ml) dropwise over 10 minutes. After 20 h. saturated aqueous sodium hydrogen carbonate (100ml) was added and stirring continued for 0.5 h. The layers were separated and the aqueous layer extracted with DCM (150ml). The combined organics were dried (Na₂SO₄), filtered and the solvent removed under reduced pressure to afford a pale orange foam (4.8g). The sample was dissolved in the minimum of DCM and one half of the solution applied to a 40M silica column. Elution with 2% MeOH in DCM (2.5L) then 3% MeOH in DCM (2.4L) afforded the title compound diastereoisomer pair 1 (0.16g) ^1H NMR (CDCl_3) δ : 0.97 (3H, s), 1.01 (3H, t, $J = 7.6\text{Hz}$), 1.25-1.35 (2H, q, $J = 8\text{Hz}$), 1.55-1.75 (4H, m), 2.55-2.70 (4H, m), 3.93 (3H, s), 4.84 (1H, d, $J = 0.9\text{Hz}$), 7.20-7.45 (7H, m), 7.54 (1H, s). Mass spectrum (Electrospray LC/MS). Found 503 (MH^+). $\text{C}_{25}\text{H}_{28}\text{F}_6\text{N}_2\text{O}_2$ requires 502. Ret. Time: 2.27min.

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Further elution with 5% MeOH in DCM afforded the title compound diastereoisomer pair 2 (0.36g). ^1H NMR (CDCl_3) δ : 0.75-0.85 (3H, t), 1.03 (3H, s), 1.35-1.55 (1H, m), 1.60-1.72 (4H, m), 1.72-1.90 (1H, m), 2.70-2.85 (4H, m), 3.92 (3H, s), 4.83 (1H, d, $J = 3.6\text{Hz}$) 7.20-7.40 (7H, m), 7.53 (1H, s). Mass spectrum (Electrospray LC/MS). Found 503 (MH^+).

5 $\text{C}_{25}\text{H}_{28}\text{F}_6\text{N}_2\text{O}_2$ requires 502. Ret. Time: 2.30min.

Example 258: *N*-[2-Methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]-2-(methylthio)-4,6-bis(trifluoromethyl)benzamide chiral



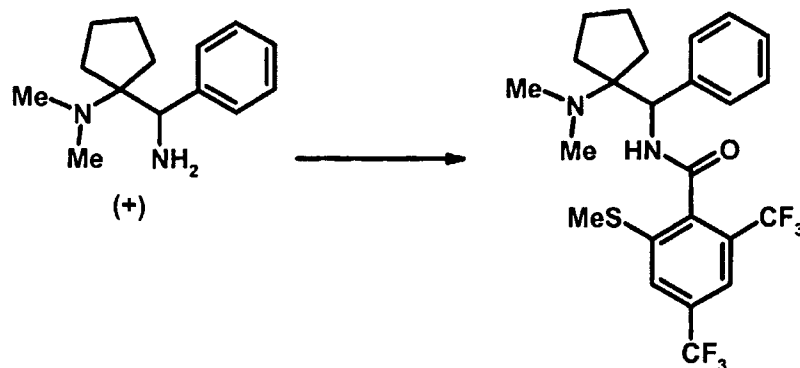
10 A solution of 2-(methylthio)-4,6-bis(trifluoromethyl)benzoyl chloride D55 (60mg; 0.19mmol) in dry DCM (1ml) was treated with (+)-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]amine D6 (60mg, 0.27mmol) followed by triethylamine (5drops) and left overnight at room temperature. The volatile components were removed under reduced pressure and the residue chromatographed on silica gel. Elution with 0-80% ethyl acetate

15 in pentane gave the title product as an oil (80mg, 85%). ^1H NMR (CDCl_3) δ : 0.94 (3H, s), 1.00 (3H, s), 1.69 (4H, overlapping m), 2.54 (3H, s), 2.62 (2H, m), 2.72 (2H, m), 4.78 (1H, s), 7.25 - 7.45 (6H, overlapping m), 7.68 (1H, s), 7.72 (1H, s). Mass Spectrum (Electrospray LC/MS): Found 505 (MH^+) $\text{C}_{24}\text{H}_{26}\text{F}_6\text{N}_2\text{OS}$ requires 504. Ret time 2.24 min.

20 The title product was converted to the hydrochloride salt (85mg) by addition of excess 1M HCl in ether to a DCM solution of the amine and removal of the solvent under reduced pressure.

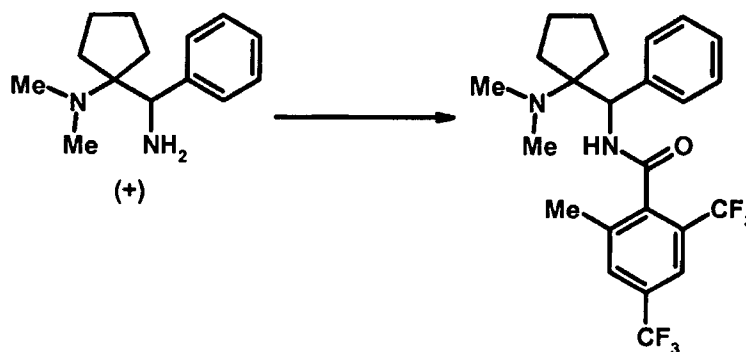
136

Example 259: *N*-[[1-(Dimethylamino)cyclopentyl](phenyl)methyl]-2-(methylthio-4,6-bis(trifluoromethyl)benzamide chiral



- A mixture of 2-(methylthio)-4,6-bis(trifluoromethyl)benzoyl chloride and methyl 2,4-bis(trifluoromethyl)benzoate (112mg) prepared as described in D55 was dissolved in dry DCM (2ml) and treated with (+)-{1-[amino(phenyl)methyl] cyclopentyl}dimethylamine D3 enantiomer 2 (33mg; 0.15mmol) and triethylamine (42ul, 0.30mmol) and left overnight at room temperature. The volatile components were removed under reduced pressure and the residue chromatographed on silica gel. Elution with 0-80% ethyl acetate in pentane gave the title product as a crisp foam (60mg; 86%). ¹H NMR (CDCl₃) δ: 0.90 (1H, m), 1.4 – 1.9 (7H, overlapping m), 2.22 (6H, s), 2.52 (3H, s), 5.05 (1H, d, J = 4.4 Hz), 7.22 – 7.5 (6H, overlapping m), 7.68 (1H, s), 7.71 (1H, s). Mass Spectrum (Electrospray LC/MS): Found 505 (MH⁺) C₂₄H₂₆F₆N₂OS requires 504. Ret time 2.35 min.
- The title product was converted to the hydrochloride salt (60mg) by addition of excess 1M HCl in ether to a DCM solution of the amine and removal of the solvent under reduced pressure.

Example 260: *N*-[[1-(Dimethylamino)cyclopentyl](phenyl)methyl]-2-methyl-4,6-bis(trifluoromethyl)benzamide chiral



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A mixture of 2-methyl-4,6-bis(trifluoromethyl)benzoyl chloride and methyl 2,4-bis(trifluoromethyl)benzoate (approximately 0.5mmol) prepared as described in D53 was dissolved in dry DCM (3ml) and treated with (+)-(1-[amino(phenyl)methyl]cyclopentyl)dimethylamine D3 enantiomer 2 (109mg, 0.50 mmol) and triethylamine (140ul, 1.00 mmol) and left overnight at room temperature. The volatile components were removed under reduced pressure and the residue chromatographed on silica gel. Elution with 0-80% ethyl acetate in pentane gave the title product (86mg, ca.36%). ¹H NMR (CDCl₃) δ: 0.95 (1H, br m), 1.44 – 1.86 (7H, overlapping m), 2.20 (6H, s), 2.41 (3H, br s), 5.10 (1H, d, J = 5.6 Hz), 7.07 (1H, br s), 7.26 – 7.42 (5H, overlapping m), 7.67 (1H, s), 7.77 (1H, s). Mass Spectrum (Electrospray LC/MS): Found 473 (MH⁺) C₂₄H₂₆F₆N₂O requires 472. Ret time 2.25 min.

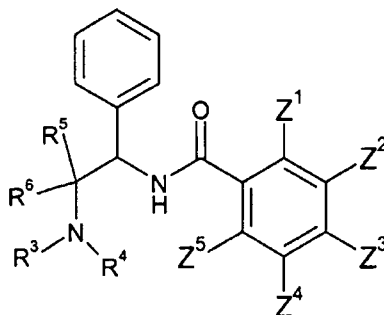
The title product was converted to the hydrochloride salt (90mg) by addition of excess 1M HCl in ether to a chloroform solution of the amine and removal of the solvent under reduced pressure.

The compounds of the Examples above could be converted to their corresponding hydrochloride salts by dissolving the parent free base in DCM or DCM / methanol mixtures and adding 1M hydrogen chloride in ether, followed by evaporation and drying *in vacuo*. Compounds purified by Mass Directed Auto-Purification were isolated as the formate salt which could be converted to the free base via an SCX column and to the corresponding hydrochloride salt by reaction with 1M hydrogen chloride in ether as described above.

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Claims

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



(I)

wherein

Z¹ is selected from the group consisting of C₁₋₄alkyl, C₃₋₆cycloalkyl, C₁₋₄alkoxy, C₁₋₄alkylthio, haloC₁₋₄alkyl, phenyl, haloC₁₋₄alkoxy, halophenyl, C₁₋₄alkylsulfoxy, C₁₋₄alkylsulfonyl, bromo and chloro;

Z² is selected from the group consisting of hydrogen, halogen, cyano, C₁₋₄alkyl, phenyl, haloC₁₋₄alkyl, haloC₁₋₄alkoxy, halophenyl, C₁₋₄alkoxyC₁₋₄alkyl and C₃₋₆cycloalkyl;

Z³ is selected from the group consisting of hydrogen, halogen, C₁₋₄alkyl, C₁₋₄alkoxy, C₁₋₄alkylthio, haloC₁₋₄alkyl, haloC₁₋₄alkoxy, and C₃₋₆cycloalkyl;

Z⁴ is selected from the group consisting of hydrogen, halogen, C₁₋₃alkyl, haloC₁₋₄alkyl, C₁₋₄alkoxy, C₁₋₄alkylthio, phenyl, haloC₁₋₄alkoxy, halophenyl, C₁₋₄alkoxyC₁₋₄alkyl and C₃₋₆cycloalkyl;

Z⁵ is selected from the group consisting of hydrogen, fluoro, chloro, bromo, iodo, hydroxy, C₁₋₄alkyl, C₁₋₄alkoxy, C₁₋₄alkylthio, phenyl, haloC₁₋₄alkyl, haloC₁₋₄alkoxy, halophenyl, C₁₋₄alkoxyC₁₋₄alkyl and C₃₋₆cycloalkyl;

whereby if more than one of Z¹ to Z⁵ is methoxy, then only Z¹ and Z⁵ are methoxy

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R³ and R⁴ are independently selected from hydrogen and C₁₋₄alkyl, optionally substituted with one or more groups Y; or R³ and R⁴ together with the nitrogen atom to which they are attached form a saturated or partially unsaturated 4-, 5- 6-or 7-membered carbocyclic ring optionally substituted with a group Y';

5

Y is selected from the group consisting of C₁₋₄alkoxy, hydroxy, haloC₁₋₄alkoxy and C₃₋₅cycloalkyl;

10

Y' is selected from the group consisting of C₁₋₄alkyl, C₁₋₄alkoxy, halogen, hydroxy, haloC₁₋₄alkoxy, C₃₋₅cycloalkyl and C₅₋₁₀aryl or Y' forms a -CH₂- or -CH₂-CH₂- bridge between two atoms on the 4-, 5-, 6- or 7-membered carbocyclic ring;

15

R⁵ and R⁶ are independently C₁₋₄alkyl, optionally substituted with one or more groups X; or R⁵ and R⁶ together with the carbon atom to which they are attached form a saturated 5- or 6-membered ring carbocyclic optionally substituted with one or more groups X', in the case of R⁵ and R⁶ together with the carbon atom to which they are attached forming a 5-membered saturated carbocyclic ring, that ring may optionally further comprising an additional heteroatom group selected from O, N and S(O)_m; where m = 0, 1 or 2.

20

X is selected from the group consisting of halogen, hydroxy, C₁₋₄alkoxy, haloC₁₋₄alkyl, haloC₁₋₄alkoxy and C₅₋₁₀aryl; and

X' is selected from the group consisting of halogen, hydroxy, C₁₋₄alkyl, C₁₋₄alkoxy, haloC₁₋₄alkyl, haloC₁₋₄alkoxy and C₅₋₁₀aryl;

25

whereby R³, R⁴, R⁵ and R⁶ are not all simultaneously unsubstituted methyl;

with the provisos that

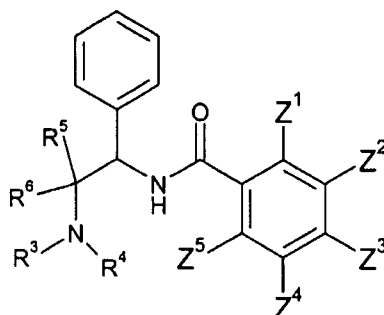
30

- when simultaneously Z1 is propyloxy, Z3 is chloro, Z2=Z4=Z5=H, and R5 and R6 are both methyl, then R³ and R⁴ together with the nitrogen atom to which they are attached do not form a 2-methylpyrrolidine group;
- when simultaneously Z1 is methyl, Z3 is methoxy, Z2=Z4=Z5=H, and R5 and R6 are both methyl, then R³ and R⁴ together with the nitrogen atom to which they are attached do not form a pyrrolidine group.

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2. A compound as claimed in claim 1 that is a compound of formula (Ia) or a salt or solvate thereof:



5

(Ia)

wherein

10 Z¹ is selected from the group consisting of C₁₋₄alkyl, C₁₋₂alkoxy, C₁₋₄alkylthio, haloC₁₋₄alkyl, and chloro;

Z² is selected from the group consisting of hydrogen, halogen, haloC₁₋₄alkyl, and C₁₋₄alkyl;

15 Z³ is selected from the group consisting of hydrogen, halogen, haloC₁₋₄alkyl and C₁₋₄alkyl;

Z⁴ is selected from the group consisting of hydrogen and halogen;

Z⁵ is selected from the group consisting of bromo, C₁₋₄alkyl, C₁₋₄alkoxy and haloC₁₋₄alkyl;

20 R³ and R⁴ are independently unsubstituted methyl or ethyl, or R³ and R⁴ together with the nitrogen atom to which they are attached form a saturated 5- or 6-membered carbocyclic ring;

25 R⁵ and R⁶ are independently methyl or ethyl, or R⁵ and R⁶ together with the carbon atom to which they are attached form a saturated 5-membered carbocyclic ring;

and at least one of the pairs of groups R³ / R⁴ and R⁵ / R⁶ forms a cyclic group with the Nitrogen or Carbon atom to which they are respectively attached.

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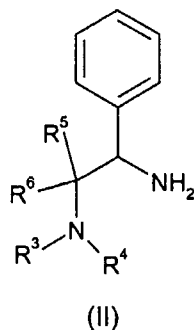
3. A compound as claimed in claim 1 or claim 2 which is any of Examples 1 to 260 or a salt or solvate thereof.
4. A compound as claimed in any one of claims 1 to 3 for use in therapy.
5. A compound as claimed in claim 4 for use in the treatment of a disorder mediated by GlyT1.
6. A compound as claimed in claim 5, wherein the disorder is psychosis, including schizophrenia, dementia or attention deficit disorder.
7. A method of treating a mammal, including a human, suffering from or susceptible to a disorder mediated by GlyT1, which comprises administering an effective amount of a compound as claimed in claim 4.
8. A method as claimed in claim 7, wherein the disorder is psychosis, including schizophrenia, dementia or attention deficit disorder.
9. Use of a compound as claimed in claim 1 in the preparation of a medicament for the treatment of a disorder mediated by GlyT1.
10. Use as claimed in claim 9, wherein the disorder is psychosis, including schizophrenia, dementia or attention deficit disorder.
11. A pharmaceutical composition comprising a compound as claimed in claim 4, and at least one pharmaceutically acceptable carrier, diluent or excipient.
12. A pharmaceutical composition as claimed in claim 11 further comprising one or more other therapeutic agents, selected from antidepressant agents selected from 5HT3 antagonists, serotonin agonists, NK-1 antagonists, selective serotonin reuptake inhibitors (SSRI), noradrenaline re-uptake inhibitors (SNRI), tricyclic antidepressants, dopaminergic antidepressants, H3 antagonists, 5HT1A antagonists, 5HT1B antagonists, 5HT1D antagonists, D1 agonists, M1 agonists, anticonvulsant agents; atypical antipsychotic drugs and cognitive enhancers.

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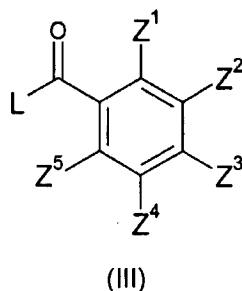
13. A method of preparing a compound as defined in any one of claims 1 to 3, comprising the step of:

reacting a compound of formula (II):

5



wherein R³, R⁴, R⁵ and R⁶ are as defined in formula (I) in any one of claims 1 to 3, with a
10 compound of formula (III):



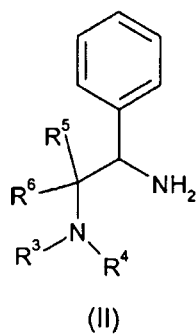
15 wherein Z¹, Z², Z³, Z⁴ and Z⁵ are as defined in formula (I) in any one of claims 1 to 3 and L represents a suitable leaving group;

and thereafter optionally:

- removing any protecting groups and/or
- 20 • converting a compound of formula (I) into another compound of formula (I) and/or
- forming a salt or solvate.

14. A compound of formula (II):

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- wherein R^3 , R^4 , R^5 and R^6 are as defined in formula (I) in any one of claims 1 to 3 and
- 5 wherein compound (II) is not the compound wherein simultaneously R^3 and R^4 together with the nitrogen atom to which they are attached form an unsubstituted piperidine ring and R^5 and R^6 together with the carbon atom to which they are attached form an unsubstituted cyclopentyl ring.

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2005/004951A. CLASSIFICATION OF SUBJECT MATTER
C07C233/78 A61K31/166 C07C211/36

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07C C07D A61K

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

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

EPO-Internal, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	P.N. BECKER ET AL.: "A New Method for 1,2-Diamination of Alkenes Using Cyclopentadienylnitrosylcobalt Dimer/NO/LiAlH ₄ " J. AM. CHEM. SOC., vol. 102, 1980, pages 5676-5677, XP002374266 Table I, third entry (2-methyl-1-phenylpropane-1,2-diamine) ----- -/--	14

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

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

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

Date of the actual completion of the international search

28 March 2006

Date of mailing of the international search report

18/04/2006

Name and mailing address of the ISA/

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Bueno Torres, M

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2005/004951

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	A. VISO ET AL.: "Highly Diastereoselective [3+2]Cycloadditions between Nonracemic p-Tolylsulfinimines and Iminoesters: An Efficient Entry to Enantiopure Imidazolidines and Vicinal Diaminoalcohols" CHEM. EUR. J., vol. 9, 2003, pages 2867-2876, XP002374267 Compound 18a -----	14
A	WO 03/055478 A (SMITHKLINE BEECHAM P.L.C.) 10 July 2003 (2003-07-10) cited in the application the whole document -----	1-14
X	US 3 145 209 A (KRAPCHO JOHN) 18 August 1964 (1964-08-18) Claims 1, 2, 6, examples 1, 2, example 5, example 6, example 16, ex 18, ex 24 -----	14

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB2005/004951

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Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

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

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 7 and 8 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/GB2005/004951

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 03055478	A	10-07-2003	AU 2002352483 A1	15-07-2003
			EP 1455777 A1	15-09-2004
			JP 2005519048 T	30-06-2005
			US 2005267152 A1	01-12-2005
US 3145209	A	18-08-1964	NONE	

Compuestos

La presente invención se refiere a compuestos inhibidores del transportador de glicina, su uso en la fabricación de medicamentos para tratar trastornos neurológicos y neuropsiquiátricos, en particular psicosis, demencia o trastorno de déficit de atención. La invención comprende adicionalmente procedimientos para preparar estos compuestos y las formulaciones farmacéuticas de los mismos.

La clonación molecular ha revelado la existencia en cerebros de mamíferos de dos clases de transportadores de glicina denominados GlyT1 y GlyT2. El GlyT1 se encuentra predominantemente en el prosencéfalo y su distribución corresponde a la de las rutas glutaminérgicas y receptores NMDA (Smith, y col., Neuron, 8, 1992: 927 - 935). La clonación molecular ha revelado adicionalmente la existencia de tres variantes de GlyT1, denominadas GlyT-1a, GlyT-1b y GlyT-1c (Kim y col., Molecular Pharmacology, 45, 1994: 608 - 617), cada una de las cuales muestra una única distribución en el cerebro y tejidos periféricos. Las variantes surgen mediante ajuste diferencial y uso de exones, y se diferencian en sus regiones N-terminales. Por el contrario, GlyT2, se encuentra predominantemente en el tronco cerebral y médula espinal, y su distribución corresponde estrechamente a la de los receptores de glicina sensibles a estricnina (Liu y col., J. Biological Chemistry, 268, 1993: 22802 - 22808; Jursky y Nelson, J. Neurochemistry, 64, 1995: 1026 - 1033). Otra característica de diferenciación del transporte de glicina mediado por GlyT2 es que no está inhibido por la sarcosina como es el caso del transporte de glicina

mediado por GlyT1. Estos datos son consistentes con la visión de que, mediante la regulación de los niveles sinápticos de la glicina, GlyT1 y GlyT2 influyen selectivamente en la actividad de los receptores NMDA y receptores de glicina sensibles a estricnina, respectivamente.

- 5 Los receptores NMDA están críticamente implicados en la memoria y aprendizaje (Rison y Staunton, Neurosci. Biobehav. Rev., 19 533 - 552 (1995); Danysz *et al*, Behavioral Pharmacol., 6 455 - 474 (1995)); y, además, la disminución de la función de la neurotransmisión mediada por NMDA parece que es la razón fundamental o contribuye a, los síntomas de esquizofrenia
- 10 (Olney y Farber, Archives General Psychiatry, 52, 998-1007 (1996). De este modo, los agentes que inhiben GlyT1 y por lo tanto incrementan la activación de glicina de los receptores NMDA se pueden usar como antipsicóticos novedosos y agentes antidemencia, y para tratar otras enfermedades en las que se alteran los procesos cognitivos, tal como trastornos de déficit de
- 15 atención y síndromes cerebrales orgánicos. De manera inversa, la sobre activación de los receptores NMDA ha estado implicada en numerosos estados patológicos, en particular la muerte neuronal asociada a apoplejía y posiblemente enfermedades neurodegenerativas, tal como enfermedad de Alzheimer, demencia multiinfarto, demencia de SIDA, enfermedad de
- 20 Huntington, enfermedad de Parkinson, esclerosis lateral amiotrófica u otras afecciones en las que se produce muerte neuronal, tal como apoplejía o trauma cefálico. Coyle y Puttfarcken, Science, 262, 689 - 695 (1993); Lipton y Rosenberg, New Engl. J. of Medicine, 330, 613 - 622 (1993); Choi, Neuron, 1, 623 - 634 (1988). De este modo, los agentes farmacológicos que incrementan
- 25 la actividad de GlyT1 darán como resultado un descenso en la activación de

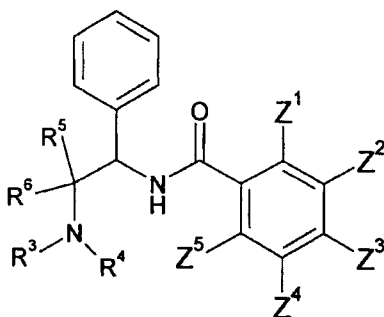
glicina de los receptores de NMDA, dicha actividad se puede usar para tratar estas enfermedades y estados patológicos relacionados. De manera similar, los fármacos que bloquean directamente el sitio de glicina de los receptores NMDA se pueden usar para tratar éstos y los estados patológicos relacionados.

- 5 Los inhibidores del transporte de glicina se conocen ya en la técnica, por ejemplo como se describe en la solicitud de patente internacional publicada WO03/055478 (SmithKline Beecham).

Sin embargo, todavía permanece la necesidad de identificar compuestos adicionales que pueden inhibir los transportadores GlyT1, incluyendo los que
10 inhiben los transportadores GlyT1 selectivamente sobre los transportadores GlyT2.

Ahora se ha encontrado que una clase novedosa de compuestos inhiben los transportadores GlyT1 y son de esta manera útiles en el tratamiento de ciertos trastornos neurológicos y neuropsiquiátricos, incluyendo esquizofrenia.

- 15 De este modo, en un primer aspecto, se proporciona un compuesto de fórmula (I) o una sal o solvato del mismo.



(I)

20

en la que

Z^1 se selecciona entre el grupo constituido por alquilo C_{1-4} , cicloalquilo C_{3-6} , alcoxi C_{1-4} , alquil C_{1-4} tio, haloalquilo C_{1-4} , fenilo, haloalcoxi C_{1-4} , halofenilo, alquil C_{1-4} sulfoxi, alquil C_{1-4} sulfonilo, bromo y cloro;

- 5 Z^2 se selecciona entre el grupo constituido por hidrógeno, halógeno, ciano, alquilo C_{1-4} , fenilo, haloalquilo C_{1-4} , haloalcoxi C_{1-4} , halofenilo, alcoxi C_{1-4} alquilo C_{1-4} y cicloalquilo C_{3-6} ;

- Z^3 se selecciona entre el grupo constituido por hidrógeno, halógeno, alquilo C_{1-4} , alcoxi C_{1-4} , alquil C_{1-4} tio, haloalquilo C_{1-4} , haloalcoxi C_{1-4} , y cicloalquilo C_{3-6} ;
- 10

Z^4 se selecciona entre el grupo constituido por hidrógeno, halógeno, alquilo C_{1-3} , haloalquilo C_{1-4} , alcoxi C_{1-4} , alquil C_{1-4} tio, fenilo, haloalcoxi C_{1-4} , halofenilo, alcoxi C_{1-4} alquilo C_{1-4} y cicloalquilo C_{3-6} ;

15

Z^5 se selecciona entre el grupo constituido por hidrógeno, fluoro, cloro, bromo, yodo, hidroxil, alquilo C_{1-4} , alcoxi C_{1-4} , alquil C_{1-4} tio, fenilo, haloalquilo C_{1-4} , haloalcoxi C_{1-4} , halofenilo, alcoxi C_{1-4} alquilo C_{1-4} y cicloalquilo C_{3-6} ;

- 20 en la que si más de uno de Z^1 a Z^5 es metoxi, entonces solamente Z^1 y Z^5 son metoxi

- R^3 y R^4 se seleccionan independientemente entre hidrógeno, alquilo C_{1-4} , opcionalmente sustituido con uno o más grupos Y; o R^3 y R^4 junto con el
- 25 átomo de nitrógeno al que están unidos forman un anillo carbocíclico saturado

o parcialmente insaturado de 4-, 5-, 6- ó 7-miembros opcionalmente sustituido con un grupo Y';

Y se selecciona entre el grupo constituido por alcoxi C₁₋₄, hidroxi, haloalcoxi C₁₋₄,
5 y cicloalquilo C₃₋₅;

Y' se selecciona entre el grupo constituido por alquilo C₁₋₄, alcoxi C₁₋₄, halógeno, hidroxi, haloalcoxi C₁₋₄, cicloalquilo C₃₋₅ y arilo C₅₋₁₀ o Y' forma un puente -CH₂- o -CH₂-CH₂- entre dos átomos sobre el anillo carbocíclico de 4-,
10 5-, 6- ó 7-miembros;

R⁵ y R⁶ son independientemente alquilo C₁₋₄, opcionalmente sustituido con uno o más grupos X; o R⁵ y R⁶ junto con el átomo de carbono al que están unidos forman un anillo carbocíclico saturado de 5- ó 6- miembros opcionalmente
15 sustituido con uno o más grupos X', en el caso de que R⁵ y R⁶ junto con el átomo de carbono al que están unidos formen un anillo carbocíclico saturado de 5- miembros, ese anillo puede opcionalmente adicionalmente comprender un grupo heteroátomo adicional seleccionado entre O, N y S(O)_m; donde m = 0, 1 ó 2.

20

X se selecciona entre el grupo constituido por halógeno, hidroxi, alcoxi C₁₋₄, haloalquilo C₁₋₄, haloalcoxi C₁₋₄ y arilo C₅₋₁₀; y

X' se selecciona entre el grupo constituido por halógeno, hidroxi, alquilo C₁₋₄,
25 alcoxi C₁₋₄, haloalquilo C₁₋₄, haloalcoxi C₁₋₄ y arilo C₅₋₁₀;

en la que R^3 , R^4 , R^5 y R^6 no son todos simultáneamente metilo no sustituido;

con la condición de que

- 5 - cuando simultáneamente Z1 es propilo, Z3 es cloro, $Z2 = Z4 = Z5 = H$,
 y R^5 y R^6 son ambos metilo, entonces R^3 y R^4 junto con el átomo de
 nitrógeno al que están unidos no forman un grupo 2-metilpirrolidina;
- cuando simultáneamente Z1 es metilo, Z3 es metoxi, $Z2 = Z4 = Z5 = H$,
 y R^5 y R^6 son ambos metilo, entonces R^3 y R^4 junto con el átomo de
10 nitrógeno al que están unidos no forman un grupo pirrolidina.

 Como se usa en esta memoria descriptiva, el término "alquilo" se refiere
 a un grupo alquilo lineal o ramificado en todas las formas isoméricas. Los
 ejemplos de alquilo C_{1-4} incluyen metilo, etilo, propilo, isopropilo, butilo,
15 isobutilo, sec-butilo y terc-butilo.

 Como se usa en esta memoria descriptiva, el término "cicloalquilo" se
 refiere a un anillo hidrocarburo saturado cíclico no aromático. Los ejemplos de
 cicloalquilo C_{3-6} incluyen ciclopropilo, ciclobutilo, ciclopentilo, y ciclohexilo.

20

 Como se usa en esta memoria descriptiva, el término "alcoxi" se refiere
 al grupo -O-alquilo en el que alquilo es como se ha definido anteriormente. El
 término "metoxi" se refiere al grupo -O-metilo.

Como se usa en esta memoria descriptiva, el término "alquiltio" se refiere al grupo -S-alquilo en el que alquilo es como se ha definido anteriormente. El término "metiltio" se refiere al grupo -S-metilo.

5 Como se usa en esta memoria descriptiva, el término "alquilsulfoxi" se refiere al grupo -S(O)-alquilo en el que alquilo es como se ha definido anteriormente.

10 Como se usa en esta memoria descriptiva, el término "alquilsulfonilo" se refiere al grupo -S(O)₂-alquilo en el que alquilo es como se ha definido anteriormente.

15 Como se usa en esta memoria descriptiva, el término "arilo C₅₋₁₀" se refiere a un grupo aromático monocíclico de 5- ó 6- miembros o un grupo aromático bicíclico de 8- a 10- miembros. Los ejemplos de arilo C₅₋₁₀ incluyen fenilo, indenilo, azulenilo y naftilo.

20 Como se usa en esta memoria descriptiva, los términos "halógeno" y su abreviatura "hal" se refieren a flúor, cloro, bromo o yodo.

25 Como se usa en esta memoria descriptiva, el término "haloalquilo" se refiere a un grupo alquilo como se ha definido anteriormente que está sustituido con cualquier número de átomos de flúor, cloro, bromo o yodo, incluyendo mezclas de aquellos átomos. Un grupo haloalquilo puede, por ejemplo, contener 1, 2 ó 3 átomos de halógeno. Por ejemplo, un grupo haloalquilo puede

tener todos los átomos de hidrógeno reemplazados por átomos de halógeno. Los ejemplos de grupos haloalquilo incluyen fluorometilo, difluorometilo y trifluorometilo.

- 5 Como se usa en esta memoria descriptiva, el término "sal" se refiere a cualquier sal de un compuesto de acuerdo con la presente invención preparada a partir de un ácido o base orgánico o inorgánico, sales de amonio cuaternario y sales formadas internamente. Las sales fisiológicamente aceptables son particularmente adecuadas para aplicaciones médicas debido a su mayor
- 10 solubilidad acuosa con relación a los compuestos precursores. Dichas sales deben presentar claramente un anión o catión fisiológicamente aceptable. Las sales fisiológicamente aceptables adecuadas de los compuestos de la presente invención incluyen sales de adición de ácidos formadas con ácidos inorgánicos tales como ácidos clorhídrico, bromhídrico, yodhídrico, fosfórico, metafosfórico,
- 15 nítrico y sulfúrico, y con ácidos orgánicos, tales como ácidos tartárico, acético, trifluoroacético, cítrico, málico, láctico, fumárico, benzoico, fórmico, propiónico, glicólico, glucónico, maleico, succínico, alcanforsulfúrico, isotiónico, mícico, gentísico, isonicotínico, sacárico, glucurónico, furoico, glutámico, ascórbico, antranílico, salicílico, fenilacético, mandélico, embónico (pamoico),
- 20 metanosulfónico, etanosulfónico, pantoténico, esteárico, sulfinílico, algínico, galacturónico y arilsulfónico, por ejemplo bencenosulfónico y p-toluenosulfónico; sales de adición de base formadas con metales alcalinos y metales alcalinotérreos y bases orgánicas tales como N,N-dibenciletilendiamina, cloroprocaína, colina, dietanolamina, etilendiamina,
- 25 meglumaína (N-metilglucamina), lisina y procaína; y las sales formadas

internamente. Las sales que tienen un anión o catión no fisiológicamente aceptable están dentro del alcance de la invención como intermedios útiles para la preparación de sales fisiológicamente aceptables y/o para uso en situaciones no terapéuticas, por ejemplo *in vitro*.

5

Como se usa en esta memoria descriptiva, el término "solvato" se refiere a un complejo de estequiometría variable formado por un soluto (en esta invención, un compuesto de fórmula (I) o una sal del mismo) y un disolvente. Tales disolventes para el propósito de la invención pueden no interferir con la actividad biológica del soluto. Los ejemplos de disolventes adecuados incluyen, pero no se limitan a, agua, metanol, etanol y ácido acético. Preferiblemente el disolvente usado es un disolvente farmacéuticamente aceptable. Los ejemplos de los disolventes farmacéuticamente aceptables incluyen agua, etanol y ácido acético. Lo más preferiblemente el disolvente usado es agua.

15

En una realización, R^3 y R^4 son ambos simultáneamente el mismo alquilo C_{1-4} , el mismo alquilo C_{1-4} sustituido con uno o más grupos Y, o R^3 y R^4 junto con el átomo de nitrógeno al que están unidos forman un anillo carbocíclico saturado de 5- ó 6- miembros opcionalmente sustituido con un grupo Y'.

20

En una realización, R^3 y R^4 son ambos alquilo C_{1-4} , por ejemplo metilo o etilo, por ejemplo metilo.

Y puede, por ejemplo, seleccionarse entre el grupo constituido por alcoxi C_{1-4} , haloalcoxi C_{1-4} y arilo C_{5-10} . En una realización, Y se selecciona entre el grupo constituido por alcoxi C_{1-4} , arilo C_{5-10} .

5 Y' puede, por ejemplo, seleccionarse entre el grupo constituido por halógeno, alquilo C_{1-4} , alcoxi C_{1-4} , haloalcoxi C_{1-4} y arilo C_{5-10} . En una realización, Y' se selecciona entre el grupo constituido por alquilo C_{1-4} , alcoxi C_{1-4} , arilo C_{5-10} .

10 En una realización, R^3 y R^4 se seleccionan independientemente entre hidrógeno, metilo y etilo, opcionalmente sustituido con un grupo Y, o R^3 y R^4 junto con el átomo de nitrógeno al que están unidos forman un anillo carbocíclico saturado o parcialmente insaturado (por ejemplo saturado) de 4-, 5-, 6- ó 7- miembros opcionalmente sustituido con un grupo Y'.

15

En una realización adicional, R^3 y R^4 se seleccionan entre metilo y etilo, opcionalmente sustituido con un grupo Y, o R^3 y R^4 junto con el átomo de nitrógeno al que están unidos forman un anillo carbocíclico saturado de 4-, 5- ó 6- miembros opcionalmente sustituido con un grupo Y'. Por ejemplo, R^3 y R^4
20 son ambos metilo no sustituido, o R^3 y R^4 junto con el átomo de nitrógeno al que están unidos forman un anillo carbocíclico saturado de 5- ó 6- miembros.

Y puede, por ejemplo, seleccionarse entre el grupo constituido por alcoxi C_{1-4} , hidroxi y cicloalquilo C_{3-5} .

25

Y' puede, por ejemplo, seleccionarse entre el grupo constituido por halógeno y alquilo C₁₋₄ o Y' puede formar un puente -CH₂- entre dos átomos sobre el anillo carbocíclico de 5- o 6- miembros.

- 5 En una realización, R⁵ y R⁶ son ambos simultáneamente el mismo alquilo C₁₋₄, el mismo alquilo C₁₋₄ sustituido con uno o más grupos X, ó R⁵ y R⁶ junto con el átomo de carbono al que están unidos forman un anillo carbocíclico saturado de 5- ó 6- miembros opcionalmente sustituido con un grupo X', el anillo carbocíclico saturado de 5- o 6- miembros puede opcionalmente
- 10 comprender adicionalmente un grupo heteroátomo adicional seleccionado entre O, N y S(O)_m (en el que m es 0, 1, ó 2);

- En una realización adicional, R⁵ y R⁶ junto con el átomo de carbono al que están unidos forman un anillo carbocíclico saturado de 5- ó 6- miembros,
- 15 por ejemplo un anillo carbocíclico de 5-miembros.

X, por ejemplo, se selecciona entre el grupo constituido por halógeno, alcoxi C₁₋₄, haloalquilo C₁₋₄, haloalcoxi C₁₋₄ y arilo C₅₋₁₀.

- 20 En una realización, R⁵ y R⁶ se seleccionan independientemente entre metilo y etilo, opcionalmente sustituido con uno o más grupos X; o R⁵ y R⁶ junto con el átomo de carbono al que están unidos forman un anillo carbocíclico saturado de 5- ó 6- miembros y en el caso de que R⁵ y R⁶ junto con el átomo de carbono al que están unidos formen un anillo carbocíclico saturado de 5-

miembros, ese anillo opcionalmente puede adicionalmente comprender un heteroátomo de oxígeno.

Por ejemplo, en una realización R^5 y R^6 se seleccionan
5 independientemente entre metilo y etilo, o R^5 y R^6 junto con el átomo de carbono al que están unidos forman un anillo carbocíclico saturado de 5- miembros. Por ejemplo, en una realización adicional, R^5 y R^6 son ambos metilo, o R^5 y R^6 junto con el átomo de carbono al que están unidos forman un anillo carbocíclico saturado de 5- miembros.

10

X puede, por ejemplo, seleccionarse entre el grupo constituido por hidroxi y alcoxi C_{1-4} .

X' puede, por ejemplo, seleccionarse entre el grupo constituido por
15 hidroxi y alcoxi C_{1-4} .

En una realización, al menos uno de los pares de grupos R^3 / R^4 y R^5 / R^6 forma un grupo cíclico con el átomo de nitrógeno o carbono al que están unidos respectivamente. Por ejemplo, ese grupo cíclico puede ser un anillo
20 carbocíclico de 5- miembros.

En una realización de la invención, Z^1 se selecciona entre el grupo constituido por cloro, alquilo C_{1-4} , haloalquilo C_{1-4} , alcoxi C_{1-4} , haloalcoxi C_{1-4} , alquil C_{1-4} tio, fenilo, y halofenilo;

25

Z^2 se selecciona entre el grupo constituido por hidrógeno, yodo, bromo, cloro, fluoro, alquilo C_{1-4} , haloalquilo C_{1-4} , haloalcoxi C_{1-4} , fenilo, y halofenilo;

Z^3 se selecciona entre el grupo constituido por hidrógeno, yodo, bromo, cloro, alquilo C_{1-4} , haloalquilo C_{1-4} , alcoxi C_{1-4} , haloalcoxi C_{1-4} ;

Z^4 se selecciona entre el grupo constituido por hidrógeno, yodo, bromo, cloro, fluoro, alcoxi C_{1-4} , haloalcoxi C_{1-4} , fenilo, y halofenilo; y

Z^5 se selecciona entre el grupo constituido por hidrógeno, yodo, bromo, cloro, alquilo C_{1-4} , alcoxi C_{1-4} , haloalcoxi C_{1-4} , fenilo, y halofenilo;

en la que no más de tres de Z^1 , Z^2 , Z^3 , Z^4 , y Z^5 son hidrógeno.

En otra realización, Z^1 se selecciona entre el grupo constituido por cloro, haloalquilo C_{1-4} , alcoxi C_{1-4} , haloalcoxi C_{1-4} , fenilo, y halofenilo, y Z^2 , Z^3 , Z^4 y Z^5 son hidrógeno.

En una realización adicional,

Z^1 se selecciona entre el grupo constituido por, cloro, alquilo C_{1-4} , y alcoxi C_{1-4} ;

Z^2 se selecciona entre el grupo constituido por hidrógeno, haloalquilo C_{1-4} , y alquilo C_{1-4} ;

25

Z^3 es hidrógeno;

Z^4 es hidrógeno; y

5 Z^5 se selecciona entre el grupo constituido por hidrógeno, y alquilo C_{1-4} ;

en la que no más de tres de Z^1 , Z^2 , Z^3 , Z^4 , y Z^5 son hidrógeno.

En una realización, Z^1 se selecciona entre el grupo constituido por
10 alquilo C_{1-4} , cicloalquilo C_{3-6} , alcoxi C_{1-2} , alquil C_{1-4} tio, haloalquilo C_{1-4} , fenilo, haloalcoxi C_{1-4} , halofenilo, alquil C_{1-4} sulfoxi, alquil C_{1-4} sulfonilo, bromo y cloro.

En una realización, Z^1 se selecciona entre el grupo constituido por
alquilo C_{1-4} , alcoxi C_{1-2} , alquil C_{1-4} tio, haloalquilo C_{1-4} , fenilo, haloalcoxi C_{1-4} ,
15 halofenilo y cloro;

Por ejemplo, Z^1 se selecciona entre el grupo constituido por alquilo C_{1-4} ,
alcoxi C_{1-2} , alquil C_{1-4} tio, haloalquilo C_{1-4} , y cloro, particularmente entre el grupo
constituido por alquilo C_{1-4} y alcoxi C_{1-2} . Por ejemplo, Z^1 se puede seleccionar
20 entre metilo, metiltio, etoxi y metoxi.

En una realización, Z^2 se selecciona entre el grupo constituido por
hidrógeno, halógeno, alquilo C_{1-4} , fenilo y haloalquilo C_{1-4} . Por ejemplo, Z^2 se
puede seleccionar entre el grupo constituido por hidrógeno, halógeno, y alquilo

C_{1-4} . Por ejemplo Z^2 se puede seleccionar entre hidrógeno, bromo y metilo. Por ejemplo Z^2 puede ser hidrógeno

En una realización, Z^3 se selecciona entre el grupo constituido por hidrógeno, halógeno, alquilo C_{1-4} , alcoxi C_{1-4} y haloalquilo C_{1-4} . Por ejemplo, Z^3 se puede seleccionar entre el grupo constituido por hidrógeno, halógeno, alquilo C_{1-4} y haloalquilo C_{1-4} . Por ejemplo Z^3 se puede seleccionar entre hidrógeno, fluoro, cloro y trifluorometilo.

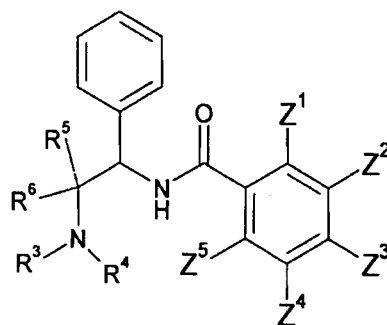
En una realización, Z^4 se selecciona entre el grupo constituido por hidrógeno, halógeno, alquilo C_{1-3} , fenilo, alcoxi C_{1-4} y haloalquilo C_{1-4} . Por ejemplo, Z^4 se puede seleccionar entre el grupo constituido por hidrógeno y halógeno. Por ejemplo Z^4 puede ser hidrógeno.

En una realización, Z^5 se selecciona entre el grupo constituido por hidrógeno, hidroxilo, fluoro, cloro, bromo, alquilo C_{1-4} , alcoxi C_{1-4} , haloalquilo C_{1-4} y haloalcoxi C_{1-4} ; Z^5 se puede seleccionar entre el grupo constituido por cloro, bromo, alquilo C_{1-4} , alcoxi C_{1-4} y haloalquilo C_{1-4} . Por ejemplo, Z^5 se puede seleccionar entre el grupo constituido por bromo, metilo, y trifluorometilo.

20

En una realización, Z^1 y Z^5 son ambos simultáneamente no hidrógeno. En una realización adicional, Z^1 , Z^3 y Z^5 son todos simultáneamente no hidrógeno.

De acuerdo con lo anterior, en una realización, la presente invención proporciona un compuesto de fórmula (Ia) o una sal o solvato del mismo:



(Ia)

5

en la que

Z¹ se selecciona entre el grupo constituido por alquilo C₁₋₄, alcoxi C₁₋₂,
10 alquil C₁₋₄ tio, haloalquilo C₁₋₄, y cloro;

Z² se selecciona entre el grupo constituido por hidrógeno, halógeno,
haloalquilo C₁₋₄, y alquilo C₁₋₄;

15 Z³ se selecciona entre el grupo constituido por hidrógeno, halógeno,
haloalquilo C₁₋₄ y alquilo C₁₋₄;

Z⁴ se selecciona entre el grupo constituido por hidrógeno y halógeno;

Z^5 se selecciona entre el grupo constituido por bromo, alquilo C_{1-4} , alcoxi C_{1-4} y haloalquilo C_{1-4} ;

R^3 y R^4 son independientemente metilo o etilo no sustituido, o R^3 y R^4 junto con el átomo de nitrógeno al que están unidos forman un anillo carbocíclico saturado de 5- ó 6- miembros;

R^5 y R^6 son independientemente metilo o etilo, o R^5 and R^6 junto con el átomo de carbono al que están unidos forman un anillo carbocíclico saturado de 5- miembros;

y al menos uno de los pares de los grupos R^3 / R^4 y R^5 / R^6 forma un grupo cíclico con el átomo de nitrógeno o carbono al que están respectivamente unidos.

15

Se ha de entender que las características de una realización de la invención descrita con referencia a un parámetro se pueden combinar con las características de otra realización. La descripción en esta memoria descriptiva incluye de esta manera la combinación de las características de una realización cualquiera con las características de cualquier otra realización descrita. Todas las realizaciones y características de los compuestos de fórmula (I) se aplican a los compuestos de fórmula (Ia).

20

Los ejemplos de los compuestos de la invención incluyen los ejemplos 1 a 257 mostrados más adelante, así como las sales y los solvatos de los mismos.

5 Los compuestos de fórmula (I) pueden tener la capacidad de cristalizar en más de una forma. Esta es una característica conocida como polimorfismo, y se ha de entender que tales formas polimórficas ("polimorfos") están dentro del alcance de la fórmula (I). El polimorfismo generalmente se puede producir como respuesta a cambios en temperatura o presión o ambos y también se
10 puede producir por variaciones en el proceso de cristalización. Los polimorfos se pueden distinguir por diversas características físicas conocidas en la técnica tales como patrones de difracción de rayos X, solubilidad, y punto de fusión.

Ciertos de los compuestos descritos en esta memoria descriptiva
15 pueden existir en formas estereoisoméricas (es decir, pueden contener uno o más átomos de carbono asimétricos o pueden exhibir isomería cis - trans). Los estereoisómeros individuales (enantiómeros y diastereómeros) y las mezclas de estos están incluidos dentro del alcance de la presente invención. Del mismo modo, se ha de entender que los compuestos de fórmula (I) pueden
20 existir en formas tautómeras distintas de la mostrada en la fórmula y éstas están también incluidas dentro del alcance de la presente invención.

Como se ha indicado anteriormente, todos los enantiómeros individuales de los compuestos de fórmula (I) se pueden preparar. En una realización
25 preferida, se desea un enantiómero ópticamente puro. El término "enantiómero

ópticamente puro" significa que el compuesto contiene más que aproximadamente 90% del isómero deseado en peso, preferiblemente más que aproximadamente el 95% del isómero deseado en peso, y lo más preferiblemente más que aproximadamente el 99% del isómero deseado en peso, dicho porcentaje en peso basándose en el peso total del (de los) isómero(s) del compuesto. En algunos casos, un enantiómero de una estructura particular puede tener una actividad significativamente mayor que el otro enantiómero de la misma estructura. Compuestos quiralmente puros, o quiralmente enriquecidos se pueden preparar mediante síntesis quiralmente selectiva o mediante separación de enantiómeros. La separación de enantiómeros se puede llevar a cabo en el producto final o, como alternativa sobre un intermedio adecuado.

Los compuestos de esta invención se pueden preparar mediante una diversidad de procedimientos, incluyendo química convencional. Como se ha definido previamente variable continuará teniendo el significado definido previamente salvo que se indique de otra manera. Los procedimientos generales sintéticos ilustrativos se exponen más adelante y después los compuestos específicos de la invención se preparan en los ejemplos operativos.

Los compuestos de la fórmula general (I) se pueden preparar mediante procedimientos conocidos en la técnica de la síntesis orgánica como se ha expuesto en parte de los siguientes esquemas de síntesis. También se reconoce que en todos los esquemas descritos más adelante, se entenderá

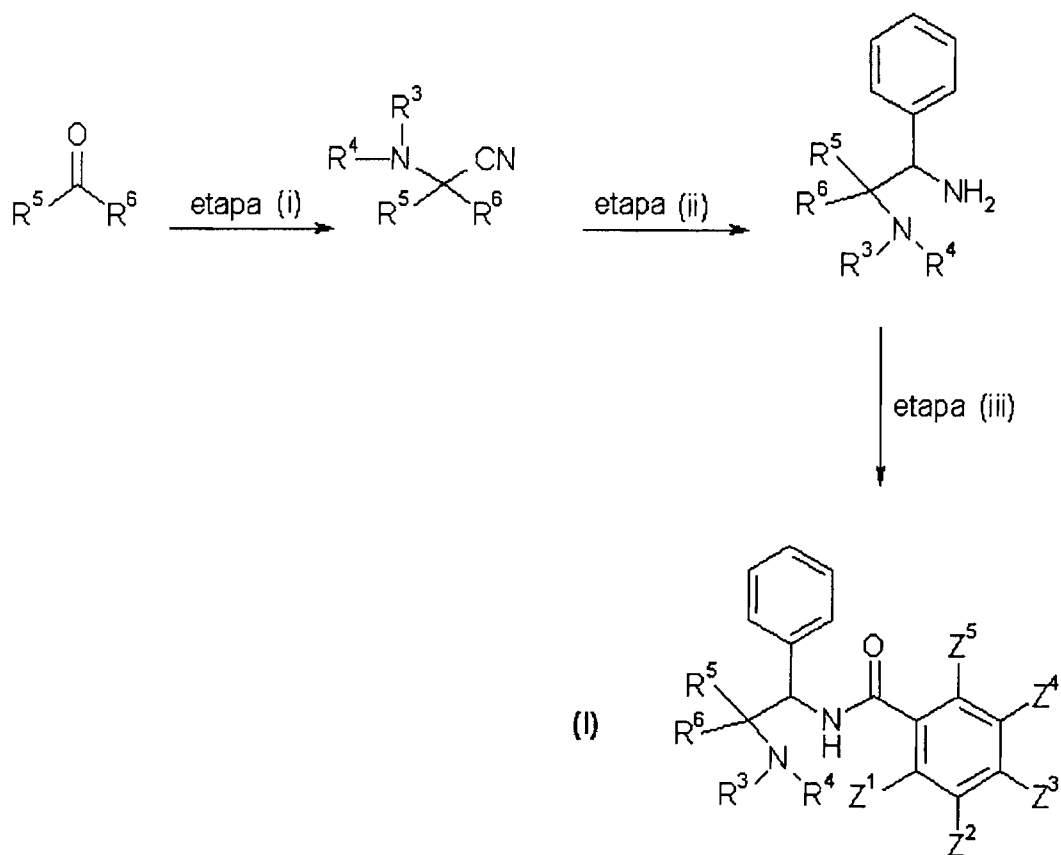
que se emplean grupos protectores para grupos sensibles o reactivos cuando sean necesarios de acuerdo con los principios generales de química. Los grupos protectores se manipulan de acuerdo con procedimientos convencionales de la síntesis orgánica (T. W. Greene and P. G. M. Wuts (1991) Protecting Groups in Organic Synthesis, John Wiley y Sons). Estos grupos se retiran en una fase conveniente de la síntesis del compuesto usando procedimientos que son fácilmente evidentes para los expertos en la técnica. La selección de procedimientos así como las condiciones de reacción y orden de su ejecución serán consistentes con la preparación de los compuestos de fórmula (I). Los expertos en la técnica reconocerán si existe un estereocentro en los compuestos de fórmula (I). De acuerdo con lo anterior, la presente invención incluye ambos estereoisómeros posibles e incluye no solamente los compuestos racémicos sino los enantiómeros individuales también. Cuando se indica que la estereoquímica es variable en ciertas posiciones, se puede obtener una mezcla de estereoisómeros, habiéndose separado esta mezcla cuando se indique. Los estereoisómeros se pueden separar mediante cromatografía líquida de alta resolución u otros medios apropiados. Cuando se desea un compuesto en forma de un enantiómero individual, se puede obtener mediante síntesis estereoespecífica o mediante resolución del producto final o cualquier intermedio conveniente. La resolución del producto final, un intermedio, o material de partida se puede efectuar mediante cualquier procedimiento adecuado en la técnica. Véase, por ejemplo, Stereochemistry of Organic Compounds por E. L. Eliel, S. H. Wilen, y L. N. Mander (Wiley-Interscience, 1994).

Las vías típicas de reacción para la preparación de un compuesto de fórmula (I) como se ha definido en esta memoria descriptiva anteriormente, se muestran en los siguientes esquemas. Los materiales de partida y reactivos se conocen por los expertos en la técnica y /o se pueden preparar usando
5 procedimientos conocidos en la técnica.

Los compuestos de fórmula (I) se pueden sintetizar mediante procedimientos conocidos; por ejemplo mediante, pero sin limitación a, la vía de síntesis indicada en el siguiente esquema.

10

Esquema 1



en la que R^3 , R^4 , R^5 , R^6 , Z^1 , Z^2 , Z^3 , Z^4 y Z^5 son como se han definido para el compuesto de fórmula (I).

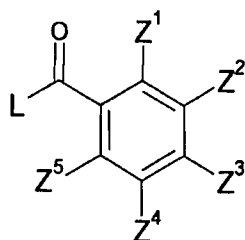
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La etapa (i) se lleva a cabo por ejemplo mediante reacción de una cetona con una amina o sal de amina en presencia de cianuro inorgánico, por ejemplo cianuro de potasio, en un disolvente tal como agua o mediante reacción de una cetona con una amina y cianuro de trimetilsililo en o bien la

10 ausencia de disolvente o en un disolvente tal como ácido acético.

La etapa (ii) se puede lograr mediante reacción sucesiva con un reactivo organometálico adecuado, por ejemplo fenil litio, en un disolvente inerte adecuado por ejemplo tetrahidrofurano, seguido de reducción con un agente reductor, por ejemplo, borohidruro de sodio en un disolvente adecuado, por ejemplo metanol.

La etapa de acilación (iii) se puede lograr mediante reacción con un compuesto de fórmula (III):



(III)

en la que Z¹, Z², Z³, Z⁴ y Z⁵ son como se han definido en la fórmula (I) y L representa un grupo saliente adecuado. Los ejemplos de grupos salientes incluyen halógeno, hidroxilo, OC(=O)alquilo, OC(=O)O-alquilo y OSO₂Me. L puede ser halógeno y la acilación en la etapa (iii) se puede llevar a cabo en un disolvente inerte tal como diclorometano en presencia de una base tal como trietilamina. Cuando L representa hidroxilo, la reacción preferiblemente tiene lugar en un disolvente inerte tal como diclorometano en presencia de un reactivo de acoplamiento, por ejemplo un reactivo diimida tal como N,N-diciclohexilcarbodiimida (DCC), clorhidrato de N-(3-(dimetilamino)propil)-N-etilcarbodiimida (EDC), EDC soportado por polímero, DCC soportado por

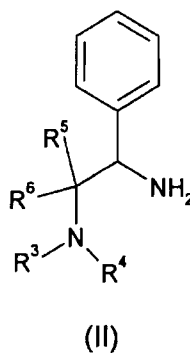
polímero o hexafluorofosfato de O-(7-azabenzotriazol-1-il)-1,1,3,3-tetrametiluronio (HATU).

Dentro del esquema existe el alcance de convertir un grupo R^3 en otro grupo R^3 y de manera similar para los grupos R^4 , R^5 y R^6 , y Z^1 , Z^2 , Z^3 , Z^4 y Z^5 .

De acuerdo con lo anterior, en un segundo aspecto, la presente invención proporciona un procedimiento de preparación de un compuesto de fórmula (I), que comprende la etapa de:

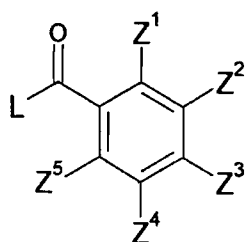
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hacer reaccionar un compuesto de fórmula (II):



15

en la que R^3 , R^4 , R^5 y R^6 son como se han definido en la fórmula (I), con un compuesto de fórmula (III):



(III)

en la que Z¹, Z², Z³, Z⁴ y Z⁵ son como se han definido en la fórmula (I) y L
5 representa un grupo saliente adecuado;

y después opcionalmente:

- retirar cualesquiera grupos protectores y/o
- convertir un compuesto de fórmula (I) en otro compuesto de fórmula (I) y/o
- 10 • formar una sal o solvato.

Los grupos salientes L adecuados incluyen halógeno, hidroxí, OC(=O)alquilo, OC(=O)O-alquilo y OSO₂Me.

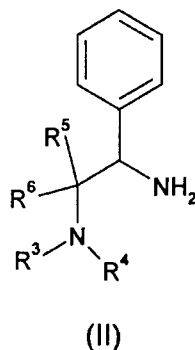
- 15 Los compuestos de fórmula (I) se pueden convertir en compuestos adicionales de fórmula (I) usando técnicas habituales. Por ejemplo, y a modo de ilustración más que como limitación, las posibles reacciones de conversión incluyen acilación con un agente acilante adecuado tal como cloruro de acetilo, alquilación usando un reactivo de alquilación apropiado tal como yoduro de
- 20 metilo, y sulfonilación usando un agente de sulfonilación tal como anhídrido metanosulfónico y N-alquilación mediante aminación reductora usando una

cetona o un aldehído en presencia de un agente reductor tal como triacetoxiborohidruro de sodio.

Las sales farmacéuticamente aceptables se pueden preparar
5 convencionalmente mediante reacción con el ácido o derivado de ácido apropiado.

En un aspecto adicional, la presente invención proporciona un compuesto de fórmula (II):

10



en la que R^3 , R^4 , R^5 y R^6 son como se han definido en la fórmula (I), con
15 la condición de que el compuesto de fórmula (II) no sea el compuesto en el que simultáneamente R^3 y R^4 junto con el átomo de nitrógeno al que están unidos forman un anillo de piperidina no sustituido y R^5 y R^6 junto con el átomo de carbono al que están unidos forman un anillo ciclopentilo no sustituido.

20 Los compuestos de fórmula (II) son útiles como intermedios en la síntesis de los compuestos de la invención.

Los compuestos de la presente invención inhiben el transportador de GlyT1. Los compuestos pueden inhibir selectivamente el transportador GlyT1 sobre el transportador GlyT2.

5

Tales compuestos serían adecuados para el tratamiento de ciertos trastornos neurológicos y neuropsiquiátricos. Como se usa en esta memoria descriptiva, los términos "tratamiento" y "tratar" se refieren al alivio y/o cura de síntomas establecidos así como profilaxis.

10

Las afinidades de los compuestos de esta invención por el transportador GlyT1 se pueden determinar mediante el siguiente ensayo.

Células HEK293 que expresan el transportador de glicina (Tipo 1) se hicieron crecer en medio de cultivo de células [mezcla DMEM/NUT F12 que
15 contiene L-glutamina 2 mM, 0,8 mg/ml de G418 y de suero de ternera fetal inactivado por calor al 10%] a 37°C y CO₂ al 5%. Las células desarrolladas hasta 70-80% de confluencia en matraces T175 se recogieron y se volvieron a suspender a $1,32 \times 10^6$ células/ml en tampón de ensayo [NaCl 140 mM, KCl 5,4 mM, CaCl₂ 1,8 mM, MgSO₄ 0,8 mM, HEPES 20 mM, glucosa 5 mM y
20 alanina 5 mM, pH 7,4]. Los compuestos se diluyeron en serie 2,5 veces en DMSO a partir de una concentración superior de 2,5 mM con cada uno de los compuestos proporcionando 11 puntos de datos dosis - respuesta. 100 nl del compuesto a cada concentración se añadió a la placa de ensayo. Un volumen igual de perlas WGA SPA Leadseeker™ (12,5 mg/ml suspendidos en tampón
25 de ensayo) se añadieron a la suspensión de células ($1,32 \times 10^6$) y 5 µl de la

suspensión de células/perlas se transfirieron a cada pocillo de una placa de 384 pocillos de fondo sólido de color blanco (3300 células /pocillo) que contiene 100 nl de los compuestos de ensayo. Se añadió sustrato (5 μ l) a cada pocillo [dilución 1:100 de solución madre de [^{3} H]-glicina en tampón de ensayo que contenía glicina 2,5 μ M). La concentración final en DMSO era 1% v/v. Se recogieron los datos usando un equipo Perkin Elmer Viewlux. Los valores de pCl_{50} se determinaron usando ActivityBase.

También se puede usar el siguiente ensayo:

Células HEK293 que expresan el transportador de Glicina (Tipo 1) se hacen crecer en medio celular (mezcla DMEM/NUT F12) que contiene L-glutamina 2 mM, 0,8 mg/ml de G418 y suero de ternera fetal inactivado por calor al 10% (Gibco BRL) a 37°C en CO₂ al 5%. Las células desarrolladas hasta 70 - 80% de confluencia en matraces T175 se recogen y se vuelven a suspender a 4×10^5 células/ml en tampón de ensayo [NaCl (140 mM), KCl (5,4 mM), CaCl₂ (1,8 mM), MgSO₄ (0,8 mM), HEPES (20 mM), glucosa (5 mM) y alanina (5 mM), pH 7,4]. Un volumen igual de perlas SPA de Leadseeker™ (12,5 mg/ml suspendidas en tampón de ensayo) se añade a la suspensión celular. Los compuestos se preparan en forma de soluciones madre 10 mM en DMSO. Se preparan diluciones en serie 2,5x de los compuestos en DMSO a partir de una concentración superior de 2,5 mM. 100 nl del compuesto en cada concentración se añade a la placa de ensayo (placa de fondo sólido de color blanco de 384 pocillos) usando el dispensador de colibrí. 5 μ l de la mezcla de célula/perla se añaden después a la parte superior del compuesto usando un dispensador de multigotas. Después se añade sustrato (5 μ l) a cada pocillo (dilución 1:100 de H3-glicina en tampón de ensayo que contiene glicina 2,5

μM). Los datos se recogen usando un equipo PerkinElmer Viewlux como exposiciones de 5 minutos. Los datos pCl_{50} se determinaron usando Activity Base.

- 5 Los compuestos se pueden ensayar en su forma de base libre o en la forma de una sal, por ejemplo la sal clorhidrato o la sal formiato. Los ensayos descritos anteriormente se considera generalmente que proporcionan datos que son correctos a ± 3 desviaciones típicas = $\pm 0,5$.
- 10 Los compuestos que tienen un valor de pCl_{50} en el transportador GlyT1 mayor o igual que 5 se considera que son activos en el transportador GlyT1. Los compuestos de los ejemplos más adelante se encontró que tenían un valor de pCl_{50} en el transportador GlyT1 mayor o igual que 5.
- 15 De acuerdo con lo anterior, en un aspecto adicional de la invención, se proporciona un compuesto de fórmula (I) o una sal o solvato del mismo: para uso en terapia.

En otro aspecto de la invención, se proporciona un compuesto de

20 fórmula (I) como se ha descrito en esta memoria descriptiva anteriormente o una sal o solvato del mismo, para uso en el tratamiento de un trastorno mediado por GlyT1.

Como se usa en esta memoria descriptiva, el término "un trastorno

25 mediado por GlyT1" se refiere a un trastorno que se puede tratar mediante la

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administración de un medicamento que altera la actividad del transportador de GlyT1. Como se ha descrito en esta memoria descriptiva anteriormente, la acción de los transportadores GlyT1 afecta a la concentración local de glicina alrededor de los receptores NMDA. Ya que una cierta cantidad de glicina se

5 necesita para el funcionamiento eficaz de los receptores NMDA, cualquier cambio de esa concentración local puede afectar a la neurotransmisión mediada por NMDA. Como se ha descrito en esta memoria descriptiva anteriormente, los cambios en la neurotransmisión mediada por NMDA han estado implicados en ciertos trastornos neuropsiquiátricos tales como

10 demencia, depresión y psicosis, por ejemplo esquizofrenia, y trastornos de aprendizaje y memoria, por ejemplo trastornos de déficit de atención y autismo. De este modo, las alteraciones en la actividad del transportador de GlyT1 se espera que influyan en tales trastornos.

15 Los trastornos mediados por GlyT1 referidos en esta memoria descriptiva incluyen trastornos neurológicos y neuropsiquiátricos, incluyendo psicosis tales como esquizofrenia, demencia y otras formas de cognición alterada tal como trastornos con déficit de atención y síndromes del cerebro orgánicos. Otros trastornos neuropsiquiátricos incluyen psicosis inducida por

20 fármacos (fenciclidina, ketamina y otros anestésicos disociativos, anfetamina y otros psicoestimulantes y cocaína), psicosis asociada a trastornos afectivos, breve psicosis reactiva, psicosis esquizoafectiva, y psicosis NOS, trastornos de "espectro de esquizofrenia" tales como trastornos de personalidad esquizoide o esquizotipal, o enfermedad asociada a psicosis (tal como depresión mayor,

25 trastorno maniaco depresivo (bipolar), enfermedad de Alzheimer y síndrome de

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estrés postraumático), y trastornos relacionados con receptores NMDA tales como autismo, depresión, olvido benigno, trastornos de aprendizaje en la infancia y lesión no abierta de la cabeza.

5 Los compuestos de fórmula (I) son de uso como agentes antipsicóticos por ejemplo en el tratamiento de esquizofrenia, trastornos esquizoafectivos, enfermedades esquizofreniformes, depresión psicótica, manía, manía aguda, trastornos paranoides y alucinatorios.

10 Dentro del contexto de la presente invención, los términos usados en esta memoria descriptiva están clasificados en el Diagnostic and Statistical Manual of Mental Disorders (Manual Diagnóstico y Estadístico de Trastornos Mentales), 4ª edición, publicado por la American Psychiatric Association (Asociación Americana de Psiquiatría) (DMS-IV) y/o la International
15 Classification of Diseases (Clasificación Internacional de Enfermedades), edición 10 (ICD-10). Los diversos subtipos de los trastornos mencionados en esta memoria descriptiva se contemplan como parte de la presente invención. Los números entre paréntesis después de las enfermedades enumeradas más adelante se refieren al código de clasificación en DSM-.IV.

20

 En particular, los compuestos de fórmula (I) son de uso en el tratamiento de esquizofrenia incluyendo los subtipos de tipo paranoide (295.30), de tipo desorganizado (295.10), de tipo catatónico (295.20), de tipo indiferenciado (295.90) y de tipo residual (295.60); trastorno esquizofreniforme (295.40);
25 trastorno esquizoafectivo (295.70) incluyendo los subtipos de tipo bipolar y de

tipo depresivo; trastorno alucinatorio (297.1) incluyendo los subtipos tipo erotomaniaco, tipo grandioso, tipo celoso, tipo persecutorio, tipo somático, tipo mixto y tipo inespecífico; trastorno psicótico breve (298.8); trastorno psicótico compartido (297.3); trastorno psicótico debido a una afección médica general
5 que incluye los subtipos con delirios y con alucinaciones; trastorno psicótico inducido por sustancias incluyendo los subtipos con delirios (293.81) y con alucinaciones (293.82); y trastorno psicótico no especificado de otra manera (298.9).

10 Los compuestos de fórmula (I) son también de uso en el tratamiento de trastornos de ánimo incluyendo episodio depresivo mayor, episodio maniaco, episodio mixto y episodio hipomaniaco; trastornos depresivos incluyendo trastorno depresivo mayor, trastorno distímico (300.4), trastorno depresivo no especificado de otra manera (311); trastornos bipolares incluyendo trastorno
15 bipolar I, trastorno bipolar II (episodios depresivos mayores recurrentes con episodios hipomaniacos) (296.89), trastorno ciclotímico (301.13) y trastorno bipolar no especificado de otra manera (296.80); otros trastornos de ánimo incluyendo trastorno de ánimo debido a una afección médica general (293.83) que incluye los subtipos con características depresivas, con episodio de tipo
20 depresivo mayor, con características maníacas y con características mixtas), trastorno de ánimo inducido por sustancias (incluyendo los subtipos con características depresivas, con características maníacas y con características mixtas) y trastorno de ánimo no especificado de otra manera (296.90).

Los compuestos de fórmula (I) son también de uso en el tratamiento de trastornos de ansiedad incluyendo ataque de pánico, agorafobia, trastorno de pánico, agorafobia sin historial de trastorno de pánico (300.22), fobia específica (300.29) incluyendo los subtipos de tipo animal, de tipo ambiente natural, de tipo sangre-inyección-lesión, de tipo situacional y de otro tipo), fobia social (300.23), trastorno obsesivo compulsivo (300.3), trastorno de estrés postraumático (309.81), trastorno de estrés agudo (308.3), trastorno de ansiedad generalizada (300.02), trastorno de ansiedad debido a una afección médica general (293.84), trastorno de ansiedad inducido por sustancias y

10 trastorno de ansiedad no especificado de otra manera (300.00).

Los compuestos de fórmula (I) son también de uso en el tratamiento de trastornos relacionados con sustancias incluyendo trastornos de uso de sustancias tales como dependencia de sustancias y abuso de sustancias; trastornos inducidos por sustancias tales como intoxicación por sustancias,

15 abstinencia de sustancias, delirio inducido por sustancias, demencia persistente inducida por sustancias, trastorno amnésico persistente inducido por sustancias, trastorno psicótico inducido por sustancias, trastorno de ánimo inducido por sustancias, trastorno de ansiedad inducido por sustancias, disfunción sexual inducida por sustancias, trastorno del sueño inducido por

20 sustancias y trastorno de percepción persistente por alucinógenos (escenas retrospectivas); trastornos relacionados con alcohol tales como dependencia del alcohol (303.90), abuso de alcohol (305.00), intoxicación por alcohol (303.00), abstinencia de alcohol (291.81), delirio por intoxicación por alcohol, delirios por abstinencia de alcohol, demencia persistente inducida por alcohol,

25 trastorno amnésico persistente inducido por alcohol, trastorno psicótico

inducido por alcohol, trastorno de ánimo inducido por alcohol, trastorno de ansiedad inducido por alcohol, disfunción sexual inducida por alcohol, trastorno del sueño inducido por alcohol y trastorno relacionado con alcohol no especificado de otra manera (291.9); trastornos relacionados con anfetaminas

5 (o de tipo anfetaminas) tales como dependencia de anfetaminas (304.40), abuso de anfetaminas (305.70), intoxicación por anfetaminas (292.89), abstinencia de anfetaminas (292.0), delirio de intoxicación por anfetaminas, trastorno psicótico inducido por anfetaminas, trastorno de ánimo inducido por anfetaminas, trastorno de ansiedad inducido por anfetaminas, disfunción sexual

10 inducida por anfetaminas, trastorno de sueño inducido por anfetaminas y trastorno relacionado con anfetamina no especificado de otra manera (292.9); trastornos relacionados con cafeína tales como intoxicación por cafeína (305.90), trastorno de ansiedad inducido por cafeína, trastorno de sueño inducido por cafeína y trastorno relacionado con cafeína no especificado de

15 otra manera (292.9); trastornos relacionados con marihuana tales como dependencia de marihuana (304.30), abuso de marihuana (305.20), intoxicación por marihuana (292.89), delirio por intoxicación por marihuana, trastorno psicótico inducido por marihuana, trastorno de ansiedad inducido por marihuana y trastorno relacionado con marihuana no especificado de otra

20 manera (292.9); trastornos relacionados con cocaína tales como dependencia de cocaína (304.20), abuso de cocaína (305.60), intoxicación por cocaína (292.89), abstinencia de cocaína (292.0), delirio por intoxicación por cocaína, trastorno psicótico inducido por cocaína, trastorno de ánimo inducido por cocaína, trastorno de ansiedad inducido por cocaína, disfunción sexual

25 inducida por cocaína, trastorno de sueño inducido por cocaína y trastorno

relacionado con cocaína no especificado de otra manera (292.9); trastornos relacionados con alucinógeno tales como dependencia de alucinógeno (304.50), abuso de alucinógeno (305.30), intoxicación por alucinógeno (292.89), trastorno de percepción persistente por alucinógeno (escenas retrospectivas) (292.89), delirio por intoxicación por alucinógeno, trastorno psicótico inducido por alucinógeno, trastorno de ánimo inducido por alucinógeno, trastorno de ansiedad inducido por alucinógeno y trastorno relacionado con alucinógeno no especificado de otra manera (292.9); trastornos relacionados con inhaladores tales como dependencia de inhaladores (304.60), abuso de inhaladores (305.90), intoxicación por inhaladores (292.89), delirio por intoxicación por inhaladores, demencia persistente inducida por inhaladores, trastorno psicótico inducido por inhaladores, trastorno de ánimo inducido por inhaladores, trastorno de ansiedad inducido por inhaladores y trastorno relacionado con inhaladores no especificado de otra manera (292.9); trastornos relacionados con nicotina tales como dependencia de nicotina (305.1), abstinencia de nicotina (292.0) y trastorno relacionado con nicotina no especificado de otra manera (292.9); trastornos relacionados con opioides tales como dependencia de opioides (304.00), abuso de opioides (305.50), intoxicación por opioides (292.89), abstinencia de opioides (292.0), delirio por intoxicación por opioides, trastorno psicótico inducido por opioides, trastorno de ánimo inducido por opioides, disfunción sexual inducida por opioides, trastorno del sueño inducido por opioides, y trastorno relacionado con opioides no especificado de otra manera (292.9); trastornos relacionados con fenciclidina (o de tipo fenciclidina) tales como dependencia de fenciclidina (304.60), abuso de fenciclidina (305.90),

intoxicación por fenciclidina (292.89), delirio por intoxicación por fenciclidina, trastorno psicótico inducido por fenciclidina, trastorno de ánimo inducido por fenciclidina, trastorno de ansiedad inducido por fenciclidina y trastorno relacionado con fenciclidina no especificado de otra manera (292.9); trastornos

5 relacionados con sedantes, hipnóticos, o ansiolíticos tales como dependencia de sedantes, hipnóticos, o ansiolíticos (304.10), abuso de sedantes, hipnóticos, o ansiolíticos (305.40), intoxicación por sedantes, hipnóticos, o ansiolíticos (292.89), abstinencia de sedantes, hipnóticos, o ansiolíticos (292.0), delirio por intoxicación por sedantes, hipnóticos, o ansiolíticos, delirio por abstinencia de

10 sedantes, hipnóticos, o ansiolíticos, demencia persistente por sedantes, hipnóticos, o ansiolíticos, trastorno amnésico persistente por sedantes, hipnóticos, o ansiolíticos, trastorno psicótico inducido por sedantes, hipnóticos, o ansiolíticos, trastorno de ánimo inducido por sedantes, hipnóticos, o ansiolíticos, trastorno de ansiedad inducido por sedantes, hipnóticos, o

15 ansiolíticos, disfunción sexual inducida por sedantes, hipnóticos, o ansiolíticos, trastorno del sueño inducido por sedantes, hipnóticos, o ansiolíticos y trastorno relacionado con sedantes, hipnóticos, o ansiolíticos no especificado de otra manera (292.9); trastornos relacionados con polisustancias tales como dependencia de polisustancias (304.80) y trastornos relacionados con otras

20 sustancias (o desconocidas) tales como esteroides anabólicos, inhaladores de nitrato y óxido nitroso.

Los compuestos de fórmula (I) son también útiles en el tratamiento de trastornos del sueño incluyendo trastornos primarios del sueño tales como

25 disomnias tales como insomnio primario (307.42), hipersomnio primario

- (307.44), narcolepsia (347), trastornos del sueño relacionados con la respiración (780.59), trastorno del sueño de ritmo circadiano (307.45), y disomnio no especificado de otra manera (307.47); trastornos primarios del sueño tales como parasomnias tales como trastorno de pesadillas (307.47),
- 5 trastorno de terror del sueño (307.46), trastorno de sonambulismo (307.46) y parasomnias no especificados de otra manera (307.47); trastornos del sueño relacionados con otro trastorno mental tal como insomnio relacionado con otro trastorno mental (307.42) e hipersomnio relacionado con otro trastorno mental (307.44); trastorno del sueño debido a una afección médica general; y trastorno
- 10 del sueño inducido por sustancias incluyendo los subtipos de tipo insomnio, tipo hipersomnio, tipo parasomnia y tipo mixto.

- Los compuestos de fórmula (I) son también de uso en el tratamiento de trastornos de alimentación tales como anorexia nerviosa (307.1) incluyendo los
- 15 subtipos tipo restrictivo y tipo alimentación por comilona/purgante; bulimia nerviosa (307.51) incluyendo los subtipos tipo purgante y tipo no purgante; obesidad; trastorno de alimentación compulsivo; y trastorno de alimentación no especificado de otra manera (307.50).

- 20 Los compuestos de fórmula (I) son también de uso en el tratamiento de trastorno de autismo (299.00), trastorno de déficit de atención/hiperactividad incluyendo los subtipos tipo combinado de trastorno de déficit de atención/hiperactividad (314.01), tipo predominantemente de inatención de trastorno déficit de atención/hiperactividad (314.00), tipo hiperactivo - de
- 25 impulso de trastorno déficit de atención/hiperactividad (314.01) y trastorno

déficit de atención/hiperactividad no especificado de otra manera (314.9); trastorno hiperactivo; trastornos de comportamiento disruptivo tales como trastorno de conducta incluyendo los subtipos tipo comienzo de la infancia (321.81), tipo comienzo de adolescencia (312.82) y comienzo no especificado (312.89), trastorno desafiante oposicional (313.81) y trastorno del comportamiento disruptivo no especificado de otra manera; y trastornos de tic tales como síndrome de Tourette (307.23).

Los compuestos de fórmula (I) son también de uso en el tratamiento de

10 trastornos de personalidad incluyendo los subtipos trastorno de personalidad paranoide (301.0), trastorno de personalidad esquizoide (301.20), trastorno de personalidad esquizotípica (301.22), trastorno de personalidad antisocial (301.7), trastorno de personalidad límite (301.83), trastorno de personalidad histriónica (301.50), trastorno de personalidad narcisista (301.81), trastorno de anulación

15 de personalidad (301.82), trastorno de personalidad dependiente (301.6), trastorno de personalidad obsesiva compulsiva (301.4) y trastorno de personalidad no especificado de otra manera (301.9).

Los compuestos de fórmula (I) son también de uso en la potenciación de

20 la cognición incluyendo el tratamiento de alteración de cognición en otras enfermedades tales como esquizofrenia, trastorno bipolar, depresión, otros trastornos psiquiátricos y afecciones psicóticas asociadas a alteración cognitiva. Dentro del contexto de la presente invención, el término alteración cognitiva incluye por ejemplo el tratamiento de alteración de funciones

25 cognitivas incluyendo atención, orientación, trastornos de aprendizaje, memoria

(es decir, trastornos de memoria, amnesia, trastornos amnésicos, síndrome de amnesia global transitoria y alteración de la memoria asociada a la edad) y función del lenguaje; alteración cognitiva como resultado de apoplejía, enfermedad de Alzheimer, enfermedad de Huntington, enfermedad de Pick,

5 demencia relacionada con sida u otros estados de demencia tales como demencia multiinfarto, demencia alcohólica, demencia relacionada con hipotiroidismo, y demencia asociada a otros trastornos degenerativos tales como atrofia cerebelar y esclerosis lateral amiotrófica; otras afecciones agudas o subagudas que pueden provocar deterioro cognitivo tal como trauma por

10 delirio o depresión (estados de pseudodemencia), trauma cefálico, deterioro cognitivo relacionado con la edad, apoplejía, neurodegeneración, estados inducidos por fármacos, agentes neurotóxicos, alteración cognitiva suave, alteración cognitiva relacionada con la edad, alteración cognitiva relacionada con autismo, síndrome de Down, déficit cognitivo relacionado con psicosis, y

15 trastornos cognitivos relacionados con el post tratamiento electroconvulsivo; y trastornos discinéticos tales como enfermedad de Parkinson, parquinsonismo inducido por neurolépticos, y discinesias tardías.

Los compuestos de fórmula (I) son también de uso en el tratamiento de

20 disfunciones sexuales incluyendo trastornos del deseo sexual tales como trastorno del deseo sexual hipoactivo (302.71), y trastorno de aversión sexual (302.79); trastornos de excitación sexual tales como trastorno de excitación sexual femenino (302.72) y disfunción eréctil masculina (302.72); trastornos orgásmicos tales como trastorno orgásmico femenino (302.73), trastorno

25 orgásmico masculino (302.74) y eyaculación precoz (302.75); trastorno de

dolor sexual como dispareunia (302.76) y vaginismo (306.51); disfunción sexual no especificada de otra manera (302.70); parafilias tales como exhibicionismo (302.4), fetichismo (302.81), froteurismo (302.89), pedofilia (302.2), masoquismo sexual (302.83), sadismo sexual (302.84), fetichismo de travestís (302.3), voyeurismo (302.82) y parafilia no especificada de otra manera (302.9); trastornos de identidad de género tales como trastornos de identidad de género en niños (302.6) y trastornos de identidad de género en adolescentes o adultos (302.85); y trastorno sexual no especificado de otra manera (302.9).

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La invención también proporciona un compuesto de fórmula (I) como se ha descrito en esta memoria descriptiva anteriormente o una sal o solvato farmacéuticamente aceptable del mismo para uso en el tratamiento de esquizofrenia, trastornos de ánimo, trastornos de ansiedad, trastornos relacionados con sustancias, trastornos del sueño, trastornos de alimentación, trastorno autístico, trastorno de déficit de atención/hiperactividad, trastorno de comportamiento disruptivo, trastornos de tic, trastornos de personalidad, alteración de cognición en otras enfermedades, disfunción sexual, enfermedad de Parkinson, trastornos discinéticos, depresión, trastorno bipolar, alteración cognitiva, obesidad, emesis, trastornos del movimiento, trastornos obsesivos compulsivos, amnesia, agresión, vértigo, demencia y trastornos del ritmo circadiano.

La invención también proporciona un compuesto de fórmula (I) como se ha descrito en esta memoria descriptiva anteriormente o una sal o solvato

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farmacéuticamente aceptable del mismo para uso en el tratamiento de trastornos psicóticos, abuso de sustancias, alteración cognitiva, obesidad, y trastornos de motilidad gástrica.

- 5 En otro aspecto de la invención, se proporciona un procedimiento de tratamiento de un mamífero, incluyendo un ser humano, que sufre de o es susceptible a un trastorno mediado por GlyT1, que comprende la administración de una cantidad eficaz de un compuesto de fórmula (I) como se ha definido en esta memoria descriptiva anteriormente o una sal o solvato del
- 10 mismo.

La invención también proporciona un procedimiento de tratamiento de esquizofrenia, trastornos de ánimo, trastornos de ansiedad, trastornos relacionados con sustancias, trastornos del sueño, trastornos de la

15 alimentación, trastorno autístico, trastorno de déficit de atención/hiperactividad, trastorno de comportamiento disruptivo, trastornos de tic, trastornos de personalidad, alteración de cognición en otras enfermedades, disfunción sexual, enfermedad de Parkinson, trastornos discinéticos, depresión, trastorno bipolar, alteración cognitiva, obesidad, emesis, trastornos del movimiento,

20 trastornos obsesivos compulsivos, amnesia, agresión, vértigo, demencia y trastornos del ritmo circadiano que comprende la administración a un mamífero en necesidad del mismo de una cantidad eficaz de un compuesto de fórmula (I) como se ha descrito en esta memoria descriptiva anteriormente o una sal o solvato farmacéuticamente aceptable del mismo.

La invención también proporciona un procedimiento de tratamiento de trastornos psicóticos, abuso de sustancias, alteración cognitiva, obesidad y trastornos de motilidad gástrica que comprende la administración a un mamífero en necesidad del mismo de una cantidad eficaz de un compuesto de fórmula (I) como se ha descrito en esta memoria descriptiva anteriormente o una sal o solvato farmacéuticamente aceptable del mismo.

Los compuestos de fórmula (I) son también de uso como anticonvulsivos. Los compuestos de fórmula (I) son de esta manera útiles en el tratamiento de convulsión en mamíferos, y particularmente epilepsia en seres humanos. La "epilepsia" pretende incluir las siguientes convulsiones: convulsiones parciales simples, convulsiones parciales complejas, convulsiones generalizadas secundarias, convulsiones generalizadas que incluyen convulsiones por ausencia, convulsiones mioclónicas, convulsiones clónicas, convulsiones tónicas, convulsiones clónicas tónicas y convulsiones atónicas. La invención también proporciona un procedimiento de tratamiento de convulsiones, que comprende la administración a un mamífero en necesidad del mismo de una cantidad eficaz de un compuesto de fórmula (I) como se ha descrito en esta memoria descriptiva anteriormente o una sal o solvato farmacéuticamente aceptable del mismo. El tratamiento de epilepsia se puede llevar a cabo mediante la administración de una cantidad eficaz anticonvulsiva no tóxica de un compuesto de fórmula (III) o una sal o una composición farmacéuticamente aceptable como se ha descrito en esta memoria descriptiva anteriormente.

Los compuestos de fórmula (I) también encuentran uso en el tratamiento de dolor neuropático, por ejemplo en neuropatía diabética, ciática, dolor de la parte inferior de la espalda no específico, dolor de esclerosis múltiple, fibromialgia, neuropatía relacionada con VIH, neuralgia tal como neuralgia post-herpética y neuralgia trigeminal y dolor que se produce por trauma físico, amputación, cáncer, toxinas o afecciones inflamatorias crónicas.

En otro aspecto de la invención, se proporciona el uso de un compuesto de fórmula (I) como se ha descrito en esta memoria descriptiva anteriormente o una sal o solvato del mismo en la preparación de un medicamento para el tratamiento de un trastorno mediado por GlyT1.

Preferiblemente, el trastorno mediado por GlyT1 a tratar mediante el uso o procedimiento como se ha descrito en esta memoria descriptiva anteriormente es una psicosis, incluyendo esquizofrenia, demencia y trastornos de déficit de atención, particularmente esquizofrenia.

La invención también proporciona el uso de un compuesto de fórmula (I) como se ha descrito en esta memoria descriptiva anteriormente o una sal o solvato farmacéuticamente aceptable del mismo en la fabricación de un medicamento para el tratamiento de esquizofrenia, trastornos de ánimo, trastornos de ansiedad, trastornos relacionados con sustancias, trastornos del sueño, trastornos de la alimentación, trastorno autístico, trastorno de déficit de atención/hiperactividad, trastorno de comportamiento disruptivo, trastornos de tic, trastornos de personalidad, alteración de la cognición en otras

enfermedades, disfunción sexual, enfermedad de Parkinson, trastornos discinéticos, depresión, trastorno bipolar, alteración cognitiva, obesidad, emesis, trastornos del movimiento, trastornos obsesivos compulsivos, amnesia, agresión, vértigo, demencia y trastornos del ritmo circadiano.

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La invención también proporciona el uso de un compuesto de fórmula (I) como se ha descrito en esta memoria descriptiva anteriormente o una sal o solvato farmacéuticamente aceptable del mismo en la fabricación de un medicamento para el tratamiento de trastornos psicóticos, abuso de sustancias,
10 alteración cognitiva, obesidad y trastornos de motilidad gástrica.

Como se usa en esta memoria descriptiva, el término "cantidad eficaz" significa la cantidad de un fármaco o agente farmacéutico que generará la respuesta biológica o médica de un tejido, sistema, animal o ser humano que
15 se está pretendiendo, por ejemplo, por un investigador o médico.

Los compuestos para uso de acuerdo con la invención se pueden administrar como material bruto pero los ingredientes activos preferiblemente se proporcionan en la forma de composiciones farmacéuticas.

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De acuerdo con lo anterior, en un aspecto adicional de la invención, se proporciona una composición farmacéutica que comprende un compuesto de fórmula (I) como se ha descrito en esta memoria descriptiva anteriormente o una sal o solvato del mismo, y al menos un vehículo, diluyente o excipiente
25 farmacéuticamente aceptable.

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Estas composiciones farmacéuticas se pueden usar en el tratamiento de afecciones clínicas para las que un inhibidor GlyT1 está indicado tal como, por ejemplo, esquizofrenia. El vehículo debe ser farmacéuticamente aceptable para el receptor y debe ser compatible con, es decir, no tener un efecto perjudicial sobre, los otros ingredientes en la composición. El vehículo puede ser un sólido o líquido y preferiblemente se formula con al menos un compuesto de fórmula (I) o una sal o solvato del mismo como una formulación de dosis unitaria. Si se desea, otros ingredientes fisiológicamente activos también se pueden incorporar en la composición farmacéutica de la invención.

Los expertos en la técnica apreciarán que los compuestos de acuerdo con la invención se pueden usar de manera ventajosa junto con uno o más agentes terapéuticos distintos, por ejemplo, agentes antidepresivos diferentes tales como antagonistas de 5HT₃, agonistas de serotonina, antagonistas de NK-1, inhibidores selectivos de la recaptación de serotonina (SSRI), inhibidores de la recaptación de noradrenalina (SNRI), antidepresivos tricíclicos, antidepresivos dopaminérgicos, antagonistas de H₃, antagonistas de 5HT_{1A}, antagonistas de 5HT_{1B}, antagonistas de 5HT_{1D}, agonistas de D₁, agonistas de M₁ y/o agentes anticonvulsivos, así como fármacos antipsicóticos atípicos y potenciadores cognitivos.

Los antagonistas de 5HT₃ adecuados que se pueden usar en combinación con los compuestos de las invenciones incluyen por ejemplo ondansetron, granisetron, metoclopramida.

Los agonistas de serotonina adecuados que se pueden usar en combinación con los compuestos de la invención incluyen sumatriptán, rauwolscina, yohimbina, metoclopramida.

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Los SSRI adecuados que se pueden usar en combinación con los compuestos de la invención incluyen fluoxetina, citalopram, femoxetina, fluvoxamina, paroxetina, indalpina, sertralina, zimeldina.

10 Los SNRI adecuados que se pueden usar en combinación con los compuestos de la invención incluyen venlafaxina y reboxetina.

Los antidepresivos tricíclicos adecuados que se pueden usar en combinación con un compuesto de la invención incluyen imipramina, 15 amitriptilina, clomipramina y nortriptilina.

Los antidepresivos dopaminérgicos adecuados que se pueden usar en combinación con un compuesto de la invención incluyen bupropión y amineptina.

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Los agentes anticonvulsivos adecuados que se pueden usar en combinación con los compuestos de la invención incluyen por ejemplo divalproex, carbamazepina y diazepam.

Los fármacos antipsicóticos atípicos adecuados que se pueden usar en combinación con los compuestos de la invención incluyen por ejemplo risperidona, olanzapina, ziprasidona, aripiprazol y clozapina.

- 5 Se apreciará que los compuestos de la combinación o composición se puede administrar de manera simultánea (o bien en la misma o en diferentes formulaciones farmacéuticas), de manera separada o secuencial.

- Los compuestos de fórmula (I) y sus sales y solvatos farmacéuticamente
10 aceptables de los mismos son también adecuados para combinación con otros antipsicóticos típicos y atípicos para proporcionar tratamiento mejorado de los trastornos psicóticos. Las ventajas particulares asociadas con las combinaciones, usos y procedimientos de tratamiento de los compuestos de fórmula (I) y sus sales y solvatos farmacéuticamente aceptables incluyen
15 eficacia equivalente o mejorada a dosis de administración que son menores que las comúnmente usadas para los componentes individuales. También se pueden observar tratamientos mejorados de los síntomas positivos y/o síntomas negativos y/o síntomas cognitivos del trastorno psicótico. Las combinaciones, usos y procedimientos de tratamiento de la invención pueden
20 también proporcionar ventajas en el tratamiento de pacientes que no responden adecuadamente o que son resistentes al tratamiento con ciertos agentes neurolépticos.

- Las terapias de combinación de la invención se administran
25 preferiblemente de manera auxiliar. Por administración auxiliar se quiere decir

la administración idéntica o superpuesta de cada uno de los componentes en la forma de composiciones o dispositivos farmacéuticos separados. Este régimen de administración terapéutica de dos o más agentes terapéuticos es denominado generalmente por los expertos en la técnica y en esta memoria

5 descriptiva como administración terapéutica auxiliar; también conocida como administración terapéutica anexa. Cualesquiera y todos los regímenes de tratamiento en los que el paciente recibe administración terapéutica separada pero idéntica o superpuesta de los compuestos de fórmula (I) o una sal o solvato farmacéuticamente aceptable de los mismos y al menos un agente

10 neuroléptico están dentro del alcance la presente invención. En una realización de administración terapéutica auxiliar como se describe en esta memoria descriptiva, un paciente está típicamente estabilizado en una administración terapéutica de uno o más de los componentes durante un período de tiempo y después recibe administración de otro componente. Dentro del alcance de esta

15 invención, se prefiere que los compuestos de fórmula (I) o una sal o solvato farmacéuticamente aceptable de los mismos se administre como tratamiento terapéutico auxiliar a pacientes que están recibiendo administración de al menos un agente neuroléptico, pero el alcance de la invención también incluye la administración terapéutica auxiliar de al menos un agente neuroléptico a

20 pacientes que están recibiendo la administración de compuestos de fórmula (I) o una sal o solvato farmacéuticamente aceptable de los mismos.

Las terapias de combinación de la invención también se pueden administrar de manera simultánea. Por administración simultánea se quiere

25 decir un régimen de tratamiento en el que los componentes individuales se

administran juntos, o bien en la forma de una composición o dispositivo farmacéutico individual que comprende o contiene ambos componentes, o como composiciones o dispositivos separados, comprendiendo cada uno de los cuales uno de los componentes, administrados de manera simultánea. Tales
5 combinaciones de los componentes individuales separados para la combinación simultánea se pueden proporcionar en la forma de un kit de partes.

En un aspecto adicional, la invención proporciona un procedimiento de
10 tratamiento de un trastorno psicótico mediante la administración terapéutica auxiliar de los compuestos de fórmula (I) o una sal o solvato farmacéuticamente aceptable de los mismos a un paciente que recibe la administración terapéutica de al menos un agente neuroléptico. En un aspecto adicional, la invención proporciona el uso de compuestos de fórmula (I) o una
15 sal o solvato farmacéuticamente aceptable de los mismos en la fabricación de un medicamento para la administración terapéutica auxiliar para el tratamiento de un trastorno psicótico en un paciente que recibe administración terapéutica de al menos un agente neuroléptico. La invención proporciona adicionalmente compuestos de fórmula (I) o una sal o solvato farmacéuticamente aceptable de
20 los mismos para uso para la administración terapéutica auxiliar para el tratamiento de un trastorno psicótico en un paciente que recibe la administración terapéutica de al menos un agente neuroléptico.

En un aspecto adicional la invención proporciona un procedimiento de
25 tratamiento de un trastorno psicótico mediante la administración terapéutica

auxiliar de al menos un agente neuroléptico a un paciente que recibe la administración terapéutica de los compuestos de fórmula (I) o una sal o solvato farmacéuticamente aceptable de los mismos. En un aspecto adicional, la invención proporciona el uso de al menos un agente neuroléptico en la
5 fabricación de un medicamento para la administración terapéutica auxiliar para el tratamiento de un trastorno psicótico en un paciente que recibe la administración terapéutica de los compuestos de fórmula (I) o una sal o solvato farmacéuticamente aceptable de los mismos. La invención proporciona adicionalmente al menos un agente neuroléptico para la administración
10 terapéutica auxiliar para el tratamiento de un trastorno psicótico en un paciente que recibe la administración terapéutica de los compuestos de fórmula (I) o una sal o solvato farmacéuticamente aceptable de los mismos.

En un aspecto adicional la invención proporciona un procedimiento de
15 tratamiento de un trastorno psicótico mediante la administración terapéutica simultánea de los compuestos de fórmula (I) o una sal o solvato farmacéuticamente aceptable de los mismos en combinación con al menos un agente neuroléptico. La invención proporciona además el uso de una combinación de los compuestos de fórmula (I) o una sal o solvato
20 farmacéuticamente aceptable de los mismos y al menos un agente neuroléptico en la fabricación de un medicamento para la administración terapéutica simultánea en el tratamiento de un trastorno psicótico. La invención proporciona adicionalmente el uso de los compuestos de fórmula (I) o una sal farmacéuticamente aceptable de los mismos en la fabricación de un
25 medicamento para la administración terapéutica simultánea con al menos un

agente neuroléptico en el tratamiento de un trastorno psicótico. La invención proporciona adicionalmente compuestos de fórmula (I) o una sal farmacéuticamente aceptable de los mismos para uso para administración terapéutica simultánea con al menos un agente neuroléptico en el tratamiento

5 de un trastorno psicótico. La invención proporciona adicionalmente el uso de al menos un agente neuroléptico en la fabricación de un medicamento para la administración terapéutica simultánea con los compuestos de fórmula (I) o una sal farmacéuticamente aceptable de los mismos en el tratamiento de un trastorno psicótico.

10

En aspectos adicionales, la invención proporciona un procedimiento de tratamiento de un trastorno psicótico mediante la administración terapéutica simultánea de una composición farmacéutica que comprende los compuestos de fórmula (I) o una sal o solvato farmacéuticamente aceptable de los mismos

15 y al menos un agente estabilizante del ánimo o antimaníaco, una composición farmacéutica que comprende los compuestos de fórmula (I) o una sal o solvato farmacéuticamente aceptable de los mismos y al menos un agente estabilizante del ánimo o antimaníaco, el uso de una composición farmacéutica que comprende los compuestos de fórmula (I) o una sal o solvato

20 farmacéuticamente aceptable de los mismos y al menos un agente estabilizante del ánimo o antimaníaco en la fabricación de un medicamento para el tratamiento de un trastorno psicótico, y una composición farmacéutica que comprende los compuestos de fórmula (I) o una sal o solvato farmacéuticamente aceptable de los mismos y al menos un agente

estabilizante del ánimo o antimaníaco para uso en el tratamiento de un trastorno psicótico.

En un aspecto adicional, la invención proporciona un kit de partes para
5 uso en el tratamiento de un trastorno psicótico que comprende una primera
forma de dosificación que comprende los compuestos de fórmula (I) o una sal o
solvato farmacéuticamente aceptable de los mismos y una o más formas de
dosificación adicionales comprendiendo cada una un agente neuroléptico para
la administración terapéutica simultánea.

10

Dentro del contexto de la presente invención, el término trastorno
psiquiátrico incluye aquellos trastornos mencionados anteriormente, tales como
esquizofrenia, trastornos de ánimo, trastornos de ansiedad, trastornos
relacionados con sustancias, trastornos del sueño, trastornos de la
15 alimentación, trastorno autístico, trastorno de déficit de atención/hiperactividad,
trastorno del comportamiento disruptivo, trastornos de tic, trastornos de
personalidad, alteración de cognición en otras enfermedades, disfunción
sexual, trastornos discinéticos, depresión, trastorno bipolar, alteración cognitiva
y trastornos obsesivo compulsivos y todas las diversas formas de los trastornos
20 como se ha mencionado en esta memoria descriptiva, que se contemplan
como parte de la presente invención.

Los ejemplos de fármacos neurolépticos/antipsicóticos que son útiles en
la presente invención incluyen, pero no se limitan a: butirofenonas, tales como
25 haloperidol, pimozida, y droperidol; fenotiazinas, tales como clorpromazina,

tioridazina, mesoridazina, trifluoperazina, perfenazina, flufenazina, triflupromazina, proclorperazina, y acetofenazina; tioxantenos, tales como tiotixeno y clorprotixeno; tienobenzodiazepinas; dibenzodiazepinas; benzoisoxazoles; dibenzotiazepinas; imidazolidinonas; benzoisotiazolil -
 5 piperazinas; triazina tal como lamotrigina; dibenzoxazepinas, tal como loxapina; dihidroindolonas, tal como molindona; aripiprazol; y los derivados de los mismos que tienen actividad antipsicótica.

Los ejemplos de fármacos neurolépticos que se prefieren para uso en la
 10 presente invención se muestran en la tabla A.

Tabla A

15

Fármacos neurolépticos

Nombre común	Nombre comercial	Vía de administración	Forma	Intervalo de Dosificación y (Mediana) ^a
Clozapina	CLOZARIL	oral	comprimidos	12,5 - 900 mg/día (300 - 900 mg/día)
Olanzapina	ZYPREXA	oral	comprimidos	5 - 25 mg/día

Nombre común	Nombre comercial	Vía de administración	Forma	Intervalo de Dosificación y (Mediana) ^a
				(10 - 25 mg/día)
Ziprasidona	GEODON	oral	cápsulas	20-80 mg/dos veces al día (80 - 160 mg/día)
Risperidona	RISPERDAL	oral	comprimidos solución	2 - 16 mg/día comprimidos (4 - 12 mg/día)
fumarato de Quetiapina	SEROQUEL	oral	comprimidos	50 - 900 mg/día (300 - 900 mg/día)
Sertindol	SERLECT			(4 - 24 mg/día)
Amisulprida				
Haloperidol	HALDOL	oral	comprimidos	1 - 100 mg/día (1 - 15 mg/día)
Decanoato de Haloperidol	Decanoato de HALDOL	parenteral	inyección	

202

Nombre común	Nombre comercial	Vía de administración	Forma	Intervalo de Dosificación y (Mediana) ^a
lactato de Haloperidol	HALDOL INTENSOL	oral	solución	
		parenteral	inyección	
Clorpromazina	THORAZINE	rectal	supositorios	30 - 800 mg/día (200 - 500 mg/día)
		oral	cápsulas solución comprimidos	
		parenteral	inyección	
Flufenazina	PROLIXIN			0,5 - 40 mg/día (1 - 5 mg/día)
decanoato de Flufenazina	Decanoato de PROLIXIN	parenteral	inyección	(aproximadamente la mitad de la dosificación mostrada para oral)
enantato de Flufenazina	PROLIXIN	parenteral	inyección	(la misma que antes)

Nombre común	Nombre comercial	Vía de administración	Forma	Intervalo de Dosificación y (Mediana) ^a
Clorhidrato de Flufenazina	PROLIXIN	oral	elixir solución	
		parenteral	inyección	
Tiotixeno	NAVANE	oral	cápsulas	6 - 60 mg/día (8 - 30 mg/día)
Clorhidrato de Tiotixeno	NAVANE	oral	solución	
		parenteral	inyección	
Trifluoperazina	STELAZINE			(2 - 40 mg/día)
Perfenazina	TRILAFON	oral	solución comprimidos	12 - 64 mg/día (16 - 64 mg/día)
		parenteral	inyección	
Clorhidrato de Perphenazina y Amitriptilina	ETRAFON TRIAVIL	oral	comprimidos	
Tioridazina	MELLARIL	oral	suspensión	150 - 800 mg/día (100 - 300 mg/día)
			solución	
			comprimidos	

Nombre común	Nombre comercial	Vía de administración	Forma	Intervalo de Dosificación y (Mediana) ^a
Mesoridazina				(30 - 400 mg/día)
Molindona	MOBAN			50 - 225 mg/día (15 - 150 mg/día)
Clorhidrato de Molindona	MOBAN	oral	solución	
Loxapina	LOXITANE			20 - 250 mg/día (60 - 100 mg/día)
Clorhidrato de Loxapina	LOXITANE	oral	solución	
		parenteral	inyección	
Succinato de Loxapina	LOXITANE	oral	cápsulas	
Pimozida				(1 - 10 mg/día)
Flupentixol				

Nombre común	Nombre comercial	Vía de administración	Forma	Intervalo de Dosificación y (Mediana) ^a
Promazina	SPARINE			
Triflupromazina	VESPRIN			
Clorprotixeno	TARACTAN			
Droperidol	INAPSINE			
Acetofenazina	TINDAL			
Proclorperazina	COMPAZINE			
Metotrimeprazin a	NOZINAN			
Pipotiazina	PIPOTRIL			
Aripiprazol				
Hoperidona				

- Los ejemplos de nombres comerciales y proveedores de fármacos neurolépticos seleccionados son como sigue: clozapina (disponible bajo el nombre comercial de CLOZARIL®, de Mylan, Zeriith Goldline, UDL, Novartis);
- 5 olanzapina (disponible bajo el nombre comercial de ZYPREX®, from Lilly ;
- ziprasidona (disponible bajo el nombre comercial GEODON®, de Pfizer);
- risperidona (disponible bajo el nombre comercial RISPERDAL®, de Janssen);
- fumarato de quetiapina (disponible bajo el nombre comercial SEROQUEL®, de

AstraZeneca); haloperidol (disponible bajo el nombre comercial HALDOL®, de Ortho-McNeil); clorpromazina (disponible bajo el nombre comercial THORAZINE®, de SmithKline Beecham (GSK); flufenazina (disponible bajo el nombre comercial PROLIXIN®, de Apothecon, Copley, Schering, Teva, y
5 American Pharmaceutical Partners, Pasadena); tiotixeno (disponible bajo el nombre comercial NAVANE®, de Pfizer); trifluoperazina diclorhidrato de (10-[3-(4-metil-1-piperazinil)propil]-2-(trifluorometil)fenotiazina, disponible bajo el nombre comercial STELAZINE®, de Smith Klein Beckman; perfenazina (disponible bajo el nombre comercial TRILAFON®, de Schering); tioridazina
10 (disponible bajo el nombre comercial MELLARIL®, de Novartis, Roxane, HiTech, Teva, y Alparma) ; molindona (disponible bajo el nombre comercial MOBAN®, de Endo); y loxapina (disponible bajo el nombre comercial LOXITANE®, de Watson). Adicionalmente, se pueden usar benperidol (Glanimon®), perazina (Taxilan®) o melperona (Eunerpan®)).

15

Otros fármacos neurolépticos preferidos incluyen promazina (disponible bajo el nombre comercial SPARINE®), triflurpromazina (disponible bajo el nombre comercial VESPRIN®), clorprotixeno (disponible bajo el nombre comercial TARACTAN®), droperidol (disponible bajo el nombre comercial
20 INAPSINE®), acetofenazina (disponible bajo el nombre comercial TINDAL®;), proclorperazina (disponible bajo el nombre comercial COMPAZINE®), metotrimeprazina (disponible bajo el nombre comercial NOZINAN®), pipotiazina (disponible bajo el nombre comercial PIPOTRIL®), ziprasidona, y hoperidona.

25

Los agentes neurolépticos particularmente preferidos para uso en la invención son olanzapina, risperidona, quetiapina, aripiprazol, haloperidol, clozapina, ziprasidona y osanetant.

5 Los expertos en la técnica apreciarán que los compuestos de acuerdo con la invención se pueden usar de manera ventajosa junto con uno o más agentes terapéuticos diferentes, por ejemplo, agentes antidepresivos diferentes tales como antagonistas de 5HT₃, agonistas de serotonina, antagonistas de NK-1, inhibidores selectivos de la recaptación de serotonina (SSRI), inhibidores
10 de la recaptación de noradrenalina (SNRI), antidepresivos tricíclicos, antidepresivos dopaminérgicos, antagonistas de H₃, antagonistas de 5HT_{1A}, antagonistas de 5HT_{1B}, antagonistas de 5HT_{1D}, agonistas de D₁, agonistas de M₁ y/o agentes anticonvulsivos, así como fármacos antipsicóticos atípicos y potenciadores cognitivos.

15

Los antagonistas adecuados de 5HT₃ que se pueden usar en combinación con los compuestos de la invención incluyen por ejemplo ondansetron, granisetron, metoclopramida.

20 Los agonistas adecuados de serotonina que se pueden usar en combinación con los compuestos de la invención incluyen sumatriptán, rauwolscina, yohimbina, metoclopramida.

Los SSRI adecuados que se pueden usar en combinación con los compuestos de la invención incluyen fluoxetina, citalopram, femoxetina, fluvoxamina, paroxetina, indalpina, sertralina, zimeldina.

- 5 Los SNRI adecuados que se pueden usar en combinación con los compuestos de la invención incluyen venlafaxina y reboxetina.

- Los antidepresivos tricíclicos adecuados que se pueden usar en combinación con un compuesto de la invención incluyen imipramina,
10 amitriptilina, clomipramina y nortriptilina.

- Los antidepresivos dopaminérgicos adecuados que se pueden usar en combinación con un compuesto de la invención incluyen bupropión y amineptina.

15

Los agentes anticonvulsivos adecuados que se pueden usar en combinación con los compuestos de la invención incluyen por ejemplo divalproex, carbamazepina y diazepam.

- 20 Los fármacos antipsicóticos atípicos adecuados que se pueden usar en combinación con los compuestos de la invención incluyen por ejemplo risperidona, olanzapina, ziprasidona, aripiprazol y clozapina.

Se apreciará que los compuestos de la combinación o composición se pueden administrar de manera simultánea (o bien en la misma o en diferentes formulaciones farmacéuticas), de manera separada o secuencial.

5 Para uso en medicina, los compuestos de la presente invención se administran usualmente como una composición farmacéutica habitual. La presente invención proporciona por lo tanto en un aspecto adicional una composición farmacéutica que comprende un compuesto de fórmula (I) como se ha descrito en esta memoria descriptiva anteriormente o una sal
10 farmacéuticamente (es decir, fisiológicamente) aceptable del mismo y un vehículo farmacéuticamente (es decir, fisiológicamente) aceptable. La composición farmacéutica puede ser para uso en el tratamiento de cualquiera de las afecciones descritas en esta memoria descriptiva.

15 Las formulaciones posibles incluyen las adecuadas para administración oral, sublingual, bucal, parenteral (por ejemplo, subcutánea, intramuscular, o intravenosa), rectal, tópica e intranasal y en formas adecuadas para la administración mediante inhalación o insuflación (o bien a través de la boca o de la nariz). Los medios más adecuados de administración para un paciente
20 particular dependerán de la naturaleza y gravedad de las afecciones que se están tratando y de la naturaleza del compuesto activo, pero, cuando sea posible, se prefiere la administración oral.

Las formulaciones adecuadas para la administración oral se pueden proporcionar como unidades discretas, tales como comprimidos, cápsulas,
25 sellos, o grageas, conteniendo cada uno de los cuales una cantidad

predeterminada del compuesto activo; como polvos o gránulos; como soluciones o suspensiones en líquidos acuosos o no acuosos; o como emulsiones aceite en agua o agua en aceite. Por ejemplo, un compuesto de la invención se puede preparar como una formulación con un perfil de liberación controlado. Éste puede estar en cualquiera de las formas farmacéuticas mencionadas anteriormente. Por ejemplo puede ser una formulación de gel en un vehículo oleoso no acuoso, por ejemplo Miglyol, con un agente de gelificación adecuado si se requiere, por ejemplo metilcelulosa o sílice coloidal hidrófobo.

10

Las formulaciones adecuadas para administración sublingual o bucal incluyen grageas que comprenden el compuesto activo y, típicamente, una base aromatizada, tal como azúcar y goma arábica o tragacanto y pastillas que comprenden el compuesto activo en una base inerte, tal como gelatina y glicerina o sacarosa y goma arábica.

15

Las formulaciones adecuadas para administración parenteral típicamente comprenden soluciones acuosas estériles que contienen una concentración predeterminada del compuesto activo; la solución es preferiblemente isotónica con la sangre del receptor pretendido. Aunque tales soluciones se administran preferiblemente por vía intravenosa, también se pueden administrar mediante inyección subcutánea o intramuscular.

20

Las formulaciones adecuadas para administración rectal se proporcionan preferiblemente en forma de supositorios de dosis unitaria que

25

comprenden el ingrediente activo y uno o más vehículos sólidos que forman la base de supositorio, por ejemplo, manteca de cacao.

Las formulaciones adecuadas para aplicación tópica o intranasal
5 incluyen pomadas, cremas, loción, pastas, geles, pulverizaciones, aerosoles y aceites. Los vehículos adecuados para tales formulaciones incluyen vaselina líquida, lanolina, polietilenglicoles, alcoholes, y las combinaciones de los mismos.

10 Las formulaciones de los compuestos de la invención pueden, por ejemplo, estar compuestas de manera que mejoren el perfil de exposición del compuesto de la invención.

Las composiciones adecuadas para la administración transdérmica
15 incluyen pomadas, geles y parches. Preferiblemente la composición está en forma de dosis unitaria tal como un comprimido, cápsula o ampolla.

Las formulaciones de la invención se pueden preparar mediante cualquier procedimiento adecuado, típicamente mezclando de manera uniforme
20 e íntima el (los) compuesto (s) activos con vehículos líquidos o sólidos finamente divididos, o ambos, en las proporciones requeridas y después, si es necesario, conformando la mezcla resultante en la forma deseada.

Por ejemplo, un comprimido se puede preparar comprimiendo una
25 mezcla íntima que comprende un polvo o gránulos del ingrediente activo y uno

o más ingredientes opcionales, tal como un aglutinante, lubricante, diluyente inerte, o agente dispersante tensioactivo, o mediante moldeado de una mezcla íntima de ingrediente activo en polvo y diluyente líquido inerte.

- 5 Las soluciones acuosas para la administración parenteral se preparan típicamente disolviendo el compuesto activo en agua suficiente para proporcionar la concentración deseada y después hacer la solución resultante estéril e isotónica.
- 10 Se apreciará que la dosis precisa administrada dependerá de la edad y afección del paciente y de la frecuencia y vía de administración y estará a la discreción última del médico asistente. El compuesto se puede administrar en dosis individuales o divididas y se puede administrar una o más veces, por ejemplo 1 a 4 veces al día.
- 15 Una dosis propuesta del ingrediente activo para uso de acuerdo con la invención para administración oral, sublingual, parenteral, bucal, rectal, intranasal o tópica a un ser humano (de aproximadamente 70 kg de peso corporal) para el tratamiento de trastornos neurológicos y neuropsiquiátricos
- 20 mediados por un inhibidor GlyT1, incluyendo esquizofrenia, puede estar entre aproximadamente 1 y aproximadamente 1000 mg, preferiblemente entre aproximadamente 5 y aproximadamente 500 mg, más preferiblemente entre *aproximadamente 10 y aproximadamente 100 mg del ingrediente activo por* dosis unitaria que se podría administrar, por ejemplo, 1 a 4 veces al día.

Los compuestos de la invención se pueden usar como ligandos PET (por ejemplo marcados con carbono 11 o flúor 18) o como ligandos SPECT (por ejemplo marcados con yodo 123 o tecnecio 99 meta estable) para visualización *in vivo* y cuantificación del transportador GlyT1. Por ejemplo, se pueden usar
5 en formación de imágenes de PET o SPECT del cerebro. En el contexto de esta patente, PET significará: tomografía de emisión de positrones y SPECT (= SPET) significará: tomografía de emisión (computarizada) de fotones individuales.

10 Todas las publicaciones, que incluyen pero no se limitan a las patentes y solicitudes de patentes, citadas en esta memoria descriptiva se incorporan en este documento como referencia como si cada publicación individual estuviera indicada específicamente e individualmente a incorporarse como referencia en este documento como si no obstante se expusiera completamente.

15

La invención se ilustra adicionalmente mediante los siguientes ejemplos no limitantes.

Abreviaturas:

THF	tetrahidrofurano
20 DCM	diclorometano
DMF	dimetilformamida
EDC	Clorhidrato de N-(3-(dimetilamino)propil)-N-etilcarbodiimida
HATU	hexafluorofosfato de O-(7-azabenzotriazol-1-il) - N,N,N',N'-tetrametiluronio
25 HOAt	3H-(1,2,3)-triazolo(4,5-b)piridina-3-ol
NMP	N-metilpirrolidinona

DIPEA	N,N-diisopropiletilamina
HOBt	hidrato de 1-hidroxibenzotriazol

Condiciones de cromatografía de CL/EM analítica:

5 Procedimiento A

Columna: Waters Atlantis 50 mm x 4,6 mm, 3 μ m
de tamaño de partícula

Fase móvil: A: ácido fórmico al 0,05% + agua
B: Acetonitrilo + ácido fórmico al 0,05%

10 Gradiente: 5 - min de tiempo de desarrollo: 3% de B a 97% de B durante 4 min

Caudal: 3 ml/min

Intervalo de longitud de onda UV: 220 - 330 nm

Temperatura: 30°C

15

Procedimiento B *

Columna: Waters Atlantis 20 mm x 4,6 mm,
tamaño de partícula 3 µm

Fase móvil: A: 0,1% de ácido fórmico + agua

20 B: Acetonitrilo + ácido fórmico al 0,1%

Gradiente: 5,5- min de tiempo de desarrollo: 3%
de B a 97% de B durante 5,3 min

Caudal: 1 ml/min

Intervalo de longitud de onda UV: 210 - 350 nm

25 Temperatura: Ambiente

Condiciones de cromatografía sistema de autopurificación dirigido por masa:

Columna:	Waters Atlantis 19 mm x 100 mm o 30 mm X 100 mm, 5 μ m de tamaño de partícula
5	
Fase móvil:	A: ácido fórmico al 0,1% + agua B: Acetonitrilo + ácido fórmico al 0,1%
Gradiente:	13,5 min de tiempo de desarrollo con gradiente de 10 min dependiente del tiempo de retención analítico
10	
Caudal:	20 ó 40 ml/min

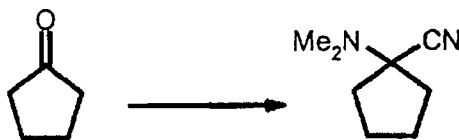
General:

- 15 A través de la sección de los ejemplos, se adopta la siguiente terminología con relación a los compuestos quirales: cuando se ha preparado una mezcla de dos enantiómeros, el compuesto se describe como ($\pm$). Cuando se ha preparado un enantiómero individual (es decir una mezcla enriquecida quiralmente en uno de los enantiómeros), se denomina "quiral". La
- 20 estereoquímica absoluta no se ha determinado en el momento de la presentación. Los enantiómeros individuales de algunos materiales preparados se identifican en virtud de las rotaciones ópticas y tales materiales se identifican como los enantiómeros (+) o (-). Cuando la información de rotación óptica no está todavía disponible, los enantiómeros individuales de los

productos se pueden identificar individualmente en virtud de las características de HPLC quiral del intermedio amina.

Cuando las reacciones se describen por haberse llevado a cabo de manera similar a reacciones anteriores descritas más completamente, las condiciones de reacción generales usadas fueron esencialmente las mismas. Las condiciones de tratamiento usadas eran de los tipos convencionales en la técnica, pero pueden haber sido adaptadas de una reacción a otra.

10 **Descripción 1: 1-(Dimetilamino)ciclopentanocarbonitrilo**



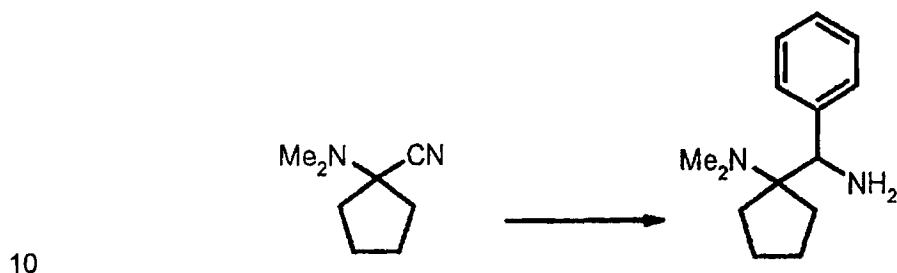
A una suspensión enfriada (baño de hielo) de clorhidrato de dimetilamina (8,15 g, 0,1 mol) en ciclopentanona (8,4 g, 0,1 mol) se le añadió gota a gota una solución de cianuro de potasio (6,5 g, 0,1 mol) en agua (50 ml) durante 10 min. Después de agitar vigorosamente a temperatura ambiente durante 18 h, la mezcla de reacción bruta se extrajo tres veces con éter dietílico (3 x 200 ml) y los extractos combinados se lavaron dos veces con agua (2 x 50 ml), se secaron (Na₂SO₄) y se evaporaron, proporcionando el compuesto del título en forma de un aceite amarillo pálido (12,5 g) que se usó sin purificación adicional.

¹H RMN (CDCl₃) δ: 1,7-2,0 (6H, m), 2,15-2,3 (2H, m), 3,3 (6H, s). Espectro de masas (Electronebulización CL/EM): Encontrado 112 (MH⁺-HCN). C₈H₁₄N₂ requiere 138.

Procedimiento alternativo:

- A una mezcla enfriada con hielo y agitada de clorhidrato de dimetilamina (26,32 g; 0,323 mol) y ciclopentanona (27,15 g, 0,323 mol) se le añadió gota a gota una solución de cianuro de potasio (21,02 g, 0,323 mol) en agua (170 ml) durante 10 min. La mezcla se agitó a temperatura ambiente durante una noche.
- 5 Después, la mezcla se extrajo en éter dietílico (2 x 200 ml) y los extractos orgánicos combinados se lavaron con salmuera (200 ml), se secaron (Na_2SO_4) y se evaporaron al vacío, proporcionando el compuesto del título en forma de un líquido incoloro (43 g, 96,5%)

Descripción 2: ($\pm$){1-[Amino(fenil)metil]ciclopentil}dimetilamina



- A una solución de 1-(dimetilamino)ciclopentanocarbonitrilo D1 (4 g, 28,9 mmol) en THF (30 ml) a -70°C en una atmósfera de argón se le añadió gota a gota una solución de fenilitio en éter dibutílico (17,7 ml de una solución 1,8 M; 32 mmol). La mezcla de reacción se dejó calentar a temperatura ambiente
- 15 durante 3 h, se enfrió de nuevo a 0°C y se añadió metanol (30 ml) seguido de la adición cuidadosa de borohidruro sódico (3,3 g, 87 mmol). Después de agitar a temperatura ambiente durante 18 h, la mezcla de reacción se enfrió a 0°C y se añadió bicarbonato sódico acuoso saturado. La fase orgánica se evaporó y la suspensión resultante se extrajo tres veces con DCM (3 x 150 ml). Los
- 20 extractos combinados se secaron (Na_2SO_4) y se evaporaron, proporcionando el compuesto bruto en forma de un aceite amarillo (6,8 g). La mitad del

compuesto bruto se cromatografió sobre gel de sílice eluyendo con DCM-metanol (9/1) y mezclas de DCM-amoniaco 2 M en metanol (de 95/5 a 9/1 a 8/2), proporcionando el compuesto del título en forma de un aceite incoloro (2,3 g). Este aceite se disolvió en éter dietílico (20 ml) y se añadió cloruro de hidrógeno en éter dietílico a 0°C. Después de 20 min, la suspensión se filtró, dando la sal diclorhidrato (2,8 g) del compuesto del título en forma de un sólido blanco. ¹H RMN (DMSO) δ: 1,25 (2H, s a), 1,36 (2H, s a), 1,66-2,13 (4H, m), 2,64 (3H, s), 2,79 (3H, s), 4,92 (1H, s a), 7,32 (3H, m), 7,54 (2H, m), 8,95 (3H, s a), 10,82 (1H, s a).

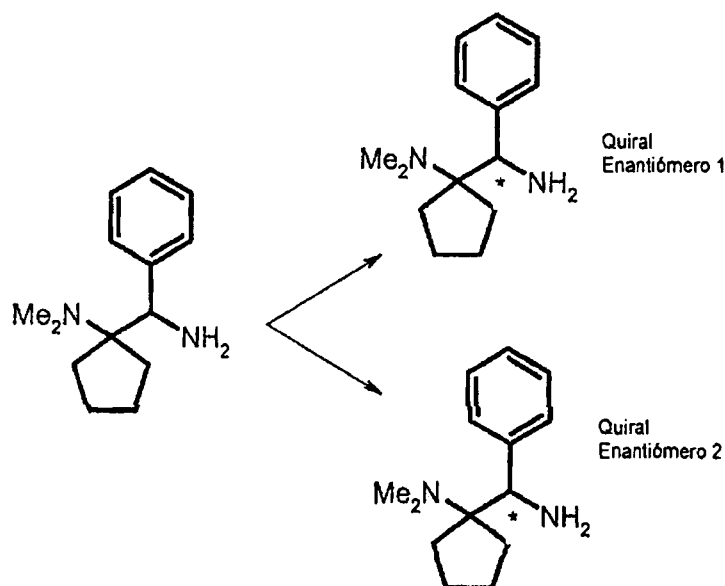
10 Procedimiento alternativo:

A una solución de 1-(dimetilamino)ciclopentanocarbonitrilo D1 (43 g, 311 mmol) en THF (1 l) a -70°C en una atmósfera de argón se le añadió gota a gota una solución de fenilitio en éter dibutílico (346 ml de una solución 1,8 M; 622 mmol) durante 10 minutos. La mezcla de reacción se agitó a -70°C durante 2 h y después se dejó calentar a temperatura ambiente y se agitó durante una noche. La mezcla de reacción se enfrió en hielo y se añadió una solución acuosa saturada de bicarbonato sódico. La mezcla se agitó durante 30 minutos, se separó y la fase acuosa se extrajo con éter dietílico. Los extractos orgánicos combinados se secaron (Na₂SO₄) y se concentraron a presión reducida, dando un aceite.

El aceite se disolvió en metanol (1,2 l) y se enfrió en hielo. Se añadió en 4 porciones borohidruro sódico (20 g) durante 5 minutos y la mezcla se agitó durante media hora con refrigeración con hielo. Después, la refrigeración se retiró y la agitación se continuó a temperatura ambiente durante una hora y media. Después, la mezcla de reacción se enfrió con hielo y se añadió agua.

La mezcla resultante se evaporó al vacío y se repartió entre HCl 2 N y acetato de etilo. Los extractos orgánicos se extrajeron con HCl 2 N. Los extractos ácidos combinados se lavaron con acetato de etilo, se basificaron con NaOH y se extrajeron en DCM. Los extractos de DCM combinados se secaron
5 (Na₂SO₄) y se evaporaron al vacío, proporcionando el compuesto en forma de un líquido verde pálido (64,66 g, 95,4%).

Descripción 3: {1-[Amino(fenil)metil]ciclopentil}dimetilamina Enantiómero 1 y Enantiómero 2



10 Procedimiento 1.

Se separó {1-[amino(fenil)metil]ciclopentil}dimetilamina racémica D2 (0,6 g, 2,75 mmol) por HPLC quiral semi-preparativa usando las condiciones que se describen a continuación, proporcionando los compuestos del título, enantiómero 1, (0,27 g); HPLC quiral: 98% de ee; ¹H RMN (CDCl₃) δ: 0,42 (1H, m), 1,32 (3H, m), 1,49 (1H, m), 1,63 (1H, m), 1,76 (1H, m), 1,95 (3H, m), 2,29
15 (6H, s), 4,39 (1H, s), 7,28 (3H, m), 7,50 (2H, d); Espectro de masas

- (Electronebulización CL/EM): Encontrado 219 (MH^+). $C_{14}H_{22}N_2$ requiere 218; y enantiómero 2 (0,28 g); HPLC quiral: 98% de ee; ^1H RMN ($CDCl_3$) δ : 0,42 (1H, m), 1,32 (3H, m), 1,49 (1H, m), 1,63 (1H, m), 1,76 (1H, m), 1,95 (3H, m), 2,29 (6H, s), 4,39 (1H, s), 7,28 (3H, m), 7,50 (2H, d); Espectro de masas
- 5 (Electronebulización CL/EM): Encontrado 219 (MH^+). $C_{14}H_{22}N_2$ requiere 218.

Condiciones de HPLC semi-preparativa:

Columna: Chiralpak AD-H 5 μm , 250 x 21 mm

Fase móvil: A: *n*-Hexano; B: Etanol + isopropilamina al 0,1%

Gradiente: B isocrático al 5%

- 10 Caudal: 7 ml/min

Intervalo de longitud de onda de UV: 225 nm

Tiempo de elución: 30 min

Condiciones de cromatografía analítica:

Columna: chiralpak AD-H 5 μm , 250 x 4,6 mm

- 15 Fase móvil: A: *n*-Hexano; B: Etanol + isopropilamina al 0,1%

Gradiente: B isocrático al 5%

Caudal: 1 ml/min

Intervalo de longitud de onda de UV: 200-400 nm

Tiempo de análisis: 10 min

- 20 Tiempo de ret.: 5,9 min (Enantiómero 1); 7,6 min (Enantiómero 2)

Procedimiento 2.

Formación de la sal:

- A una solución de {1-[amino(fenil)metil]ciclopentil}dimetilamina racémica D2 (16,9 g, 77,5 mmol) en isopropanol (170 ml) a 50°C se le añadió gota a gota
- 25 una solución de ácido (*R*)-metoxifenilacético (12,84 g, 77,5 mmol) en

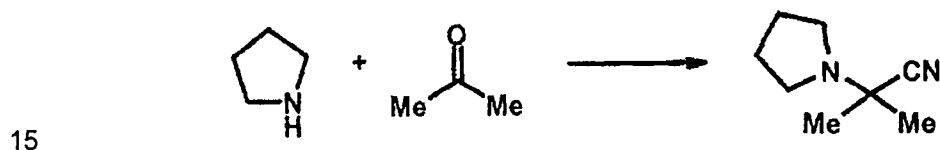
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isopropanol (75 ml). Después de 20 min, la mezcla se enfrió a temperatura ambiente y se dejó en agitación durante 4 h más. El sólido precipitado se recogió por filtración (13,42 g).

Regeneración de la base libre quiral:

- 5 Después, el sólido se trató con NaOH 1 M (50 ml) y DCM (167 ml). Las fases se separaron y la fase acuosa se lavó con DCM (4 x 167 ml). Las fases orgánicas combinadas se lavaron con NaOH 1 M (2 x 35 ml) y después con salmuera (100 ml), se secaron (Na_2SO_4) y se concentraron, produciendo el compuesto del título, enantiómero 2, en forma de un aceite incoloro (7,6 g).
- 10 HPLC quiral: >96% de ee; ^1H RMN (CDCl_3) δ : 0,42 (1H, m), 1,32 (3H, m), 1,49 (1H, m), 1,63 (1H, m), 1,76 (1H, m), 1,95 (3H, m), 2,29 (6H, s), 4,39 (1H, s), 7,28 (3H, m), 7,50 (2H, d); Espectro de masas (Electronebulización CL/EM): Encontrado 219 (MH^+). $\text{C}_{14}\text{H}_{22}\text{N}_2$ requiere 218.

Descripción 4: 2-Metil-2-(1-pirrolidinil)propanonitrilo

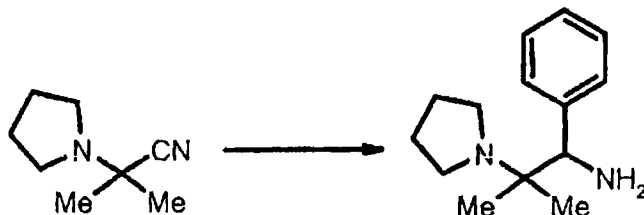


- A una mezcla agitada y enfriada con hielo de pirrolidina (8,35 ml, 0,1 mol) y acetona (7,34 ml, 0,1 mol) se le añadió gota a gota una solución de cianuro de potasio (6,51 g, 0,1 mol) en agua (50 ml) durante 10 min. Después de agitar a temperatura ambiente durante una noche, la mezcla de reacción
- 20 bruta se extrajo con éter dietílico (2 x 250 ml) y los extractos combinados se lavaron con salmuera saturada (150 ml), se secaron (MgSO_4) y se evaporaron a presión reducida, proporcionando el compuesto del título en forma de un

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líquido verde pálido (10,7 g, 78%) que se usó sin purificación adicional. ^1H RMN (CDCl_3) δ : 1,51 (6H, s), 1,80-1,90 (4H, m), 2,70-2,80 (4H, m).

Descripción 5: ($\pm$)[2-Metil-1-fenil-2-(1-pirrolidinil)propil]amina

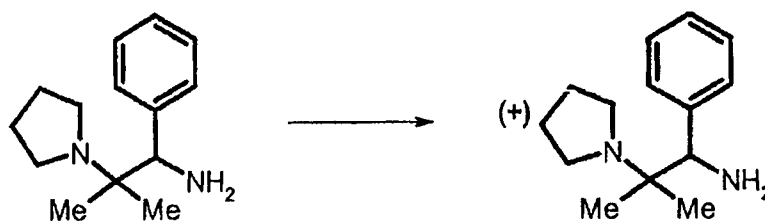


- 5 A una solución de 2-metil-2-(1-pirrolidinil)propanonitrilo D4 (10,7 g, 77,54 mmol) en THF (400 ml) a -70°C en una atmósfera de argón se añadió durante 10 minutos una solución de fenilitio en éter dibutílico (86,3 ml de una solución 1,8 M; 155 mmol). La mezcla de reacción se agitó a -70°C durante 2 horas, después se dejó calentar a temperatura ambiente y se agitó durante una
- 10 noche. La mezcla de reacción se enfrió en hielo según se añadía carbonato ácido sódico acuoso saturado (400 ml). Después de agitar durante 30 minutos más, las fases se separaron y la fase acuosa se extrajo con éter (200 ml). Los extractos orgánicos combinados se secaron (MgSO_4) y se evaporaron. El aceite ámbar residual se disolvió en metanol (400 ml), se enfrió en hielo y se
- 15 añadió en cuatro porciones borohidruro sódico (5,2 g, 137 mmol) durante 5 minutos. La mezcla de reacción se agitó mediante refrigeración con hielo durante 30 minutos, el hielo se retiró y se agitó a temperatura ambiente durante 1,5 horas. La mezcla se enfrió en hielo según se añadía agua (50 ml) antes de la concentración al vacío hasta aprox. 70 ml. La mezcla se repartió entre HCl 2
- 20 N (100 ml) y acetato de etilo (400 ml) y los extractos orgánicos se extrajeron con HCl 2 N (2 x 100 ml). Las fases acuosas ácidas combinadas se lavaron con acetato de etilo (200 ml), se basificaron con NaOH al 50% y se extrajeron

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con DCM (3 x 150 ml). Los extractos orgánicos de DCM combinados se secaron (Na_2SO_4) y se evaporaron al vacío, proporcionando el compuesto del título en forma de un sólido incoloro (15 g: 88%) ^1H RMN (CDCl_3), δ : 0,75 (3H, s), 0,99 (3H, s), 1,70-1,76 (4H, m), 1,80 (2H, s a), 2,65-2,70 (4H, m), 4,08 (1H, s), 7,20-7,42 (5H, m).

Descripción 6: (+)-[2-Metil-1-fenil-2-(1-pirrolidinil)propil]amina



Una solución de ácido (*R*)-(-)- α -metoxifenilacético (8,08 g, 49 mmol) en 2-propanol (50 ml) se añadió gota a gota durante 10 minutos a una solución agitada de [2-metil-1-fenil-2-(1-pirrolidinil)propil]amina D5 (10,64 g, 49 mmol) en 2-propanol (107 ml) a 57°C. Después de que se completara la adición, el calentamiento se continuó durante 10 minutos más. Después, el calentamiento se retiró y la agitación se continuó durante una hora y tres cuartos más. Se añadió más 2-propanol (100 ml), la mezcla se filtró, el sólido se lavó con 2-propanol (3 x 50 ml) y éter (100 ml) y se secó. El sólido se recrystalizó en 2-propanol en ebullición (1 l) y los cristales se filtraron, se lavaron con 2-propanol frío y con éter y se secaron. Se repartió una muestra entre carbonato ácido sódico acuoso saturado y DCM y la fase orgánica se pasó a través de un cartucho de separación de fases y se burbujeó con argón, proporcionando el compuesto del título en forma de un sólido incoloro. ^1H RMN (CDCl_3) δ : 0,75 (3H, s), 0,99 (3H, s), 1,70-1,79 (4H, m), 1,85 (2H, s a), 2,65-2,70 (4H, m), 4,08 (1H, s), 7,20-7,42 (5H, m). HPLC quiral: 97,5% de ee, correspondiente al

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enantiómero 2 de elución más lenta. $[\alpha]_D = +28,5^\circ$ ($c = 1$, CHCl_3 a $27,5^\circ\text{C}$). La base libre restante se liberó de manera similar (3,55 g, 66%).

Las condiciones para la resolución del racemato D5 fueron las siguientes:

5 Condiciones de cromatografía analítica:

Columna: chiralcel OD-H $5\ \mu\text{m}$, $250 \times 4,6\ \text{mm}$ d.i.

tamaño de partículas de 10 micrones

Fase móvil: Heptano:Etanol (90:10)

Gradiente: isocrático

10 Caudal: 1 ml/min

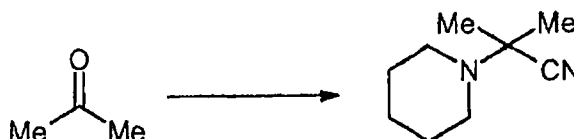
Intervalo de longitud de onda de UV: 254 nm

Tiempo de análisis: 10 min

Tiempo de ret.: 5,4 min (Enantiómero 1); 7,0 min (Enantiómero 2)

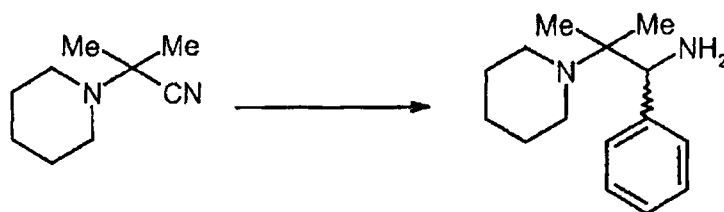
Descripción 7: 2-Metil-2-(1-piperidinil)propanonitrilo

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El compuesto del título (2,33 g, 77%) se preparó a partir de clorhidrato de piperidina (2,43 g, 20 mmol), acetona (1,16 g, 20 mmol) y cianuro de potasio (1,30 g, 20 mmol) en agua (10 ml) de manera similar a la descrita en D1. ^1H RMN (CDCl_3) δ : 1,46 (2H, m), 1,50 (6H, s), 1,63 (4H, m), 2,59 (4H, m).

20 **Descripción 8 : ($\pm$)2-Metil-1-fenil-2-(1-piperidinil)-1-propanamina**

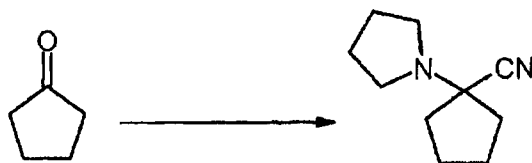


El compuesto del título (1,16 g, 56%) se preparó a partir de 2-metil-2-(1-piperidinil)propanonitrilo D7 (1,30 g, 8,6 mmol) y fenillitio en éter dibutílico (5,2 ml de una solución 1,8 M; 9,4 mmol) en THF (15 ml), seguido de reacción con

5 boro-hidruro sódico (0,975 g, 25,7 mmol) en metanol (20 ml) de manera similar a la descrita en D2. ^1H RMN (CDCl_3) δ : 0,76 (3H, s), 0,91 (3H, s), 1,44 (2H, m), 1,54-1,65 (4H, m), 1,95 (2H, m), 2,57 (4H, m), 4,19 (1H, s), 7,20-7,31 (3H, m), 7,40 (2H, m).

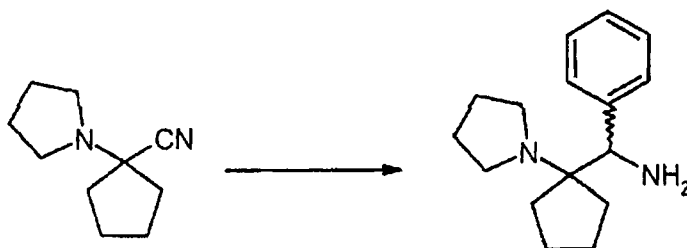
Descripción 9 : 1-(1-Pirrolidinil)ciclopentanocarbonitrilo

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El compuesto del título (2,50 g, 76%) se preparó a partir de pirrolidina (1,42 g, 20 mmol), ciclopentanona (1,68 g, 20 mmol) y cianuro de potasio (1,30 g, 20 mmol) en agua (10 ml) de manera similar a la descrita en D4. ^1H RMN (CDCl_3) δ : 1,80-1,90 (10H, m), 2,15 (2H, m), 2,71 (4H, m).

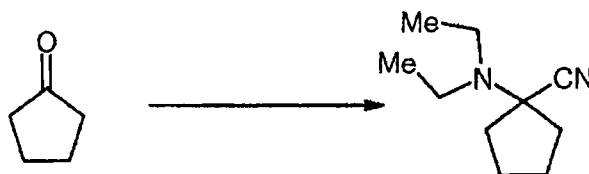
15 **Descripción 10 : ($\pm$)-1-Fenil-1-[1-(1-pirrolidinil)ciclopentil]metanamina**



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El compuesto del título (0,55 g, 56%) se preparó a partir de 1-(1-pirrolidinil)ciclopentanocarbonitrilo D9 (0,66 g, 4 mmol) y fenillitio en éter dibutílico (2,4 ml de una solución 1,8 M; 4,4 mmol) en THF (4 ml), seguido de reacción con borohidruro sódico (0,456 g, 12 mmol) en metanol (4 ml) de
5 manera similar a la descrita en D2. ^1H RMN (CDCl_3) δ : 0,41 (1H, m), 1,17 (1H, m), 1,35 (2H, m), 1,60 (2H, m), 1,73 (5H, m), 1,84-2,02 (3H, m), 2,64 -2,74 (4H, m), 4,27 (1H, s), 7,21-7,31 (3H, m), 7,48 (2H, m).

Descripción 11 : 1-(Dietilamino)ciclopentanocarbonitrilo



10 El compuesto del título (2,06 g, 62%) se preparó a partir de clorhidrato de dietilamina (2,14 g, 20 mmol), ciclopentanona (1,68 g, 20 mmol) y cianuro de potasio (1,30 g, 20 mmol) en agua (10 ml) de manera similar a la descrita en D1. ^1H RMN (CDCl_3) δ : 1,11 (6H, t, $J = 7$ Hz), 1,78-1,88 (6H, m), 2,22 (2H, m), 2,71 (4H, c, $J = 7$ Hz).

15 **Descripción 12 : ($\pm$)-1-[Amino(fenil)metil]-*N,N*-dietilciclopentanamina**

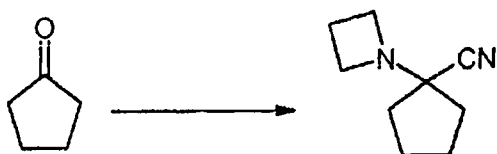


El compuesto del título (0,45 g, 47%) se preparó a partir de 1-(dietilamino)ciclopentanocarbonitrilo D11 (0,65 g, 3,9 mmol) y fenillitio en éter dibutílico (2,4 ml de una solución 1,8 M; 4,3 mmol) en THF (4 ml), seguido de

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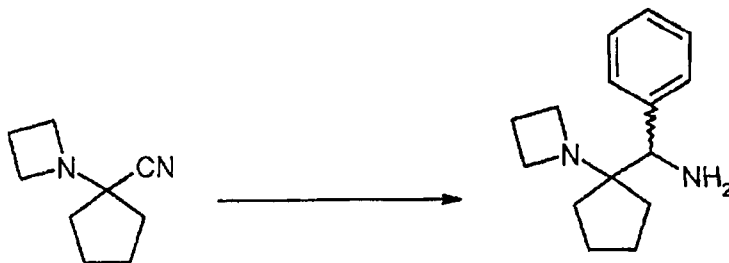
reacción con borohidruro sódico (0,445 g, 11,7 mmol) en metanol (4 ml) de manera similar a la descrita en D2. ^1H RMN (CDCl_3) δ : 0,42 (1H, m), 1,10 (6H, m), 1,35 (3H, m), 1,55 (1H, m), 1,66 (2H, m), 1,80-2,08 (3H, m), 2,53-2,70 (4H, m), 4,22 (1H, s), 7,20-7,31 (3H, m), 7,47 (2H, m).

5 **Descripción 13 : 1-(1-Azetidinil)ciclopentanocarbonitrilo**



El compuesto del título (1,29 g, 43%) se preparó a partir de clorhidrato de azetidina (1,85 g, 20 mmol), ciclopentanona (1,68 g, 20 mmol) y cianuro de potasio (1,30 g, 20 mmol) en agua (10 ml) de manera similar a la descrita en D1. ^1H RMN (CDCl_3) δ : 1,70-1,82 (6H, m), 1,86 (2H, m), 2,07 (2H, quin., $J = 7$ Hz), 3,32 (4H, t, $J = 7$ Hz).

Descripción 14 : ($\pm$)1-[1-(1-Azetidinil)ciclopentil]-1-fenilmetanamina



El compuesto del título (0,45 g, 47%) se preparó a partir de 1-(1-azetidini)ciclopentanocarbonitrilo D13 (0,60 g, 4,0 mmol) y fenillitio en éteres (2,6 ml de una solución 1,7 M; 4,4 mmol) en THF (5 ml), seguido de reacción con borohidruro sódico (0,456 g, 12 mmol) en metanol (5 ml) de manera similar a la descrita en D2. ^1H RMN (CDCl_3) δ : 0,67 (1H, m), 1,06 (1H, m), 1,32 (4H,

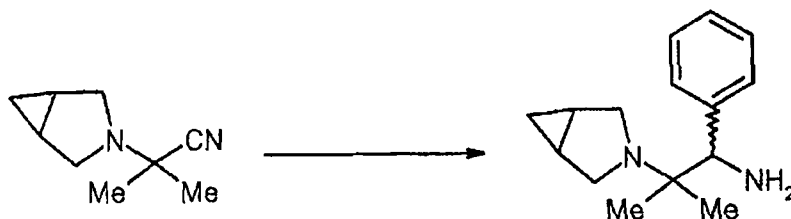
m), 1,48 (2H, m), 1,91-2,03 (4H, m), 3,24 (4H, m), 3,83 (1H, s), 7,20-7,32 (3H, m), 7,44 (2H, m).

Descripción 15 : 2-(3-Azabicyclo[3.1.0]hex-3-il)-2-metilpropanonitrilo



5 El compuesto del título (583 mg, 84%) se preparó a partir de clorhidrato de 3-azabicyclo[3.1.0]hexano (550 mg, 4,6 mmol) [Pestic. Chem: Hum. Welfar Environ., Proc. Int. Congr. Pestic. Che., 5^a, 1982, 1,159-64, 1983], acetona (267 mg, 4,6 mmol) y cianuro de potasio (300 mg, 4,6 mmol) en agua (2,5 ml) de manera similar a la descrita en D1. ¹H RMN (CDCl₃) δ: 0,40 (1H, m), 0,58 (1H, m), 1,43 (8H, m), 2,64 (2H, m), 3,10 (2H, d, J = 8 Hz).

Descripción 16 : (±)2-(3-Azabicyclo[3.1.0]hex-3-il)-2-metil-1-fenil-1-propanamina



15 El compuesto del título (393 mg, 44%) se preparó a partir de 2-(3-azabicyclo[3.1.0]hex-3-il)-2-metilpropanonitrilo D15 (583 mg, 3,9 mmol) y fenilitio en éter dibutílico (2,15 ml de una solución 2,0 M; 4,3 mmol) en THF (7 ml), seguido de reacción con borohidruro sódico (445 mg, 11,7 mmol) en metanol (10 ml) de manera similar a la descrita en D2. ¹H RMN (CDCl₃) δ: 0,38 (1H, m), 0,66 (1H, m), 0,74 (3H, s), 0,93 (3H, s), 1,30-1,40 (2H, m), 1,74 (2H, s

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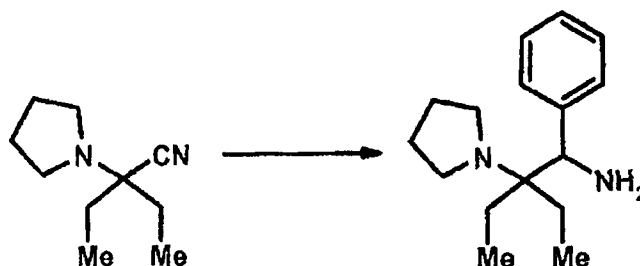
a), 2,67 (2H, m), 2,91 (2H, t, $J = 8$ Hz), 4,03 (1H, s), 7,20-7,30 (3H, m), 7,38 (2H, m).

Descripción 17: 2-Etil-2-(1-pirrolidinil)butanonitrilo



5 El compuesto del título (8,8 g, 100%) se preparó a partir de pirrolidina (8,96 ml, 0,107 mol), 3-pentanona (8,61 g, 0,1 mol) y cianuro de potasio (6,51 g, 0,1 mol) en agua (50 ml) de manera similar a la descrita en D4. ^1H RMN (CDCl_3) δ : 0,95 (6H, t, $J = 7,6$ Hz), 1,67-1,90 (8H, m), 2,67-2,72 (4H, m).

Descripción 18: ($\pm$)[2-Etil-1-fenil-2-(1-pirrolidinil)butil]amina



10

El compuesto del título (11,5 g, 88%) se preparó a partir de 2-etil-2-(1-pirrolidinil)butanonitrilo D17 (8,8 g, 0,053 mol) y fenilitio en éter dibutílico (59 ml de una solución 1,8 M; 0,106 mol) en THF (350 ml), seguido de reacción con borohidruro sódico (3,9 g, 0,103 mol) en metanol (300 ml) de manera similar a la descrita en D5. ^1H RMN (CDCl_3) δ : 0,75 (3H, t), 0,95 (3H, t, $J = 7,6$ Hz), 1,50-1,90 (10H, m), 2,70-2,95 (4H, m), 4,01 (1H, s), 7,19-7,41 (5H, m).

Descripción 19: 2-(Dimetilamino)-2-etilbutanonitrilo



El compuesto del título (8,05 g, 57,5%) se preparó a partir de clorhidrato de dimetilamina (8,154 g, 0,1 mol), 3-pentanona (8,61 g, 0,1 mol) y cianuro de potasio (6,51 g, 0,1 mol) en agua (50 ml) de manera similar a la descrita en D1.

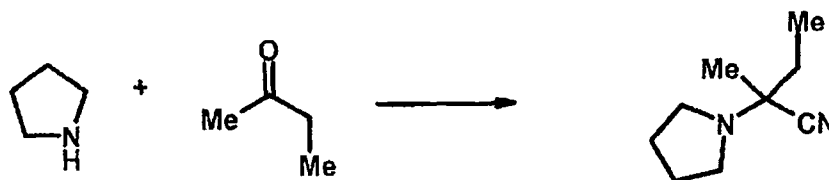
5 ^1H RMN (CDCl_3) δ : 0,96 (6H, t, $J = 7,6$ Hz), 1,67-1,90 (4H, m), 2,33 (6H, s).

Descripción 20: ($\pm$){1-[Amino(fenil)metil]-1-etilpropil}dimetilamina



El compuesto del título (11,12 g, 88%) se preparó a partir de 2-(dimetilamino)-2-etilbutanonitrilo D19 (8,05 g, 0,0575 mol) y fenillitio en éter dibutílico (64 ml) de una solución 1,8 M; 0,115 mol) en THF (350 ml), seguido de reacción con borohidruro sódico (3,9 g, 0,103 mol) en metanol (300 ml) de manera similar a la descrita en D5. ^1H RMN (CDCl_3) δ : 0,72 (3H, t, $J = 7,6$ Hz), 0,97 (3H, t, $J = 7,6$ Hz), 1,40-1,68 (4H, m), 1,70 (2H, m a), 2,43 (6H, s), 4,09 (1H, s), 7,19-7,43 (5H, m).

15 **Descripción 21:** 2-Metil-2-(1-pírolidínil)butanonitrilo



El compuesto del título (9,6 g, 63%) se preparó a partir de pirrolidina (8,35 ml, 0,1 mol), 2-butanona (8,96 g, 0,1 mol) y cianuro de potasio (6,51 g, 0,1 mol) en agua (50 ml) de manera similar a la descrita en D4. ^1H RMN (CDCl_3) δ : 1,06 (3H, t, $J = 7,2$ Hz), 1,45 (3H, s), 1,66-1,93 (6H, m), 2,70-2,75 (4H, m).

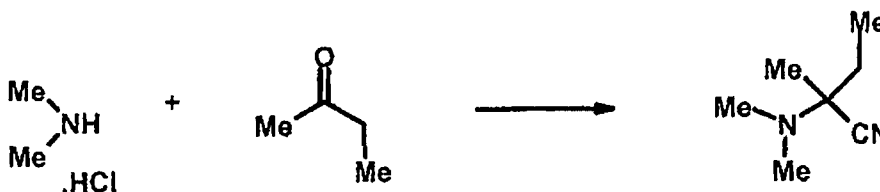
Descripción 22: ($\pm$)[2-Metil-1-fenil-2-(1-pirrolidinil)butil]amina



El compuesto del título (13,4 g, 94%) se preparó a partir de 2-metil-2-(1-pirrolidinil)butanonitrilo D21 (9,6 g, 0,063 mol) y fenillitio en éter dibutílico (63 ml de una solución 2 M; 0,126 mol) en THF (200 ml), seguido de reacción con borohidruro sódico (3,5 g, 0,092 mol) en metanol (200 ml) de manera similar a la descrita en D5, con la excepción de que después de la adición del borohidruro sódico la agitación se continuó mediante refrigeración con hielo durante 0,5 horas y después a temperatura ambiente durante 66 horas.

Espectro de masas (Electronebulización CL/EM), EN^+ : Encontrado 233 (MH^+). $\text{C}_{15}\text{H}_{24}\text{N}_2$ requiere 232. Tiempos de retención 0,78 y 1,06 min.

Descripción 23: 2-(Dimetilamino)-2-metilbutanonitrilo



232

El compuesto del título (9,95 g, 78%) se preparó a partir de clorhidrato de dimetilamina (8,15 g, 0,1 mol), 2-butanona (8,96 ml, 0,1 mol) y cianuro de potasio (6,51 g, 0,1 mol) en agua (50 ml) de manera similar a la descrita en D1.

^1H RMN (CDCl_3) δ : 1,00 (3H, t, $J = 7,2$ Hz), 1,43 (3H, s), 1,75-1,87 (2H, m), 2,33

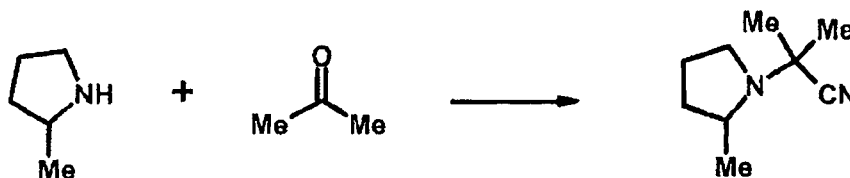
5 (6H, s).

Descripción 24: ($\pm$){1-[Amino(fenil)metil]-1-metilpropil}dimetilamina



El compuesto del título (15 g, 93%) se preparó a partir de 2-(dimetilamino)-2-metilbutanonitrilo D23 (9,9 g, 0,078 mol) y fenillitio en éter
10 dibutílico (87,3 ml de una solución 1,8 M; 0,157 mol) en THF (400 ml), seguido de reacción con borohidruro sódico (5,25 g, 0,138 mol) en metanol (450 ml) de manera similar a la descrita en D5. Espectro de masas (Electronebulización CL/EM), EN^+ : Encontrado 207 (MH^+). $\text{C}_{13}\text{H}_{22}\text{N}_2$ requiere 206. Tiempos de retención 0,83 y 1,10 min.

15 **Descripción 25: 2-Metil-2-(2-metil-1-pirrolidinil)propanonitrilo**



A una mezcla agitada y enfriada con hielo de 2-(*RS*)-metilpirrolidina (4,25 g, 0,05 mol) y acetona (3,67 ml, 0,05 mol) se le añadió gota a gota una
20 solución de cianuro de potasio (3,25 g, 0,05 mol) en agua (25 ml) durante 10 min. Después de agitar a temperatura ambiente durante una noche, la mezcla

de reacción bruta se extrajo con éter dietílico (2 x 200 ml) y los extractos combinados se lavaron con salmuera (200 ml), se secaron (Na_2SO_4) y se evaporaron a presión reducida, proporcionando un aceite amarillo pálido. Éste se disolvió en DCM y se añadió PS-isocianato (4,5 g de resina con carga de 1,53 mmol/g). La mezcla se agitó durante 3 horas, se filtró y el filtrado se evaporó, proporcionando el compuesto del título en forma de un semi-sólido incoloro (2,82 g, 37,5%). ^1H RMN (CDCl_3) δ (inter alia): 1,10 (3H, d), 1,45 (3H, s), 1,55 (3H, s), 1,75-2,00 (4H, m) 2,65 (1H, m) y 3,05-3,20 (2H, m).

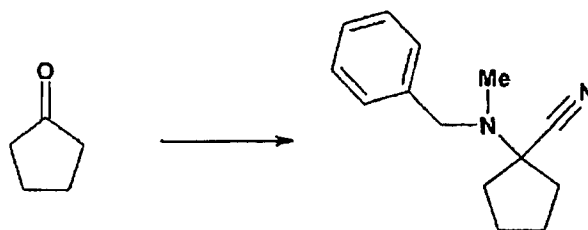
Descripción 26: ($\pm$)[2-Metil-2-(2-metil-1-pirrolidinil)-1-fenilpropil]amina



A una solución de 2-metil-2-(2-metil-1-pirrolidinil)propanonitrilo D25 (2,82 g, 18,56 mmol) en THF (100 ml) a -70°C en una atmósfera de argón se le añadió durante 15 minutos una solución de fenilitio en éter dibutílico (20,6 ml de una solución 1,8 M; 37,11 mmol). La mezcla de reacción se agitó a -70°C durante 2 horas, después se dejó calentar a temperatura ambiente y se agitó durante una noche. Se añadió carbonato ácido sódico acuoso saturado (100 ml) y la agitación se continuó durante 10 minutos más. La mezcla se extrajo con éter dietílico (2 x 150 ml). Los extractos orgánicos combinados se secaron (Na_2SO_4) y se evaporaron al vacío. El aceite amarillo residual se disolvió en metanol (100 ml) y se añadió en porciones borohidruro sódico (2,12 g, 0,056 mol) durante 5 minutos. La mezcla de reacción se agitó a temperatura ambiente durante 4 horas, se añadió más borohidruro sódico (1 g, 0,026 mol) y la mezcla se calentó a 60°C durante 1,5 horas. La mezcla se enfrió y el exceso

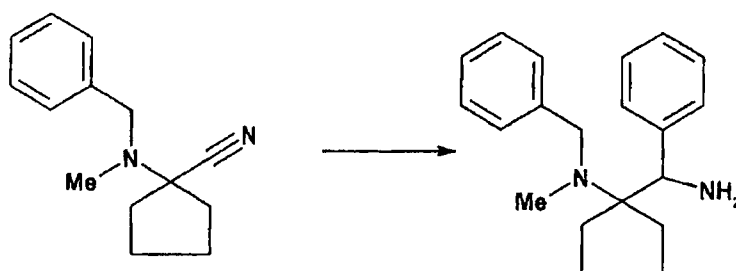
de borohidruro sódico se descompuso mediante la adición gota a gota de agua. La mezcla de reacción se evaporó al vacío y el residuo se repartió entre carbonato ácido sódico saturado (150 ml) y DCM (150 ml). Se añadió carbonato potásico sólido y la fase acuosa se extrajo con DCM (150 ml). Los extractos orgánicos combinados se secaron (Na_2SO_4) y se evaporaron, dando un aceite verde. Éste se dividió en 8 porciones y cada porción se pasó a través de una columna SCX de 10 g. Después de lavar cada columna con DCM, DCM al 50% en metanol y metanol, el compuesto se eluyó con amoníaco 1 M en metanol, produciendo el compuesto del título en forma de un aceite amarillo pálido (3,46 g: 80%). Espectro de masas (Electronebulización CL/EM), EN^+ : Encontrado 233 (MH^+). $\text{C}_{15}\text{H}_{24}\text{N}_2$ requiere 232. Tiempos de retención 0,96 y 1,07 min.

Descripción 27: 1-[Metil(fenilmetil)amino]ciclopentanocarbonitrilo



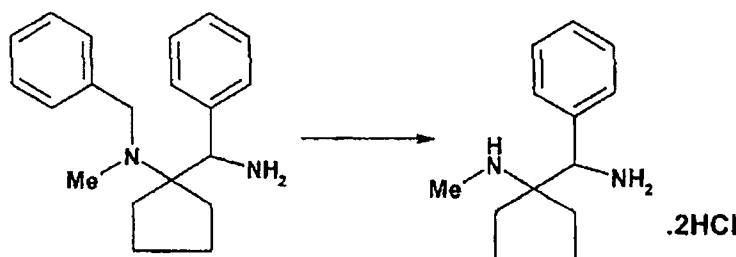
El compuesto del título (15 g, 84%) se preparó a partir de *N*-metilbencilamina (10,08 g, 83 mmol), ciclopentanona (7 g, 83 mmol) y cianuro de potasio (5,41 g, 83 mmol) en agua (45 ml) de manera similar a la descrita en D1. ^1H RMN (CDCl_3) δ : 1,90 (6H, m), 2,20 (3H, s), 2,3 (2H, m), 3,62 (2H, s), 7,25 (1H, m), 7,32 (4H, m); Espectro de masas (Electronebulización CL/EM): Encontrado 188 ($\text{MH}^+ - \text{HCN}$). $\text{C}_{14}\text{H}_{18}\text{N}_2$ requiere 214. Tiempo de retención 1,21 min.

Descripción 28: ($\pm$)-{1-[Amino(fenil)metil]ciclopentil}metil(fenilmetil)amina



El compuesto del título (3,90 g, 47%) se preparó a partir de 1-[metil(fenilmetil)amino]ciclopentanocarbonitrilo D28 (6,0 g, 28 mmol) y fenillitio en di-*n*-butil éter (16,21 ml de una solución 1,9 M; 30,8 mmol) en THF (60 ml),
 5 seguido de reacción con borohidruro sódico (3,2 g, 84 mmol) en metanol (60 ml) de manera similar a la descrita en D2. Espectro de masas (Electronebulización CL/EM), IPA⁺: Encontrado 295 (MH⁺). C₂₀H₂₆N₂ requiere 294. Tiempo de retención 2,12 min.

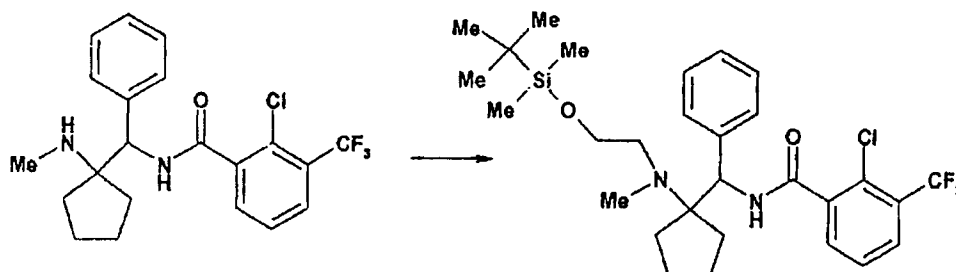
Descripción 29: Diclorhidrato de (±)-{1-[amino(fenil)-
 10 metil]ciclopentil}metilamina



A una solución de (±)-{1-[amino(fenil)metil]-
 ciclopentil}metil(fenilmetil)amina D28 (0,5 g, 1,7 mmol) en etanol se le
 añadieron HCl 3 N (1 ml) y paladio al 10% sobre carbono (0,1 g). La
 15 hidrogenación catalítica se realizó durante 16 h a temperatura ambiente y a
 presión atmosférica. El catalizador se retiró por filtración a través de kieselguhr
 y el filtrado se evaporó a presión reducida, dando el compuesto del título (0,32

g, 69%). ^1H RMN (DMSO) δ : 1,3-2,2 (8H, m), 2,5 (3H, s), 4,6 (1H, s), 7,4 (3H, m), 7,6 (2H, m), 8,0 (2H, s a), 9,0 (1H, s a).

Descripción **30:** **($\pm$)-2-Cloro-N-[[1-[(2-[(1,1-dimetiletil)(dimetil)silil]oxi)etil](metil)amino]ciclopentil](fenil)metil]-3-(trifluorometil)benzamida**

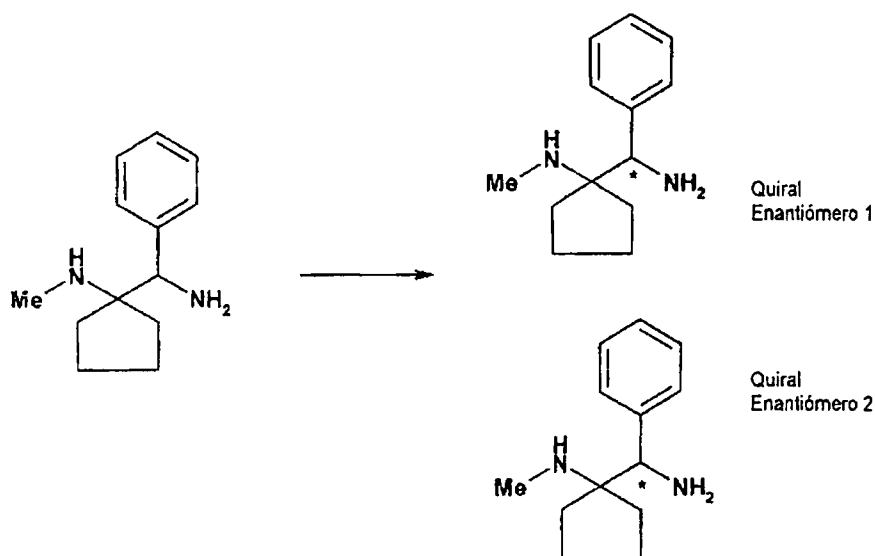


El compuesto del título (0,390 g, 99%) se preparó a partir de ($\pm$)-2-cloro-N-[[1- (metilamino)ciclopentil](fenil)metil]-3-(trifluorometil)benzamida (0,282 g, 0,686 mmol), (*tert*-butildimetilsililoxi)acetaldehído (90%; 0,265 g, 1,52 mmol) y triacetoxiborohidruro sódico (0,290 g, 1,52 mmol) en DCM (5 ml) de manera similar a la descrita en E30. Espectro de masas (Electronebulización CL/EM). Encontrado 569 (MH^+). $\text{C}_{29}\text{H}_{40}^{35}\text{ClF}_3\text{N}_2\text{O}_2\text{Si}$ requiere 568. Tiempo de retención: 3,04 min.

Descripción 31: {1-[Amino(fenil)metil]ciclopentil}metilamina Enantiómero

1 y Enantiómero 2

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Se separó (±)-{1-[amino(fenil)metil]ciclopentil}metilamina racémica D29 (0,342 g, 1,67 mmol) por HPLC preparativa quiral, proporcionando los compuestos del título enantiómero 1 (0,134 g); HPLC quiral: 99,8% de ee; ^1H RMN (CDCl_3) δ : 1,30-1,78 (11H, m), 2,33 (3H, s), 4,08 (1H, s), 7,22 (1H, m), 7,28 (2H, m), 7,35 (2H, m) y enantiómero 2 (0,127 g); HPLC quiral: 99,8% de ee; ^1H RMN (CDCl_3) δ : 1,30-1,78 (11H, m), 2,33 (3H, s), 4,08 (1H, s), 7,22 (1H, m), 7,28 (2H, m), 7,35 (2H, m).

Condiciones de HPLC analítica:

10 Columna: Chiral OD de tamaño de partículas de 10 micrones, 20 mm d.i. x 250 mm

Fase móvil: Heptano:Etanol absoluto (90:10 v/v)

Gradiente: Isocrático

Longitud de onda de UV: 215 nm

15 Caudal: 1 ml/min

Tiempo de ret.: 7,5 min (Enantiómero 1); 15,6 min (Enantiómero 2)

Condiciones de HPLC preparativa:

Columna: Chiral OD de Tamaño de partículas de 10 micrones, 20 mm d.i. x 250 mm

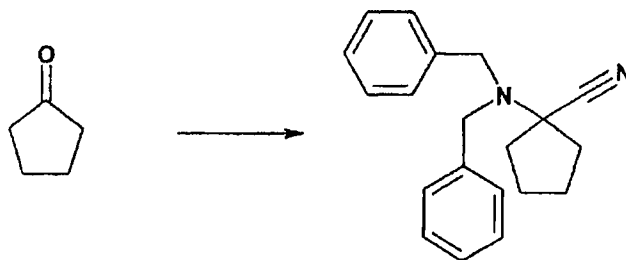
Fase móvil: Heptano:Etanol absoluto (90:10 v/v)

Gradiente: Isocrático

5 Longitud de onda de UV: 215 nm

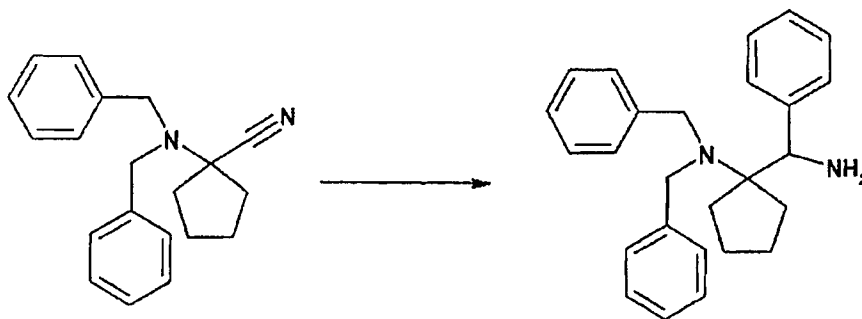
Caudal: 17 ml/min

Descripción 32: 1-[Bis(fenilmetil)amino]ciclopentanocarbonitrilo



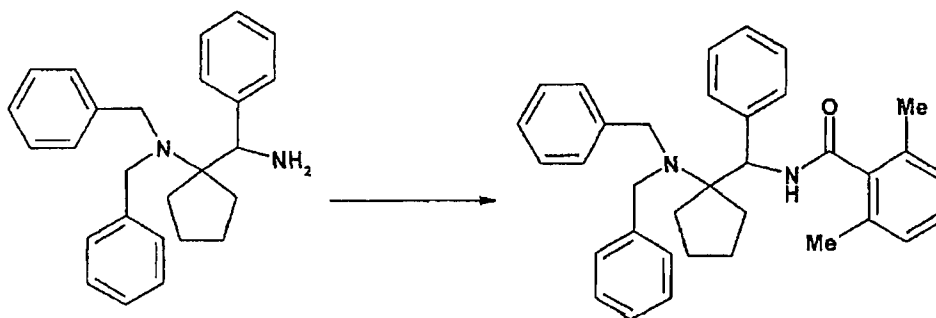
A una suspensión enfriada con hielo de clorhidrato de dibencilamina
10 (13,5 g, 0,058 mol) y ciclopentanona (4,86 g, 0,058 mol) en etanol al 25 % en
agua (100 ml) se le añadieron gota a gota etanol (60 ml) y una solución de
cianuro de potasio (3,78 g, 0,058 mol) en agua (35 ml) durante 20 minutos con
agitación. Después de 6 días, la mezcla de reacción se extrajo con acetato de
etilo, se lavó con una solución de bicarbonato sódico, se secó (Na_2SO_4) y se
15 evaporó al vacío, proporcionando el compuesto del título en forma de un sólido
blanquecino (8,32 g, 49%). ^1H RMN (CDCl_3) δ : 1,72 (6H, m), 2,12 (2H, m), 3,78
(4H, m), 7,1-7,3 (10H, m); Espectro de masas (Electronebulización CL/EM):
Encontrado 264 ($\text{MH}^+ - \text{HCN}$). $\text{C}_{20}\text{H}_{22}\text{N}_2$ requiere 290. Tiempo de retención 1,88
min.

20 **Descripción 33: ($\pm$)-{1-[Amino(fenil)metil]ciclopentil}bis(fenilmetil)amina**



El compuesto del título (2,31 g, 38%) se preparó a partir de 1-
[bis(fenilmetil)amino]ciclopentanocarbonitrilo D32 (4,0 g, 13,8 mmol) y fenillitio
en di-*n*-butil éter (8,4 ml de una solución 1,8 M; 15,2 mmol) en THF (80 ml),
5 seguido de reacción con borohidruro sódico (1,57 g, 41,4 mmol) en metanol (80
ml) de manera similar a la descrita en D2. Espectro de masas
(Electronebulización CL/EM), IPA⁺: Encontrado 371 (MH⁺). C₂₆H₃₀N₂ requiere
370. Tiempo de retención 2,62 min.

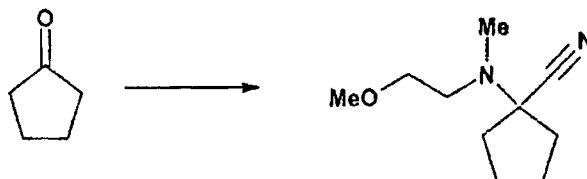
Descripción 34: (±)-*N*-[[1-[[bis(fenilmetil)amino]ciclopentil]}(fenil)metil]-2,6-
10 dimetilbenzamida



El compuesto del título (2,51 g, 80%) se preparó a partir de (±)-{1-
[amino(fenil)metil]ciclopentil}bis(fenilmetil)amina D33 (2,31 g, 6,23 mmol),
cloruro de 2,6-dimetilbenzoilo (1,15 g, 6,85 mmol) y trietilamina (1,73 ml, 12,5
15 mmol) en DCM (70 ml) de manera similar a la descrita en E13. ¹H RMN (CDCl₃)
δ: 1,40-2,05 (8H, m), 2,28 (6H, s), 3,68 (4H, s), 5,37 (1H, d), 6,78 (1H, m), 6,95-

7,36 (16H, m), 7,45 (2H, m); Espectro de masas (Electronebulización CL/EM),
IPA⁺: Encontrado 503 (MH⁺). C₃₅H₃₈N₂O requiere 502. Tiempo de retención
3,77 min.

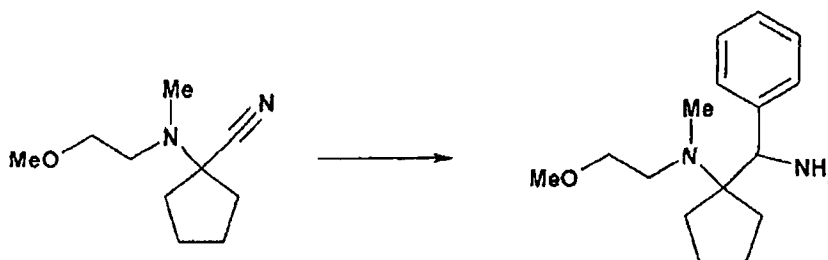
Descripción 35: 1-{Metil[2-(metiloxi)etil]amino}ciclopentanocarbonitrilo



5

El compuesto del título (3,39 g, 82%) se preparó a partir de clorhidrato
de *N*-(2-metoxietil)metilamina (2,84 g, 22,6 mmol), ciclopentanona (1,90 g, 22,6
mmol) y cianuro de potasio (1,47 g, 22,6 mmol) en agua (15 ml) de manera
similar a la descrita en D1. ¹H RMN (CDCl₃) δ: 1,83 (6H, m), 2,20 (2H, m), 2,48
10 (3H, s), 2,68 (2H, t), 3,46 (3H, s), 3,5 (2H, t).

Descripción 36: (±)-{1-[Amino(fenil)metil]ciclopentil}metil[2-(metiloxi)etil]amina

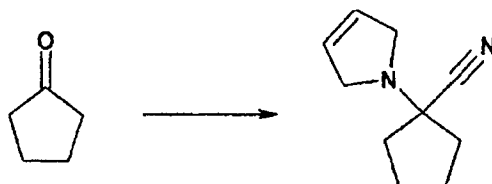


El compuesto del título (1,22 g, 42%) se preparó a partir de 1-{metil[2-
15 (metiloxi)etil]amino}ciclopentanocarbonitrilo D35 (2,0 g, 11 mmol) y fenillitio en
di-*n*-butil éter (6,7 ml de una solución 1,8 M; 12 mmol) en THF (25 ml), seguido
de reacción con borohidruro sódico (1,25 g, 33 mmol) en metanol (25 ml) de
manera similar a la descrita en D2. Espectro de masas (Electronebulización

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CL/EM). Encontrado 263 (MH^+). $C_{16}H_{26}N_2O$ requiere 262. Tiempo de retención 1,57 min.

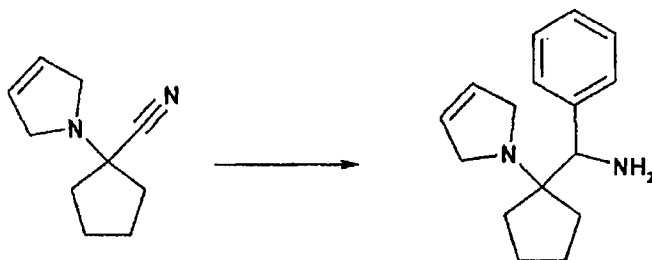
Descripción 37: 1-(2,5-Dihidro-1H-pirrol-1-il)ciclopentanocarbonitrilo



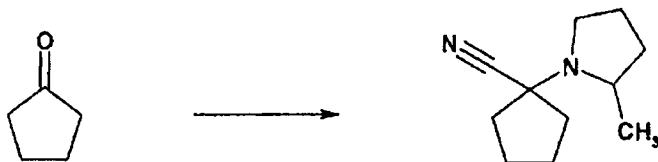
5 El compuesto del título (2,8 g, 64%) se preparó a partir de 3-pirrolina (1,86 g, 27 mmol), ciclopentanona (2,26 g, 27 mmol) y cianuro de potasio (1,75 g, 27 mmol) en agua (15 ml) de manera similar a la descrita en D1. ^1H RMN ($CDCl_3$) δ : 1,85 (6H, m), 2,08 (2H, m), 3,61 (4H, s), 5,78 (2H, s).

Descripción 38: ($\pm$)-[[1-(2,5-Dihidro-1H-pirrol-1-il)ciclopentil]

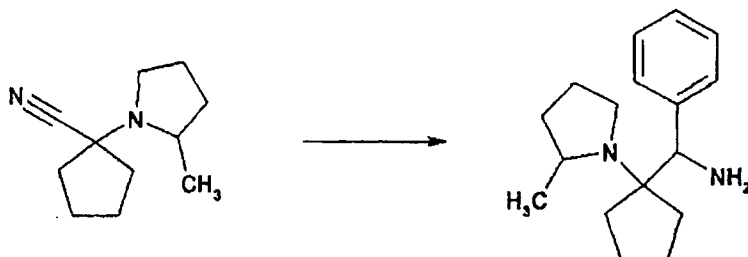
10 **(fenil)metil]amina**



El compuesto del título (1,35 g, 45%) se preparó a partir de 1-(2,5-dihidro-1H-pirrol-1-il)ciclopentanocarbonitrilo D37 (2,0 g, 12,3 mmol) y fenillitio en di-*n*-butil éter (7,5 ml de una solución 1,8 M; 13,5 mmol) en THF (20 ml),
15 seguido de reacción con borohidruro sódico (1,402 g, 36,9 mmol) en metanol (20 ml) de manera similar a la descrita en D2. Espectro de masas (Electronebulización CL/EM): Encontrado 243 (MH^+). $C_{16}H_{22}N_2$ requiere 242. Tiempo de retención 1,02 min.

Descripción 39: (±)-1-(2-Metil-1-pirrolidinil)ciclopentanocarbonitrilo

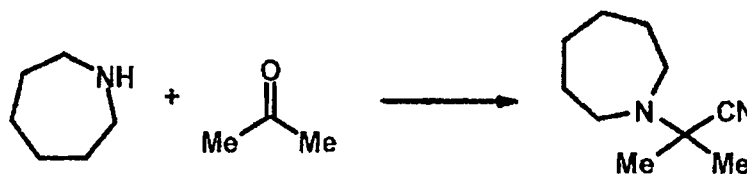
Una mezcla de ciclopentanona (1,34 g, 16 mmol) y 2-metilpirrolidina (1,36 g, 16 mmol) se enfrió a 0°C (baño de hielo). Se añadió gota a gota una
5 solución de cianuro de potasio (1,04 g, 16 mmol) en agua (10 ml) durante 10 min y toda la mezcla se agitó vigorosamente durante 18 h a 20°C y después se repartió entre acetato de etilo y agua. La fase orgánica se secó (Na₂SO₄) y se evaporó al vacío, proporcionando el compuesto del título (2,24 g, 79%). ¹RMN (CDCl₃) δ: 1,1 (3H, d), 1,45 (1H, m), 1,75-2,05 (9H, m), 2,13 (2H, m), 2,65 (1H,
10 m), 3,1 (2H, m).

Descripción 40: (±)-[[1-(2-metil-1-pirrolidinil)ciclopentil](fenil) metil]amina

Una solución de (±)-1-(2-metil-1-pirrolidinil)ciclopentanocarbonitrilo D39 (0,997 g, 5,6 mmol) en THF seco se enfrió a -70°C. A esto se le añadió
15 lentamente fenililitio (1,7 M en C₆H₁₄/éter, 1,1 equiv.). Toda la mezcla se dejó calentar lentamente a temperatura ambiente durante 3 h con agitación en una atmósfera de argón. La reacción se enfrió a 0°C, se añadió metanol seguido de borohidruro sódico (en porciones) y se dejó reaccionar a 20°C durante una noche. La reacción se enfrió a 0°C y se inactivó con bicarbonato sódico

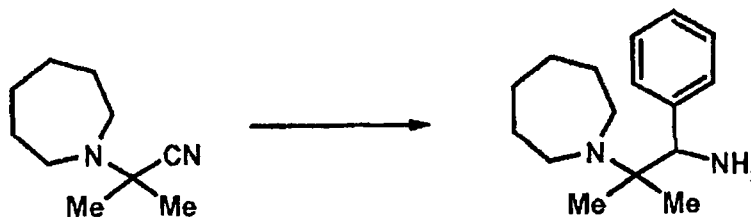
saturado, se extrajo con acetato de etilo, se secó (Na_2SO_4) y se evaporó. El compuesto se purificó por cromatografía sobre una columna SCX de 5 g eluyendo en acetato de etilo al 0-100% en éter de petróleo, metanol al 0-10% en acetato de etilo y después amoniaco 0,880 al 2% en acetato de etilo, dando el compuesto del título en forma de un aceite (0,67 g, 46%). Espectro de masas (Electronebulización CL/EM): Encontrado 259 (MH^+). $\text{C}_{17}\text{H}_{26}\text{N}_2$ requiere 258. Tiempo de retención 1,19 min.

Descripción 41: 2-(Hexahidro-1H-azepin-1-il)-2-metilpropanonitrilo



El compuesto del título (6,6 g; 80%) se preparó a partir de clorhidrato de homopiperidina (6,7 g, 49 mmol), acetona (3,67 ml, 50 mmol) y cianuro de potasio (3,25 g, 50 mmol) en agua (25 ml) de manera similar a la descrita en D1. ^1H RMN (CDCl_3) δ 1,43 (6H, s), 1,50-1,65 (8H, m), 2,66 (4H, m).

Descripción 42: ($\pm$)[2-(Hexahidro-1H-azepin-1-il)-2-metil-1-fenilpropil]amina

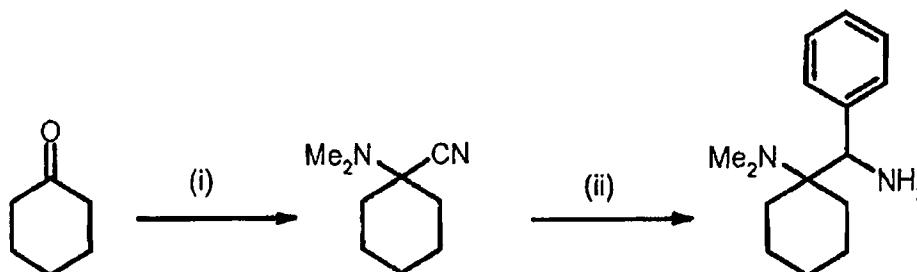


El compuesto del título (3,7 g, 83%) se preparó a partir de 2-(hexahidro-1H-azepin-1-il)-2-metilpropanonitrilo D41 (3 g, 18 mmol) y fenilitio en éter dibutílico (18 ml de una solución 2 M; 36 mmol) en THF (100 ml), seguido de

249

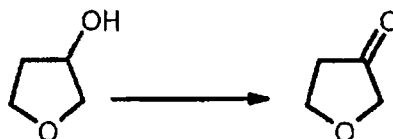
reacción con borohidruro sódico (2,13 g, 54 mmol) en metanol (100 ml) de manera similar a la descrita en D5. ^1H RMN (CDCl_3) δ 0,78 (3H, s), 0,98 (3H, s), 1,55-1,70 (8H, m), 1,83 (2H, s a), 2,67-2,79 (4H, m), 4,18 (1H, s), 7,20-7,30 (3H, m), 7,40-7,42 (2H, m).

5 **Descripción 43 : ($\pm$){1-[Amino(fenil)metil]ciclohexil}dimetilamina**



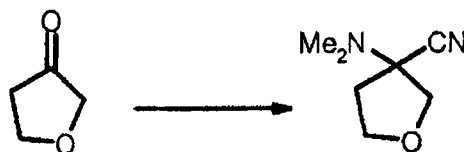
El compuesto del título se preparó en dos etapas a partir de (i) clorhidrato de dimetilamina (3,26 g, 0,04 mol), ciclohexanona (3,9 g, 0,04 mol) y cianuro de potasio (2,60 g, 0,04 mol) en agua (25 ml) de manera similar a la descrita en D1 obteniendo 1-(dimetilamino)ciclohexanocarbonitrilo (6,6 g, 100%). Éste se hizo reaccionar directamente en (ii) con fenillitio en éter dibutílico (10,5 ml de una solución 1,9 M, 0,02 mol) en THF (30 ml) seguido de borohidruro sódico (1,51 g, 0,04 mol) de manera similar a la descrita en D2, proporcionando el compuesto del título (2,5 g, 36%). ^1H RMN (CDCl_3) δ : 0,85 (1H, m), 1,00 (1H, m), 1,25 (2H, m), 1,35-1,60 (6H, m a), 1,70 (1H, m), 2,10 (1H, m), 2,46 (6H, s), 4,15 (1H, s), 7,20-7,32 (5H, m).

Descripción 44 : Dihidro-3(2H)-furanona



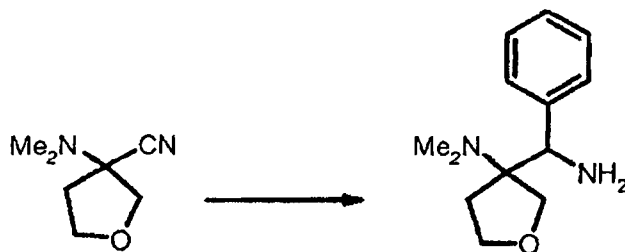
Una mezcla de 3-hidroxitetrahydrofurano (3,0 g, 0,034 mol) y clorocromato de piridinio (14,7 g, 0,068 mol) en DCM (100 ml) se agitó a temperatura ambiente durante una noche. El compuesto del título se obtuvo vertiendo el compuesto bruto a través de una capa de sílice usando acetato de etilo como eluyente. El compuesto del título se obtuvo después de 2 eluciones (2,29 g, 79%). ^1H RMN (CDCl_3) δ : 2,50 (2H, t), 3,87 (2H, s), 4,26 (2H, t).

Descripción 45 : ($\pm$)3-(Dimetilamino)tetrahydro-3-furancarbonitrilo



El compuesto del título (6,54 g, 88%) se preparó a partir de dihidro-3(2H)-furanona D44 (4,54 g, 0,053 mol), clorhidrato de dimetilamina (4,9 g, 0,06 mol) y cianuro de potasio (3,5 g, 0,054 mol) en agua (100 ml) de manera similar a la descrita en D1. ^1H RMN (CDCl_3) δ : 2,15 (1H, m), 2,33 (6H, s), 2,44 (1H, m), 3,69 (1H, d), 4,02-4,13 (2H, m), 4,17 (1H, m).

Descripción 46: ($\pm$){3-[Amino(fenil)metil]tetrahydro-3-furanil}dimetilamina diastereoisómeros



A una solución de 3-(dimetilamino)tetrahydro-3-furancarbonitrilo D45 (4,55 g, 0,032 mol) en tetrahydrofurano (30 ml) a -70°C en una atmósfera de argón se le añadió gota a gota una solución de fenillitio en éter dibutílico (36,1

ml de una solución 1,8 M; 0,064 mol). La mezcla de reacción se agitó y se mantuvo de -50 a -70°C durante 16 horas seguido de la adición cuidadosa de bicarbonato sódico acuoso saturado. La suspensión resultante se extrajo tres veces con DCM. Los extractos combinados se secaron (Na_2SO_4) y se evaporaron, proporcionando el compuesto bruto en forma de un aceite naranja que se cromatografió sobre gel de sílice eluyendo con acetato de etilo del 0 al 100%/pentano, proporcionando el intermedio imina en forma de un aceite amarillo (5,18 g). El aceite se disolvió en metanol, se añadió borohidruro sódico (1,8 g, 0,047 mol) y la mezcla se agitó a temperatura ambiente durante una noche. El metanol se evaporó y la suspensión se repartió entre DCM y bicarbonato sódico acuoso saturado. Los extractos orgánicos se secaron pasándose a través de una columna Phase-Sep y se evaporaron, proporcionando el compuesto del título (3,47 g, 49%). ^1H RMN (CDCl_3) δ : 1,68 y 2,20 (1H, 2 x m), 1,75 (2H, s a), 1,90 y 2,05 (1H, 2 x m), 2,32 y 2,35 (6H, 2 x s), 2,70 y 3,42 (1H, 2 x m), 3,66-3,98 (3H, m a), 4,32 y 4,48 (1H, 2 x s), 7,20-7,51 (5H, m).

Descripción 47: ($\pm$)-2-(Dimetilamino)-3-(((1,1-dimetiletil)(dimetil)silil)oxi)-2-metilpropanonitrilo

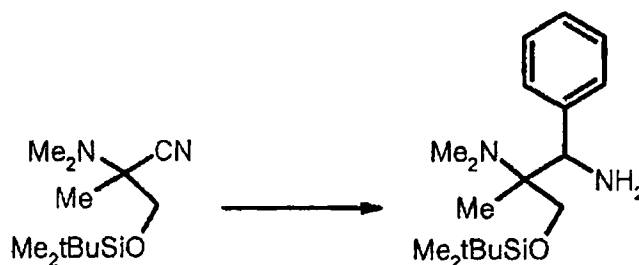


El compuesto del título (2,16 g, 45%) se preparó a partir de 1-(*t*-butildimetilsililoxi)-2-propanona (3,77 g, 0,02 mol), clorhidrato de dimetilamina (1,71 g, 0,02 mol) y cianuro de potasio (1,37 g, 0,02 mol) en agua (50 ml) de manera similar a la descrita en D1. Una etapa de purificación adicional fue

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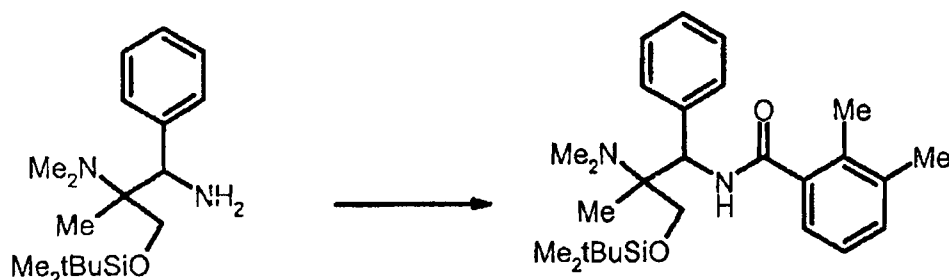
pasar el compuesto a través de resina SCX, la elución con DCM para retirar el material de partida y después la elución con amoníaco 1 M en metanol para eluir el compuesto del título. ^1H RMN (CDCl_3) δ : 0,00 (6H, d), 0,81 (9H, s), 1,38 (3H, s), 2,25 (6H, s), 3,36 (1H, d), 3,78 (1H, d).

5 **Descripción 48:** ($\pm$)[2-Amino-1-({[(1,1-dimetiletil)(dimetil)silil]oxi}metil)-1-metil-2-feniletil]dimetilamina diastereoisómeros



El compuesto del título (930 mg, 33%) se preparó a partir de 2-(dimetilamino)-3-{{[(1,1-dimetiletil)(dimetil)silil]oxi}-2-metilpropanonitrilo D47 (2,1 g, 8,67 mmol), fenilitio (10,0 ml de una solución 1,8 M en éter dibutilico, 18,0 mmol) en THF (30 ml) seguido de borohidruro sódico (830 mg, 26,0 mmol) en metanol (50 ml) de manera similar a la descrita en D2. La cromatografía (Biotage Horizon) para aislar el compuesto del título se realizó usando (i) acetato de etilo del 0 al 100%/pentano, (ii) acetato de etilo al 100% y (iii) metanol del 0 al 20%/acetato de etilo. Las fracciones que contenían el compuesto se combinaron y se evaporaron. Espectro de masas (Electronebulización CL/EM), IPA^+ : Encontrado 323 (MH^+), 306 ($\text{M}-16$). $\text{C}_{18}\text{H}_{34}\text{N}_2\text{OSi}$ requiere 322. Tiempo de retención 2,35-2,39 min. (pico ancho).

20 **Descripción 49:** ($\pm$)N-(2-(Dimetilamino)-3-{{[(1,1-dimetiletil)(dimetil)silil]oxi}-2-metil-1-fenilpropil)-2,3-dimetilbenzamida diastereoisómeros

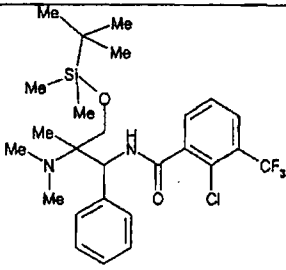


El compuesto del título (64 mg; 30%) se preparó a partir de [2-amino-1-
 {{{(1,1-dimetiletil)(dimetil)silil]oxi}metil)-1-metil-2-feniletil]dimetilamina D48 (150
 mg; 0,46 mmol), ácido 2,3-dimetilbenzoico (75 mg; 0,5 mmol), PL-
 5 díciclohexilcarbodiimida (385 mg; 0,5 mmol; Polymer Labs 1,3 mmol/g) y 1-
 hidroxibenzotriazol (77 mg; 0,5 mmol) en DCM (5 ml) de manera similar a la
 descrita en E1. Espectro de masas (Electronebulización CL/EM) : Encontrado
 455 (MH⁺), C₂₇H₄₂N₂O₂Si requiere 454. Tiempo de retención 2,57 y 2,61 min.

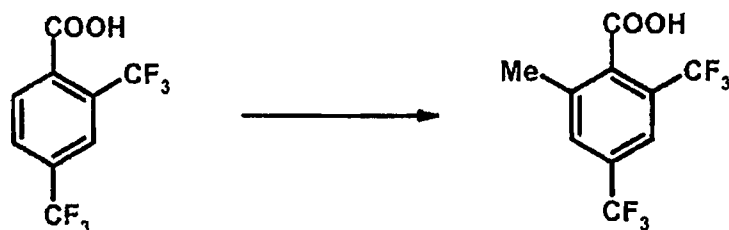
Los compuestos de la Tabla 1 mostrada a continuación se prepararon de
 10 manera similar a la descrita en la descripción D49.

Tabla 1

Descripción n	Estructura	Espectro de masas (Electronebulización n CL/EM), IPA ⁺ Tiempo de Ret (min)	Nombre
50		Encontrado 455 (MH ⁺) C ₂₇ H ₄₂ N ₂ O ₂ Si requiere 454; 2,60 y 2,62	(±)-N-(2-(dimetilamino)-3- {{{(1,1- dimetiletil)(dimetil)silil]oxi} -2-metil-1-fenilpropil)-2,6- dimetilbenzamida diastereoisómeros

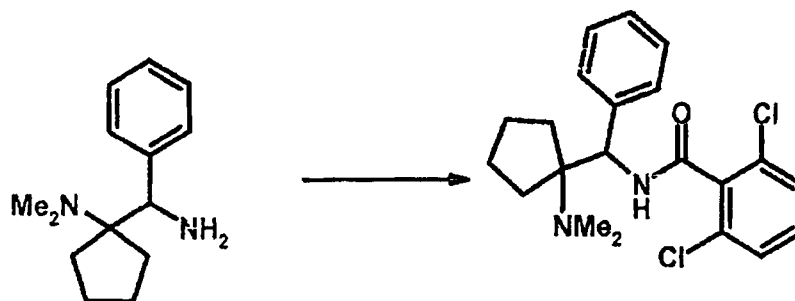
51		Encontrado 529 (MH ⁺) $C_{26}H_{36}^{35}ClF_3N_2O_2Si$ requiere 528; 2,72 y 2,79	(±)-2-cloro- <i>N</i> -(2-(dimetiletil)(dimetil)silil)oxi}-2-metil-1-fenilpropil)-3-(trifluorometil)benzamida diastereoisómeros
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Descripción 52: Ácido 2-metil-4,6-bis(trifluorometil)benzoico



Se agitó THF seco (5 ml) en una atmósfera de argón a -80°C y se trató con *sec*-butillitio (3,05 ml de una solución 1,4 M en ciclohexano, 4,27 mmol) y *N,N,N',N'*-tetrametiletenodiamina (640 µl, 4,27 mmol). Se añadió gota a gota una solución de ácido 2,4-*bis*(trifluorometil)benzoico (0,50 g, 1,94 mmol) en THF seco (2 ml) durante 30 minutos y se dejó en agitación durante 30 minutos más a -80°C. Se añadió gota a gota yodometano (483 µl, 7,76 mmol) durante 5 minutos, la reacción se agitó a -70°C durante 20 minutos más y se dejó calentar a temperatura ambiente. Se añadió gota a gota agua (1 ml) y la mezcla se repartió entre acetato de etilo y agua. La fase de agua se acidificó con ácido clorhídrico 2 M y se extrajo dos veces con acetato de etilo. Los extractos combinados se secaron sobre sulfato de magnesio y se evaporaron, proporcionando un sólido bruto (416 mg). La RMN indicó que era una mezcla de ácido 2-metil-4,6-*bis*(trifluorometil)benzoico y ácido 2,4-*bis*(trifluorometil)benzoico recuperado. Se usó sin purificación adicional.

Ejemplo 1: (±)-2,6-Dicloro-*N*-[[1-(dimetilamino)ciclopentil](fenil)metil]-benzamida



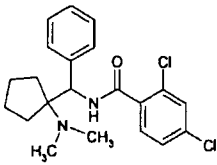
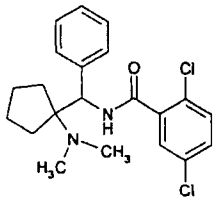
A una solución de ácido 2,6-diclorobenzoico (20 mg; 0,105 mmol) en
 5 DCM (2 ml) y *N*-metilpirrolidinona (0,1-0,5 ml) se le añadieron 1-
 hidroxibenzotriazol (18 mg; 0,11 mmol) y PL-diciclohexilcarbodiimida (88 mg;
 0,14 mmol; Polymer Labs 1,59 mmol/g). La mezcla se agitó a temperatura
 ambiente durante 1 hora, después se añadieron diclorhidrato de 1-
 [amino(fenil)metil]ciclopentil}dimetilamina D2 (20 mg; 0,07 mmol) y PS-
 10 diisopropiletilamina (82 mg; 0,21 mmol; Polymer Labs 2,59 mmol/g) y la
 agitación se continuó durante una noche a temperatura ambiente. Después, se
 añadió un exceso de PS-trisamina y después de agitar durante 4 h más, la
 mezcla se filtró y las resinas se lavaron bien con DCM y metanol. El filtrado se
 redujo en volumen por evaporación al vacío y se cargó sobre un cartucho SCX
 15 (500 mg). El lavado con DCM y después con metanol seguido de la elución con
 amoníaco 1 M en metanol proporcionó el compuesto del título (22,8 mg). ¹H
 RMN (CDCl₃) δ: 0,98 (1H, m), 1,26 (1H, m), 1,40 (2H, m), 1,68 (2H, m), 1,85
 (2H, m), 2,22 (6H, s), 5,08 (1H, s a), 7,27 (7H, m) y 7,47 (2H, m). Espectro de
 masas (Electronebulización CL/EM): Encontrado 391 (MH⁺). C₂₁H₂₄³⁵Cl₂N₂O
 20 requiere 390. Tiempo de retención 1,88 min.

Los compuestos de la Tabla 2 que se muestra a continuación se prepararon usando procedimientos similares a los descritos para el Ejemplo 1.

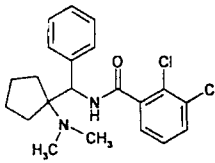
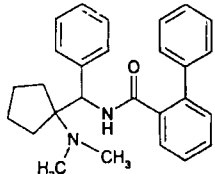
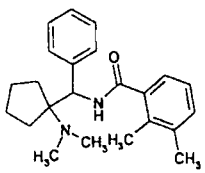
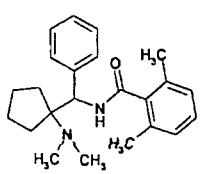
Procedimiento de acoplamiento: P = DCC con soporte polimérico

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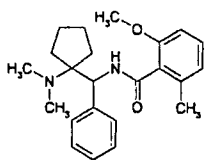
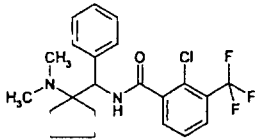
Tabla 2

Ej	Estructura	Procedi miento	Espectro de masas (Electropulverizac ión CL/EM), IPA ⁺ Tiempo de ret. (min)	Nombre
2		P	Encontrado 391 (MH ⁺) C ₂₁ H ₂₄ ³⁵ Cl ₂ N ₂ O requiere 390; 2,03	(±)-2,4-Dicloro-N-[[1-(Dimetilamino)ciclopentil](fenil)metil]benzamida
3		P	Encontrado 391 (MH ⁺) C ₂₁ H ₂₄ ³⁵ Cl ₂ N ₂ O requiere 390; 2,01	(±)-2,5-Dicloro-N-[[1-(Dimetilamino)ciclopentil](fenil)metil]benzamida

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4		P	Encontrado 391 (MH ⁺) $C_{21}H_{24}^{35}Cl_2N_2O$ requiere 390; 2,02	(±)-2,3-Dicloro-N-[[1-(Dimetilamino)ciclopentil](fenil)metil]benzamida
5		P	Encontrado 399 (MH ⁺) $C_{27}H_{30}N_2O$ requiere 398; 2,13	(±)-N-[[1-(Dimetilamino)ciclopentil](fenil)metil]-2-bifenilcarboxamida
6		P	Encontrado 351 (MH ⁺) $C_{23}H_{30}N_2O$ requiere 350; 1,96	(±)-N-[[1-(Dimetilamino)ciclopentil](fenil)metil]-2,3-dimetilbenzamida
7		P	Encontrado 351 (MH ⁺) $C_{23}H_{30}N_2O$ requiere 350; 1,87	(±)-N-[[1-(Dimetilamino)ciclopentil](fenil)metil]-2,6-dimetilbenzamida

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8		P	Encontrado 367 (MH ⁺) C ₂₃ H ₃₀ N ₂ O ₂ requiere 366; 1,80	(±)-N-[[1-(Dimetilamino)ciclopentil](fenil)metil]-2-metil-6-(metiloxi)benzamida
9		P	Encontrado 425 (MH ⁺) C ₂₂ H ₂₄ ³⁵ ClF ₃ N ₂ O requiere 424; 2,16 y 2,19.	(±)-2-Cloro-N-[[1-(dimetilamino)ciclopentil](fenil)metil]-3-(trifluorometil)benzamida

Ejemplo 10: 2-Cloro-N-[[1-(Dimetilamino)ciclopentil](fenil)metil]-3-(trifluorometil)benzamida enantiómero 2 Racémico 2-Cloro-N-[[1-

5 (Dimetilamino)ciclopentil](fenil)metil]-3-(trifluoro metil)benzamida E9 (250 mg; 0,59 mmoles) se separó mediante HPLC semi-preparativa quiral produciendo el producto enantiómero de título 1 (82 mg); HPLC Quiral > 99,8% de ee; y el producto enantiómero de título 2 (86 mg); HPLC Quiral >99,8% de ee.

10 Condiciones de cromatografía semipreparativa

Columna: Quiralpak AD-H 5 μm, 250 x 21 mm
 Fase móvil: A: n-Hexano; B: Isopropanol + isopropilamina al 0.1%
 Gradiente: isocrático 15% B

25A

Caudal: 7 ml/min

Intervalo de longitud de onda UV: 225 nm

Tiempo de análisis: 45 min

5 Condiciones de cromatografía analítica

Columna: Quiralpak AD-H 5 μ m, 250 x 4.6 mm

Fase móvil: A: n-Hexano; B: Isopropanol

Gradiente: isocrático 15% B

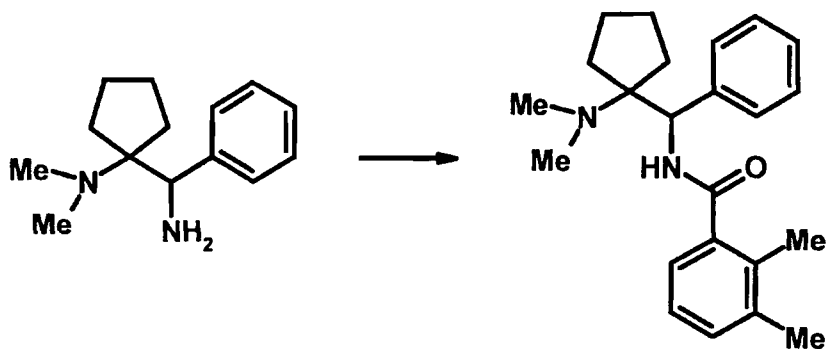
Caudal: 1 ml/min

10 Intervalo de longitud de onda UV: 200-400 nm

Tiempo de análisis: 25 min

Tiempo de ret.: 6,5 min (Enantiómero 1); 10,1min
(Enantiómero 2)

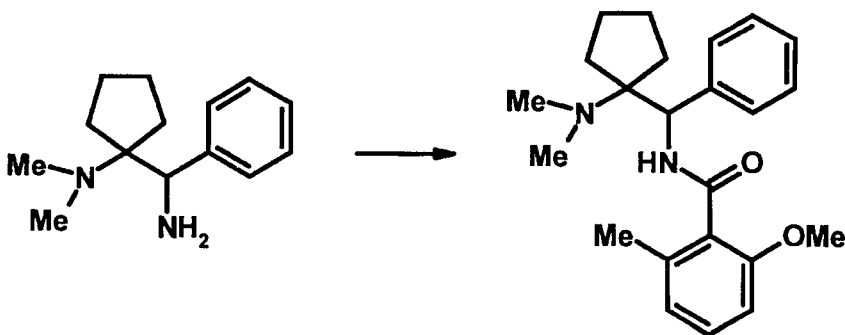
15 **Ejemplo 11: *N*-[[1-(Dimetilamino)ciclopentil](fenil)metil]-2,3-dimetil benzamida Quiral**



Una mezcla de {1-[amino(fenil)metil]ciclopentil}dimetilamina D3
enantiómero 2 (0,102 g, 0,47 mmoles), ácido 2,3-dimetilbenzoico (0,100 g, 0,67
20 mmoles), hidrato de 1-hidroxibenzotriazol (0,092 g, 0,6 mmoles) y PS-DCC

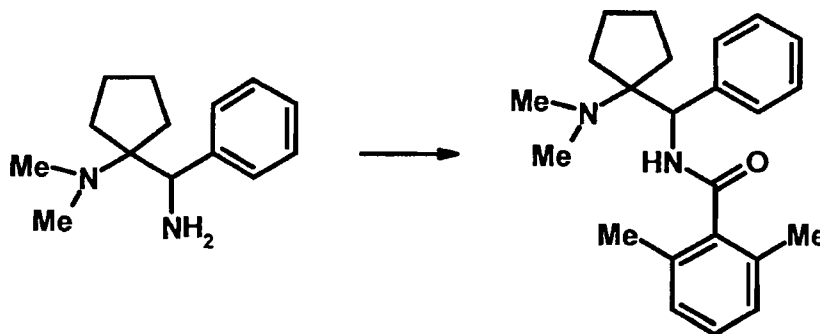
(carga 0,63g de 1,3 mmol/g, 0,82mmol) en DCM (7 ml) se agitó durante 20 h. La mezcla se filtró y la resina se lavó con DCM (2 x 4 ml). Los extractos orgánicos combinados se lavaron con carbonato ácido de sodio saturado (20 ml), se separaron las fases y la fase orgánica se aplicó a un cartucho de 2 g de SCX. El cartucho se lavó con DCM (2 volúmenes), metanol al 50% en DCM (1 volumen) y metanol (2 volúmenes). La elución con amoníaco 1 M en metanol (2 volúmenes) y la evaporación del disolvente produjo una goma incolora. La cromatografía sobre gel de sílice (10 g) eluyendo con acetato de etilo al 0 - 100% en gradiente de pentano produjo el compuesto del título en forma de un sólido incoloro (0,14 g; 86%). ^1H RMN (CDCl_3) δ : 0,90 - 1,15 (1H, m), 1,20 - 1,38 (1H, m), 1,40 - 1,55 (2H, m), 1,60 - 1,75 (2H, m), 1,79 - 1,90 (2H, m), 2,22 (6H, s), 2,28 (6H, s), 5,15 (1H, d, $J = 6\text{Hz}$), 6,98 (1H, d, $J = 6\text{Hz}$), 7,10 - 7,15 (1H, m), 7,19 - 7,27 (3H, m), 7,29 - 7,35 (2H, m), 7,39 - 7,43 (2H, m). Espectro de masas (Electropulverización CL/EM), EP^+ : Encontrado 351 (MH^+). $\text{C}_{23}\text{H}_{30}\text{N}_2\text{O}$ requiere 350. Tiempo de retención 1,90 min. El producto del título se convirtió en la sal clorhidrato correspondiente (0,150 g).

Ejemplo 12: N-[[1-(Dimetilamino)ciclopentil](fenil)metil]-2-metil-6-(metiloxi)benzamida quiral



Una mezcla de {1-[amino(fenil)metil]ciclopentil}dimetilamina D3 enantiómero 2 (0.220 g, 1 mmol), ácido 2-metoxi-6-metilbenzoico (0,200 g, 1,2 mmoles), hidrato de 1-hidroxibenzotriazol (0,183 g, 1,2 mmoles) y PS-DCC (1 g de carga 1,3 mmol/g, 1,3 mmoles) en DCM (10 ml) se agitó vigorosamente durante toda una noche. La mezcla se lavó con carbonato ácido de sodio acuoso saturado, se separaron las fases a través de un cartucho de separación de fases y la fase orgánica se aplicó a un cartucho SCX. El cartucho se eluyó con DCM (x 2), y después metanol (x 2) seguido de amoníaco 1 M en metanol. La evaporación del disolvente produjo el compuesto del título que se caracterizó. ^1H RMN (CDCl_3) δ : 1,00 - 1,10 (1H, m), 1,25 - 1,40 (1H, m), 1,40 - 1,60 (2H, m), 1,60 - 1,80 (2H, m), 1,80 - 2,00 (2H, m), 2,24 (6H, s), 2,28 (3H, s), 3,80 (3H, s), 5,17 (1H, d, $J = 6\text{Hz}$), 6,75 (1H, d, $J = 8\text{Hz}$), 6,79 (1H, d, $J = 8\text{Hz}$), 7,10 (1H, s a), 7,15 - 7,30 (4H, m), 7,44 (2H, m). Espectro de masas (Electropulverización CL/EM): Encontrado 367 (MH^+). $\text{C}_{23}\text{H}_{30}\text{N}_2\text{O}_2$ requiere 366. Tiempo de retención 1,92 min. El producto del título se convirtió en al sal clorhidrato correspondiente (0,34 g, 85%).

Ejemplo 13: N-[[1-(Dimetilamino)ciclopentil](fenil)metil]-2,6-dimetil benzamida quiral



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Una solución de cloruro de 2,6-dimetilbenzoílo (1,7 g, 10,1 mmoles) en DCM (10 ml) se añadió gota a gota a una mezcla de {1-[amino(fenil)metil]ciclopentil}dimetilamina D3 enantiómero 2 (2,0 g, 9,2 mmoles), y trietilamina (1,4 ml, 10,0 mmoles) en DCM (40 ml) y se agitó a temperatura ambiente durante 2 horas. La mezcla se lavó con carbonato ácido de sodio acuoso saturado, la fase orgánica se separó a través de un cartucho de separación de fases y después se evaporó hasta un sólido blanco. La cromatografía con eluyente acetato de etilo al 50 - 100% / pentano, después metanol al 0 - 10% / acetato de etilo produjo el producto del título en forma de un sólido blanco (3,1 g, 97 %), ^1H RMN (CDCl_3) δ : 0,85 - 1,00 (1H, m), 1,30 - 1,55 (3H, m), 1,60 - 1,75 (2H, m), 1,78 - 1,90 (2H, m), 2,21 (6H, s), 2,31 (6H, s), 5,19 (1H, d, $J = 6\text{Hz}$), 6,79 (1H, d a), 7,02 (2H, d, $J = 8\text{Hz}$), 7,16 (1H, t, $J = 8\text{Hz}$), 7,20 - 7,35 (3H, m), 7,43 (2H, m). Espectro de masas (Electropulverización CL/EM): Encontrado 351 (MH^+). $\text{C}_{23}\text{H}_{30}\text{N}_2\text{O}$ requiere 350. Tiempo de retención 2,0 min. El producto sólido blanco se convirtió en la sal de HCl usando HCl 1 M /dietiléter produciendo la sal en forma de un sólido blanco tras evaporación.

Ejemplo 13b: Sal succinato de N-[[1-

(dimetilamino)ciclopentil](fenil)metil]-2,6-dimetil benzamida quiral

A una mezcla de 26,25 g de la base libre del compuesto del ejemplo 13 y 9,286 g de ácido succínico, se añadieron 262 ml de IPA (alcohol isopropílico) en nitrógeno y la mezcla se agitó a temperatura ambiente durante 12 horas.

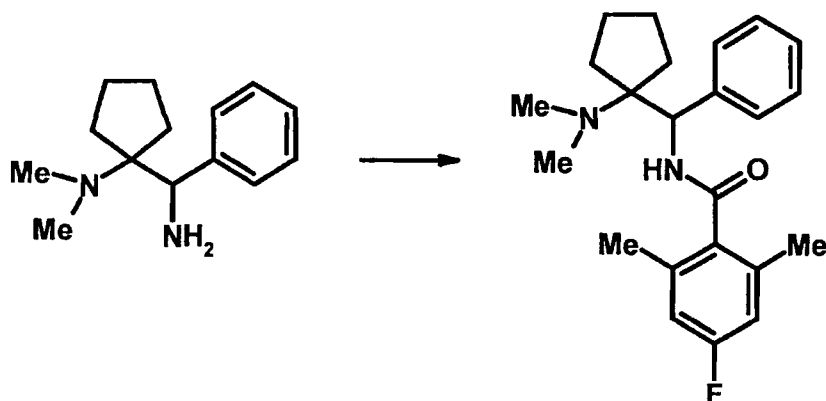
Después la mezcla se calentó hasta 40°C durante 1 hora, se enfrió a temperatura ambiente y se enfrió a 0°C durante 1 hora. Después de 30 minutos

adicionales a temperatura ambiente se recogió el sólido mediante filtración, se secó durante toda una noche a 45°C a vacío consiguiendo 31,92 g del material del título en forma de un sólido blanco.

5 **Ejemplo 13c: Formulación de N-[[1-(dimetilamino)ciclopentil](fenil)metil]-2,6-dimetil benzamida quiral**

10,6 mg de N-[[1-(Dimetilamino)ciclopentil](fenil)metil]-2,6-dimetil benzamida se disolvió en 7 ml de Miglyol 812 N. Se añadieron 217,1 mg de Methocel K4M y la suspensión se homogeneizó con un agitador de alta
10 cizalladura. Las concentraciones resultantes eran 1,5 mg ml⁻¹ de ingrediente activo y 30 mg ml⁻¹ de excipiente Methocel.

Ejemplo 14: N-[[1-(Dimetilamino)ciclopentil](fenil)metil]-4-fluoro-2,6-dimetilbenzamida quiral

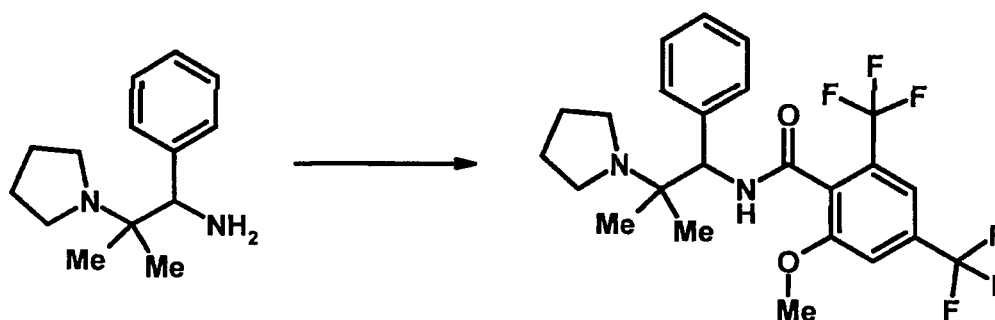


15 A {1-[amino(fenil)metil]ciclopentil}dimetilamina D3 enantiómero 2 (0,904 g; 4,147 mmol) en DCM (45 ml) en argón a temperatura ambiente se añadió trietilamina (0,573 ml; 4,15 mmoles), seguido de una solución de cloruro de 4-fluoro-2,6-dimetilbenzoilo (0,773 g; 4,144 mmol) en DCM (5 ml). Después de 16 horas se lavó la reacción con agua, se secó con MgSO₄ y se evaporó. El

residuo se cromatografió sobre gel de sílice eluyendo con un gradiente 0 a 100% de acetate de etilo - hexano proporcionando el compuesto del título (1,57 g; 100%). ^1H RMN (CDCl_3) δ : 0,85 - 1,00 (1H, m), 1,30 - 1,60 (3H, m), 1,60 - 1,75 (2H, m), 1,75 - 1,90 (2H, m), 2,22 (6H, s), 2,31 (6H, m), 5,18 (1H, d, $J =$ 5 6Hz), 6,73 (2H, d, $J = 9,6\text{Hz}$ solapamientos 1H, s a), 7,20 - 7,35 (3H, m), 7,42 (2H, m). Espectro de masas (Electropulverización CL/EM): Encontrado 369 (MH^+). $\text{C}_{23}\text{H}_{29}\text{FN}_2\text{O}$ requiere 368. Tiempo de retención 1,99 min. La base libre se disolvió en metanol. HCl 1M /dietiléter se añadió a la solución agitada y la agitación continuó a temperatura ambiente durante 5 minutos. Después la

10 solución se evaporó a presión reducida, se volvió a disolver en DCM y se evaporó a presión reducida. La espuma resultante se secó durante 16 horas a presión reducida. La sal clorhidrato se obtuvo en forma de una espuma blanca (1,45 g).

15 **Ejemplo 15: 2-(Metiloxi)-N-[2-metil-1-fenil-2-(1-pirrolidinil)propil]-4,6-bis(trifluorometil)benzamida quiral**

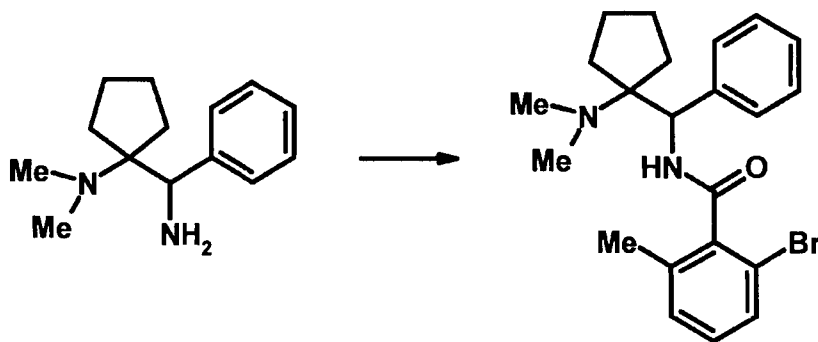


A una solución de diisopropiletilamina (0,915 ml; 5,37 mmoles), ácido 2,4-ditrifluorometil-6-metoxi-benzoico (0,511 g; 1,78 mmoles) y (+)- [2-metil-1-fenil-2-(1-pirrolidinil)propil]amina D6 (0,501 g; 1,74 mmoles) en DMF (50 ml) en

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argón se le añadió HATU (0,676 g; 1,78 mmoles) por partes. Después de agitar a temperatura ambiente durante 3 h., seguido de reposo durante aproximadamente 2 días la mezcla de reacción se purificó usando una columna de SCX y el producto resultante se repartió entre acetato de etilo y agua. El disolvente se retiró a vacío produciendo el producto del título. ^1H RMN (CDCl_3) δ : 0,94 (6H, s), 1,60 - 1,80 (4H, m), 2,55 - 2,75 (4H, m), 3,89 (3H, s), 4,78 (1H, s), 7,20 - 7,40 (7H, m), 7,52 (1H, s). Espectro de masas (Electropulverización CL/EM): Encontrado 489 (MH^+). $\text{C}_{24}\text{H}_{26}\text{F}_6\text{N}_2\text{O}_2$ requiere 488. Tiempo de retención 2,06 min. La conversión del producto del título en la sal clorhidrato correspondiente produjo un sólido blanquecino (0,893 g; 96%).

Ejemplo 16: 2-Bromo-N-[[1-(dimetilamino)ciclopentil](fenil)metil]-6-metilbenzamida quiral

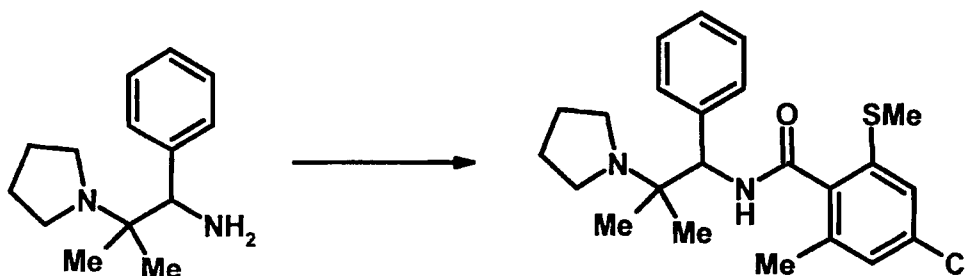


A {1-[amino(fenil)metil]ciclopentil}dimetilamina D3 enantiómero 2 (50 mg, 0,23 mmoles) en DCM (5 ml) se le añadió ácido 2-bromo-6-metilbenzoico (108 mg; 0,5 mmol), seguido de 1-hidroxibenzotriazol (45 mg; 0,3 mmoles) y PS-DCC (400 mg de carga 1,3 mmol/g, 0,52 mmol) y la mezcla se agitó a temperatura ambiente durante aproximadamente 2 días. La mezcla de reacción se filtró a través de un cartucho de separación de fases y el filtrado se agitó

con bicarbonato sódico acuoso saturado durante 30 minutos. Se retiró la fase inferior, se pasó a través de otro cartucho de separación de fases y se cargó en un cartucho SCX que se eluyó con 2 volúmenes de columna cada uno de DCM, metanol al 50% - DCM, metanol y amoníaco 1 M en metanol. Las fracciones que contenían el producto se evaporaron produciendo el compuesto del título (82 mg; 82%), ^1H RMN (CDCl_3) δ : 0,95 - 1,10 (2H, m), 1,40 - 1,60 (2H, m), 1,60 - 1,80 (2H, m), 1,80 - 1,90 (2H, m), 2,23 (6H, s), 2,33 (3H, m), 5,13 (1H, d $J = 6\text{Hz}$), 6,97 (1H, s a), 7,10 - 7,15 (2H, m), 7,24 - 7,34 (3H, m), 7,38 - 7,41 (1H, m), 7,46 - 7,48 (2H, m). Espectro de masas (Electropulverización CL/EM): Encontrado 415 (MH^+). $\text{C}_{22}\text{H}_{27}^{79}\text{BrN}_2\text{O}$ requiere 414. Tiempo de retención 1,93 min.

Ejemplo 17: 4-Cloro-2-metil-N-[2-metil-1-fenil-2-(1-pirrolidinil)propil]-6-(metiltio)benzamida quiral

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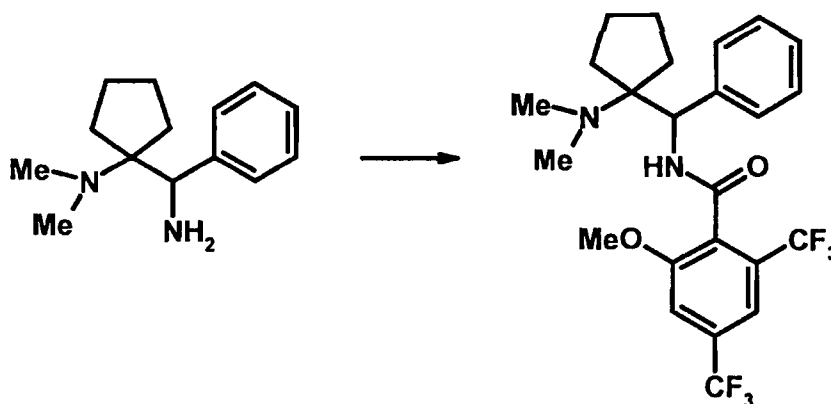
Una mezcla de (+)-[2-metil-1-fenil-2-(1-pirrolidinil)propil]amina D6 (262 mg; 1,2 mmoles), ácido 4-cloro-2-metil-6-(metiltio)benzoico (388 mg; 1,8 mmoles), hidrato de 1-hidroxibenzotriazol (276 mg; 1,8 mmoles) y EDC (345 mg; 1,8 mmoles) en DCM (16 ml) se agitó durante 16 h. Después la mezcla se repartió entre DCM y carbonato ácido de sodio acuoso saturado y se separó la

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fase orgánica, se lavó con salmuera, se secó y se evaporó. El residuo se cromatografió sobre gel de sílice eluyendo con un gradiente 0 - 100% de acetato de etilo - hexano proporcionando el compuesto del título en forma de un aceite incoloro (332 mg; 66%). ^1H RMN (CDCl_3) δ : 0,90 (3H, s), 0,98 (3H, s), 1,66 – 1,75 (4H, m), 2,31 (3H, s), 2,44 (3H, s), 2,60 – 2,65 (2H, m), 2,69 – 2,74 (2H, m), 4,82 (1H, d J = 3Hz), 7,00 (1H, m), 7,09 (1H, m), 7,11 (1H, s a), 7,23 – 7,33 (3H, m), 7,41 – 7,43 (2H, m). Espectro de masas (Electropulverización CL/EM): Encontrado 417 (MH^+). $\text{C}_{23}\text{H}_{29}^{35}\text{ClN}_2\text{OS}$ requiere 416. Tiempo de retención 2,08 min. El producto se disolvió en metanol y se añadió gota a gota una solución de HCl 1 M / dietiléter a la solución agitada. Después de agitar a temperatura ambiente durante 5 minutos, se evaporó la mezcla a presión reducida. Se volvió a disolver en DCM y se evaporó otra vez a presión reducida proporcionando la sal clorhidrato en forma de una espuma blanca (320 mg).

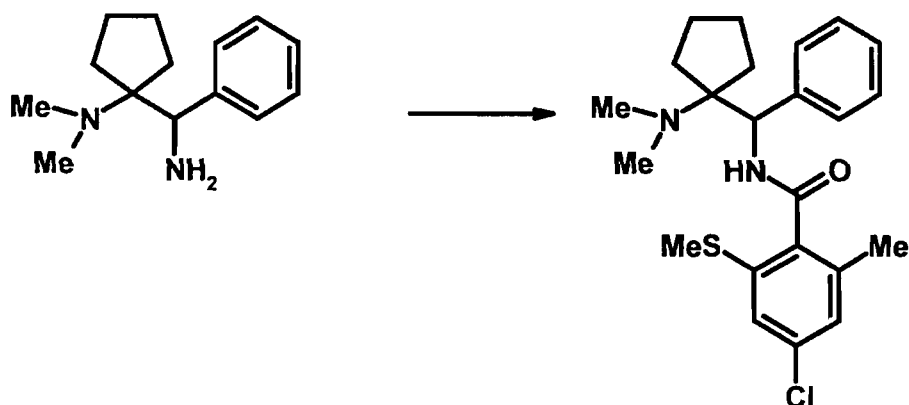
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Ejemplo 18: N-[[1-(Dimetilamino)ciclopentil](fenil)metil]-2-(metiloxi)-4,6-bis(trifluorometil)benzamida quiral



A una solución agitada de {1-[amino(fenil)metil]ciclopentil}dimetilamina D3 enantiómero 2 (0,8 g; 3,67 mmoles) y trietilamina (1,02 ml; 7,34 mmoles) en DCM (35 ml) se le añadió cloruro de 2,4-ditri fluorometil-6-metoxi-benzoílo (1,12 g; 3,67 mmoles) en DCM (5 ml) gota a gota durante 5 min. La solución
5 resultante se dejó en reposo durante 66 horas a temperatura ambiente y después se añadió solución de bicarbonato sódico acuoso saturado (40 ml). Después de agitar a temperatura ambiente durante 0,5 horas la mezcla de reacción se cargó sobre un cartucho de separación de fases y la fase orgánica eluida se evaporó a presión reducida. El residuo se disolvió en una cantidad
10 mínima de DCM y se cromatografió sobre gel de sílice eluyendo con mezclas de acetato de etilo al 0 a 95% - pentano. Después de evaporar las fracciones recogidas a presión reducida, volviendo a disolver en DCM y evaporando a presión reducida se obtuvo el compuesto del título en forma de un sólido incoloro (1,33 g; 74%). ¹H RMN (CDCl₃) δ: 0,90 – 1,05 (1H, m), 1,25 – 1,60
15 (3H, m), 1,60 – 1,75 (2H, m), 1,80 – 1,90 (2H, m), 2,20 (6H, s), 3,93 (3H, s), 5,07 (1H, d, J = 5Hz), 7,14 (1H, s a), 7,20 – 7,35 (4H, m), 7,44 (2H, m), 7,53 (1H, s). Espectro de masas (Electropulverización CL/EM): Encontrado 489 (MH⁺). C₂₄H₂₆F₆N₂O₂ requiere 488. Tiempo de retención 2,17 min.

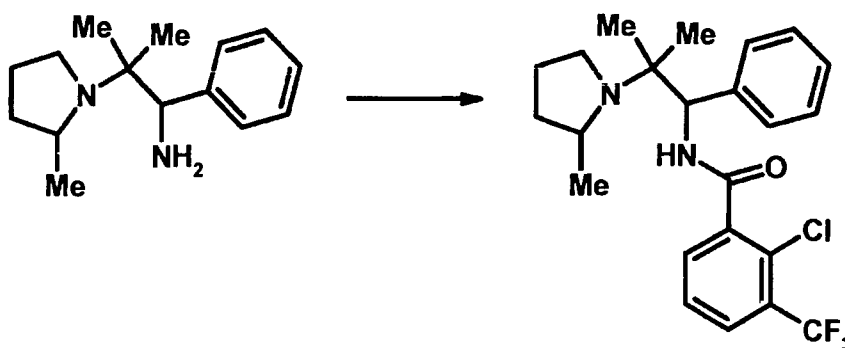
20 **Ejemplo 19: 4-Cloro-N-[[1-(dimetilamino)ciclopentil](fenil)metil]-2-metil-6-(metiltio)benzamida quiral**



Una mezcla de {1-[amino(fenil)metil]ciclopentil}dimetilamina D3 enantiómero 2 (203 mg; 0,93 mmoles), ácido 4-cloro-2-metil-6-(metiltio)benzoico (obtenible como se ha descrito en F.P. Doyle, J.H.C. Nayler, H.R.J. Waddington, J.C. Hanson y G.R. Thomas. J.Chem.Soc. 1963, 497) (202 mg; 0,93 mmoles), EDC (178 mg; 0,93 mmoles) y HOBt (143 mg; 0,93 mmoles) en DCM (20 ml) se agitó a temperatura ambiente durante 4 horas y después se dejó en reposo a temperatura ambiente durante 90 h. La mezcla de reacción resultante se lavó con bicarbonato sódico acuoso saturado (50 ml) y se separó la fase orgánica mediante un pase a través de un cartucho de separación de fases. Se evaporó la fase orgánica, el residuo se disolvió en una cantidad mínima de DCM y se cromatografió sobre gel de sílice, eluyendo con acetato de etilo 0 - 100% - pentano. Se combinaron las fracciones y se evaporaron a presión reducida produciendo el compuesto del título (200 mg; 52%). ¹H RMN (CDCl₃) δ: 0,90 - 1,10 (1H, m), 1,38 - 1,55 (3H, m), 1,60 - 1,76 (2H, m), 1,80 - 1,90 (2H, m), 2,21 (6H, s), 2,26 (3H, s), 2,47 (3H, s), 5,11 (1H, d, J = 6Hz), 6,94 (1H, d, J = 5,2Hz), 7,00 (1H, m), 7,09 (1H, m), 7,20 - 7,35 (3H, m), 7,40 - 7,50 (2H, m). Espectro de masas (Electropulverización CL/EM), EP⁺: Encontrado

417 (MH⁺). C₂₃H₂₉³⁵ClN₂OS requiere 416. Tiempo de retención 2,03 min. El producto del título se convirtió en su sal clorhidrato correspondiente (210 mg).

Ejemplo 20: (±)2-Cloro-N-[2-metil-2-(2-metil-1-pirrolidinil)-1-fenilpropil]-3-(trifluorometil)benzamida Diastereómeros



Una mezcla de [2-metil-2-(2-metil-1-pirrolidinil)-1-fenilpropil]amina D26 (0,150 g; 0,647 mmoles), ácido 2-cloro-3-(trifluorometil)benzoico (0,174 g; 0,775 mmol), EDC (0,149 g; 0.777 mmoles) y HOBt (0,020 g; 0,148 mmoles) en DCM (4 ml) se agitó a temperatura ambiente durante 66 horas. Se añadió carbonato ácido de sodio saturado (8 ml) y se continuó la agitación durante 0,5 horas. Se pasó la fase orgánica a través de un cartucho de separación de fases y se aplicó a una columna de 2 g de SCX. La columna se lavó con DCM y metanol y el producto se eluyó con amoníaco 1 M en metanol. El producto bruto se purificó mediante cromatografía sobre gel de sílice (20 g) eluyendo con gradiente de acetato de etilo al 0 - 100% en pentano produciendo el compuesto del título en forma de dos pares de enantiómeros.

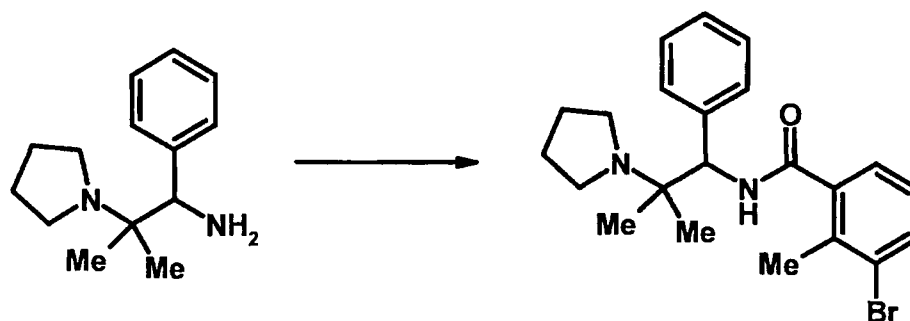
Para el par menos polar de enantiómeros (0,170 g; 60%). ¹H RMN (CDCl₃) δ: 0,97 (6H, s), 1,05 (3H, d, J = 6Hz), 1,50 (1H, m a), 1,70 - 1,85 (3H, m a), 2,76 - 2,83 (1H, m), 2,90 - 2,97 (1H, m), 3,15 - 3,20 (1H, m), 4,73 (1H, d, J =

2Hz), 7,20 - 7,42 (5H, m), 7,43 (1H, t, J = 8Hz), 7,75 - 7,79 (2H, m), 7,84 (1H, s a). Espectro de masas (Electropulverización CL/EM), EP⁺: Encontrado 439 (MH⁺). C₂₃H₂₆³⁵ClF₃N₂O requiere 438. Tiempo de retención 2,17 min. El producto del título se convirtió en su sal clorhidrato correspondiente.

- 5 Para el par más polar de enantiómeros (0,100 g; 35%). ¹H RMN (CDCl₃) δ: 0,95 - 1,10 (9H, m), 1,45 (1H, m a), 1,65 - 1,82 (3H, m a), 2,60 - 2,67 (1H, m), 2,85 - 2,93 (1H, m), 3,35 - 3,40 (1H, m), 4,76 (1H, d, J = 3,2Hz), 7,20 - 7,45 (5H, m), 7,60 (1H, m a), 7,70 - 7,80 (2H, m), 7,84 (1H, m). Espectro de masas (Electropulverización CL/EM), EP⁺: Encontrado 439 (MH⁺). C₂₃H₂₆³⁵ClF₃N₂O
10 requiere 438. Tiempo de retención 2,17 min. El producto del título se convirtió en su sal clorhidrato correspondiente.

Ejemplo 21: (±)-3-Bromo-2-metil-N-[2-metil-1-fenil-2-(1-pirrolidinil)propil] benzamida

15 benzamida

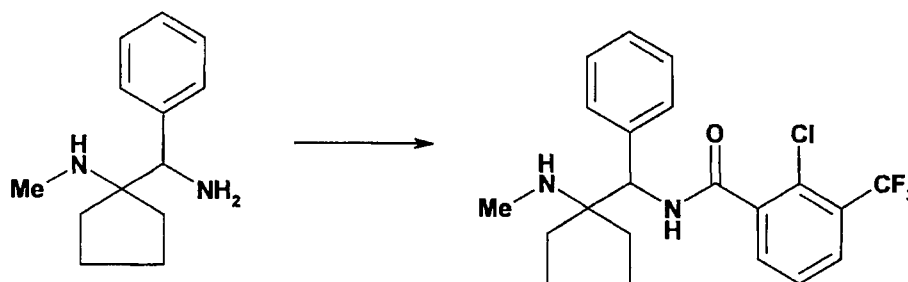


- A PS-EDC (0,068 g; 0,1 mmoles; 1,42 mmoles/g) se añadió una solución de HOAt (0,01 mmoles en 0,8 ml (THF:DCM,1:1)) seguido de la adición de ácido 3-bromo-2-metil-benzoico (0,011 g; 0.05 mmoles) en NMP:THF 1:3 (0,25
20 ml) y después [2-metil-1-fenil-2-(1-pirrolidinil)propil]amina D5 (0,011 g 0,05

- mmoles) en DCM (0,25 ml). Se dejó mezclar la reacción durante 60 h. Después de esto se añadieron PS-isocianato (0,068 g, 0,1 mmoles, 1,5 mmoles/g) y PS-CO₃ (0,068 g, 0,1 mmoles, 1,5 mmoles/g) y se dejó en agitación durante otras 24 horas. La mezcla de reacción se filtró y se pasó a través de un bloque de
- 5 SCX (500 mg) (prehumedecido con DCM). El contenido del bloque de Robbins se lavó con más disolvente (DCM:THF, 1:1) y se dejó pasar a través del SCX que después se lavó con DCM (2 ml x 2) y metanol (2 ml x 2). El SCX se eluyó después con amoníaco 0,5 M en metanol y el eluyente que contenía el producto se evaporó produciendo el producto del título (17,4 mg; 84%).
- 10 Espectro de masas (Electropulverización CL/EM): Encontrado 414 (MH⁺). C₂₂H₂₇⁷⁹BrN₂O requiere 415;

Tiempo de retención 2,64 min*

- Ejemplo 22: (±)-2-Cloro-N-[[1-(metilamino)ciclopentil](fenil)metil]-3-**
- 15 **(trifluorometil)benzamida**



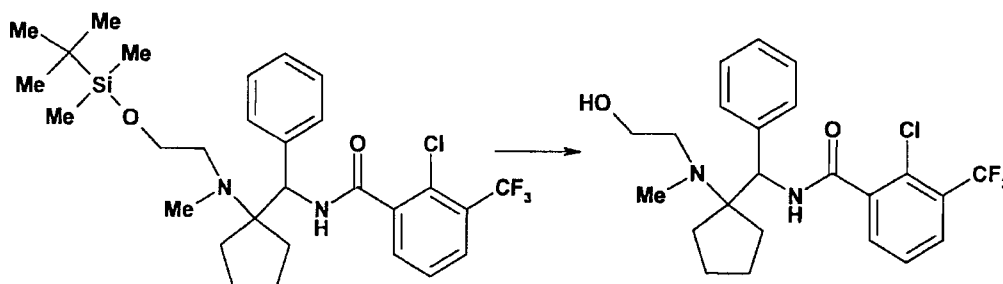
- A una solución de ácido 2-cloro-3-(trifluorometil)benzoico (0,728 g; 3,24 mmoles) en DMF (20 ml) y DIPEA (2,5 ml) se le añadió (±)-[[amino(fenil)metil]ciclopentil] metilamina D29 (1,0 g; 3,60 mmoles) y HATU
- 20 (1,23 g; 3,24 mmoles). La mezcla resultante se dejó en agitación a temperatura ambiente durante toda una noche y después se retiró por evaporación la DMF

a vacío. El material residual se repartió entre acetato de etilo y agua. La fase orgánica se secó (Na_2SO_4) y se evaporó el filtrado a vacío. El producto deseado se aisló mediante cromatografía en columna sobre gel de sílice usando dietil éter al 20% a 100% de dietil éter en n-pentano produciendo el

5 compuesto del título en forma de un sólido blanco (0,908 g; 61%). ^1H RMN (CDCl_3) δ : 1,47 - 1,83 (9H, m), 2,21 (3H, s), 5,1 (1H, m), 7,23 - 7,43 (6H, m), 7,58 (1H, m), 7,65 (1H, m), 7,73 (1H, m); Espectro de masas (Electropulverización CL/EM), IPA^+ : Encontrado 411 (MH^+). $\text{C}_{21}\text{H}_{22}^{35}\text{ClF}_3\text{N}_2\text{O}$ requiere 410. Tiempo de retención 2,04 min.

10

Ejemplo 23: ($\pm$)-2-Cloro-N-[[1-[(2-hidroxietil)(metil)amino]ciclopentil](fenil)metil]-3-(trifluorometil)benzamida



A una solución de ($\pm$)-2-cloro-N-[[1-[(2-[[1,1-dimetiletil](dimetil)silil]oxi]etil)(metil)amino]ciclopentil](fenil)metil]-3-(trifluorometil)benzamida D30 (0,390

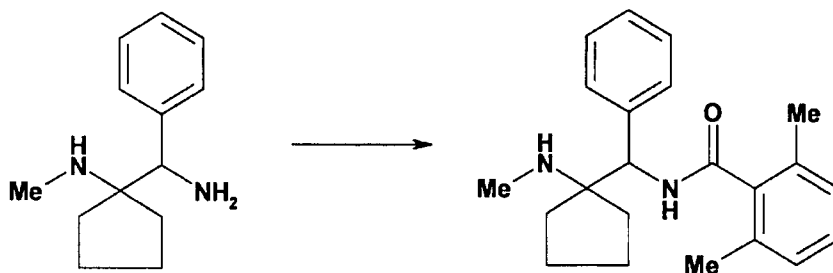
15 g; 0,685 mmol) en THF (10 ml) se le añadió fluoruro de tetrabutilamonio (solución 1 M en THF 1,6 ml; 1,6 mmoles). La mezcla de reacción se dejó en agitación a temperatura ambiente durante 4 h. El producto deseado se aisló mediante cromatografía en columna sobre sílice usando éter al 20% a 50% en

20 n-pentano, el disolvente se redujo en volumen mediante evaporación a vacío y se cargó en un cartucho de SCX. El lavado con DCM, después metanol

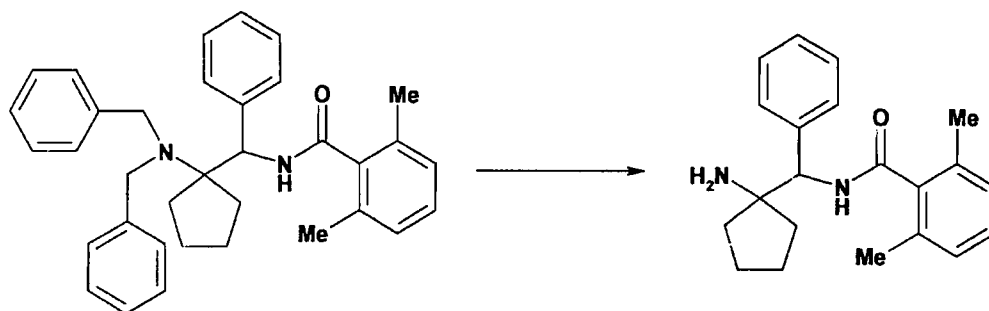
seguido de elución con amoníaco 1 M en metanol produjo el compuesto del título (170 mg, 73%). Espectro de masas (Electropulverización CL/EM). Encontrado 455 (MH⁺). C₂₃H₂₆³⁵ClF₃N₂O₂ requiere 454. Tiempo de retención: 2,09 min.

5

Ejemplo 24: 2,6-Dimetil-N-[[1-(metilamino)ciclopentil](fenil)metil] benzamida quiral



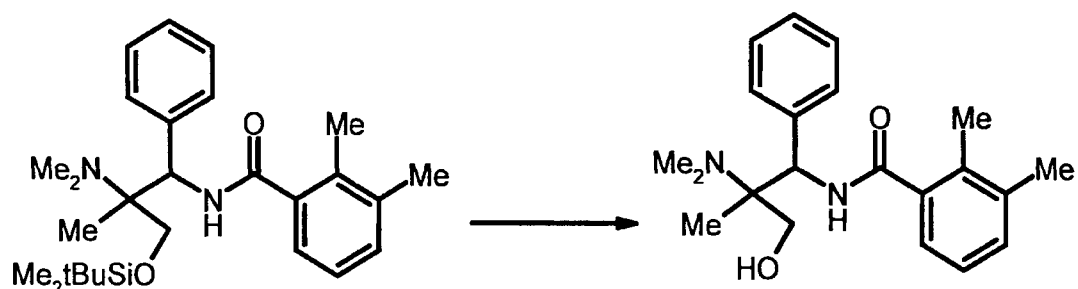
A una solución de ácido 2,6-dimetilbenzoico (0,100 g; 0,668 mmoles) en
 10 DMF (5 ml) y DIPEA (0,12ml) se añadió {[amino(fenil)metil]ciclopentil} metilamina D31 enantiómero 2 (0,124 g; 0,608 mmoles) y HATU (0,254 g; 0,668 mmol). La mezcla resultante se dejó en agitación a temperatura ambiente durante 3 días y después la DMF se retiró por evaporación a presión reducida. El material residual se repartió entre acetato de etilo y agua, se lavó
 15 con agua y la fase orgánica se secó (Na₂SO₄) y se evaporó. El material residual se disolvió en DCM (2 ml) y se cargó en un cartucho de SCX. El lavado con DCM, después metanol seguido de elución con amoníaco 1 M en metanol produjo el producto del título (155 mg; 76%). ¹H RMN (CDCl₃) δ: 1,3-1,8 (9H, m), 2,21 (3H, s), 2,28 (6H, s), 5,07 (1H, m), 7,0 (2H, m), 7,1-7,4 (7H, m).
 20 m). Espectro de masas (Electropulverización CL/EM). Encontrado 337 (MH⁺). C₂₂H₂₈N₂O requiere 336. Tiempo de retención: 1,86 min.

Ejemplo 25: ($\pm$)-N-[(1-aminociclopentil)(fenil)metil]-2,6-dimetilbenzamida

El compuesto del título (1,14 g; 71%) se preparó a partir de la
 5 hidrogenación catalítica de ($\pm$)-N-[(1-
 [bis(fenilmetil)amino]ciclopentil)(fenil)metil]-2,6-dimetilbenzamida D34 (2,51 g; 5
 mmoles) sobre Pd al 10%/Carbono (0,4 g) en HCl 3M (8 ml) and etanol (150
 ml) de una manera similar a la descrita en D29. El etanol se retiró por
 evaporación a vacío y el material residual se repartió entre DCM y solución de
 10 bicarbonato sódico y se secó (Na_2SO_4). El filtrado se redujo en volumen
 mediante evaporación a vacío y se cargó en un cartucho de SCX. El lavado
 con DCM, después metanol seguido de elución con amoníaco 1 M en metanol
 produjo el producto del título (90 mg, 88%). ^1H RMN (CDCl_3) δ : 0,98-1,96
 (10H, m), 2,23 (6H, s), 4,97 (1H, m), 7,0 (2H, m), 7,16 (1H, m), 7,22-7,41 (6H,
 15 m); Espectro de masas (Electropulverización CL/EM). Encontrado 323 (MH^+).
 $\text{C}_{21}\text{H}_{26}\text{N}_2\text{O}$ requiere 322. Tiempo de retención 1,69 min.

Ejemplo 26: ($\pm$)-N-[2-(Dimetilamino)-3-hidroxi-2-metil-1-fenilpropil]-2,3-dimetilbenzamida mezcla diastereomérica

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Una solución de ($\pm$)-*N*-(2-(dimetilamino)-3-((1,1-dimetiletil)(dimetil)silil)oxi)-2-metil-1-fenilpropil)-2,3-dimetilbenzamida D49 (56 mg; 0,12 mmoles) en THF (5 ml) se trató con una solución de fluoruro de tetrabutilamonio (solución 1,0 M en THF; 0,2 ml, 0,2 mmoles) y la mezcla se agitó a temperatura ambiente durante toda una noche. La mezcla se vertió directamente sobre una columna de cromatografía (Flashmaster II; eluyente acetato de etilo al 0 - 100% / pentano) produciendo el compuesto del título (38 mg; 63%). ^1H RMN (CDCl_3) δ : 0,73 y 1,14 (3H, 2 x s), 1,70 - 2,50 (1H, s a), 2,26 (6H, c), 2,38 y 2,48 (6H, 2 x s), 3,17, 3,39, y 3,55 (2H, 3 x d), 5,26 y 5,46 (1H, 2 x d), 6,83 y 7,89 (1H, 2 x d a), 7,07 - 7,46 (8H, m a). Espectro de masas (Electropulverización CL/EM), IPA^+ : Encontrado 341 (MH^+), $\text{C}_{21}\text{H}_{28}\text{N}_2\text{O}_2\text{Si}$ requiere 340. Tiempo de retención 1,71 y 1,76 min.

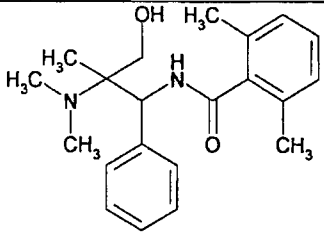
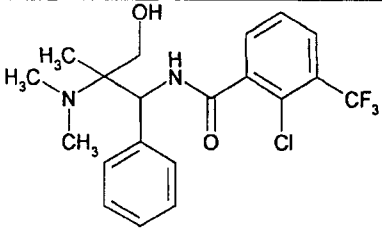
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Los ejemplos en la Tabla 3 se prepararon de una manera similar a la del ejemplo E26.

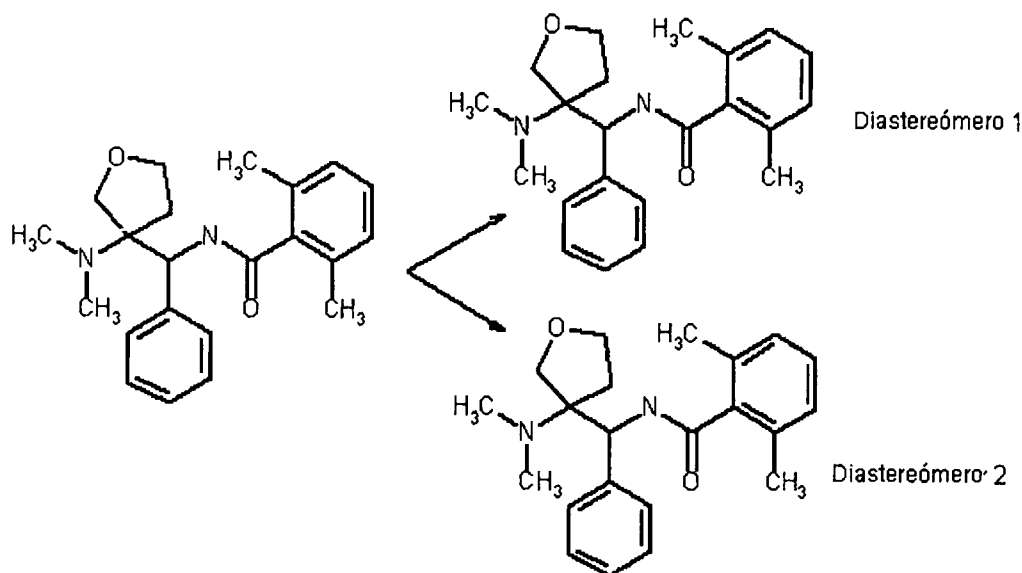
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Tabla 3

Ejemplo	Estructura	Espectro de masas (Electropulverización CL/EM), IPA ⁺ Tiempo de retención (min)	Nombre
27		Encontrado 341 (MH ⁺) C ₂₁ H ₂₈ N ₂ O ₂ requiere 340; 1,78 y 1,83.	(±)-N-[2-(dimetilamino)-3-hidroxi-2-metil-1-fenilpropil]-2,6-dimetilbenzamida
28		Encontrado 415 (MH ⁺) C ₂₀ H ₂₂ ³⁵ ClF ₃ N ₂ O ₂ requiere 414; 1,91 y 1,94.	(±)-2-cloro-N-[2-(dimetilamino)-3-hidroxi-2-metil-1-fenilpropil]-3-(trifluorometil)benzamida

Ejemplo 29: ($\pm$)*N*-[[3-(Dimetilamino)tetrahydro-3-furanil](fenil)metil]-2,6-dimetilbenzamida: Diastereómero 1 y Diastereómero 2



5

N-[[3-(dimetilamino)tetrahydro-3-furanil](fenil)metil]-2,6-dimetil benzamida racémico E204 (40 mg, 0,11 mmoles) se separó mediante HPLC quiral preparativa produciendo el producto diastereómero del título 1 (13 mg); HPLC quiral: > 95% ed; Espectro de masas (Electropulverización CL/EM): Encontrado 353 (MH^+). Tiempo de retención 1,67 min. $C_{22}H_{28}N_2O_2$ requiere 352 y diastereómero 2 (14 mg); HPLC quiral: >95% ed; Espectro de masas (Electropulverización CL/EM): Encontrado 353 (MH^+) Tiempo de retención 1,69 min. $C_{22}H_{28}N_2O_2$ requiere 352.

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Condiciones de HPLC preparativa:

- Columna: S.F.C. Etil Piridil 150 mm x 21,1 mm d. i; 6 micrones
de tamaño de partícula
- Fase móvil: Dióxido de carbono: Etanol (95:5) v/v; isocrático
mezclado por bomba
- 5 Caudal: 50 ml/min
- Presión: 100 bar (10.000 kPa)
- Temperatura: 40°C
- intervalo de longitud
- 10 de onda UV: 220nm
- Tiempo de elución: 10 min
- Tiempo de retención: 6,3 min (Diastereómero 1); 7,1 min (Diastereómero 2)

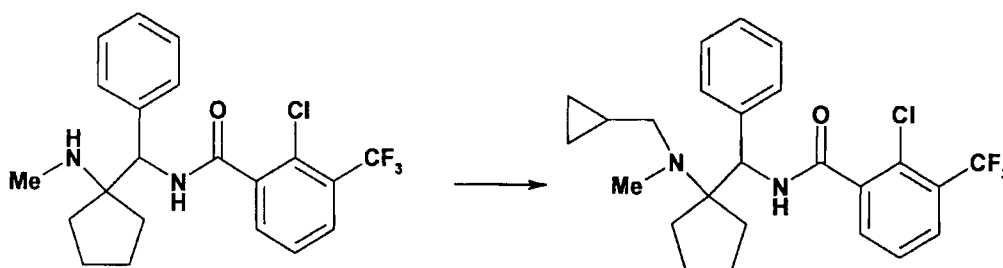
15 Condiciones de cromatografía analítica:

- Columna: S.F.C. Etil Piridil 150 mm x 4,6 mm d. i; 6 micrones
de tamaño de partícula
- Fase móvil: Dióxido de carbono: Etanol (98:2) v/v; isocrático
mezclado por bomba
- 20 Caudal: 2,35 ml/min
- Presión: 100 bar (10.000 kPa)
- Temperatura: 38°C
- Intervalo de longitud
- de onda UV: 254 nm
- 25 Tiempo de elución: 15 min

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Tiempo de retención: 12,2 min (Diastereómero 1); 13,4 min (Diastereómero 2)

**Ejemplo 30: clorhidrato de (±)-2-Cloro-*N*-[1-
5 [(ciclopropilmetil)(metil)amino]ciclopentil] (fenil)metil]-3-
(trifluorometil)benzamida**



10

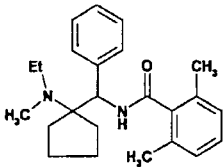
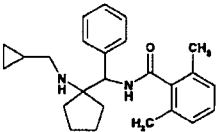
A una solución de (±)-2-cloro-*N*-[[1-(metilamino)ciclopentil](fenil)metil]-3-
(trifluorometil)benzamida E22 (143 g; 0,35 mmoles),
ciclopropanocarboxaldehído (0,026 ml; 0,035 mmoles) y ácido acético (3 gotas)
en 1,2-dicloroetano (10 ml) se añadió triacetoxiborohidruro de sodio (303 mg;
15 1,4 mmoles). La mezcla resultante se dejó agitar a temperatura ambiente en
argón durante toda una noche. Después la mezcla de reacción se diluyó con
DCM (20 ml), se lavó con solución saturada de carbonato potásico y salmuera,
se secó (Na₂SO₄) y se evaporó a vacío. La mezcla se separó mediante
cromatografía en columna sobre gel de sílice usando éter al 20% en *n*-pentano
20 a metanol al 2% en éter. El aceite obtenido se trató con HCl 1 M en éter
produciendo el producto del título en forma de una sal clorhidrato blanquecina

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(0,054 g; 33%). Espectro de masas (Electropulverización CL/EM). Encontrado 465 (MH⁺). C₂₅H₂₈³⁵ClF₃N₂O requiere 464. Tiempo de retención: 2,30 min.

Los compuestos de la tabla 4 a continuación se prepararon usando 5 procedimientos similares a los del ejemplo 30 anterior.

Tabla 4

Ejemplo	Estructura	Espectro de masas (Electropulverización CL/EM), IPA ⁺ Tiempo de retención (min)	Nombre
31		Encontrado 365 (MH ⁺). C ₂₄ H ₃₂ N ₂ O requiere 364; 1,96.	(±)-N-[(1- [etil(metil)amino] ciclopentil](fenil)metil]- 2,6-dimetilbenzamida
32		Encontrado 377 (MH ⁺). C ₂₅ H ₃₂ N ₂ O requiere 376; 2,07	(±)-N-[(1- [(ciclopropilmetil)amino] ciclopentil](fenil)metil]- 2,6-dimetilbenzamida

33		Encontrado 439 (MH^+) . $C_{23}H_{26}^{35}ClF_3N_2$ O requiere 438; 2,23.	$(\pm)$ -2-Cloro- <i>N</i> -[1- [etil(metil)amino] ciclopentil](fenil)metil]-3- (trifluorometil)benzamida
34		Encontrado 351 (MH^+) . $C_{23}H_{30}N_2O$ requiere 350; 1,82.	$(\pm)$ -2-Cloro- <i>N</i> -[[1- (etilamino)ciclopentil] (fenil)metil]-3- (trifluorometil)benzamida
35		Encontrado 391 (MH^+) . $C_{26}H_{34}N_2O$ requiere 390; 2,19	$(\pm)$ - <i>N</i> -[1- [(ciclopropilmetil)(metil) amino]ciclopentil](fenil) metil]-2,6- dimetilbenzamida

Los compuestos de la tabla 5 a continuación se prepararon usando procedimientos similares a los descritos para los ejemplos anteriores. Procedimiento de acoplamiento: A = Cloruro de ácido (usando un

5 procedimiento similar al del ejemplo 13); E = EDC (usando un procedimiento similar al del ejemplo 17); H = HATU (usando un procedimiento similar al del ejemplo 15); P = DCC soportado por polímero (usando un procedimiento similar al del ejemplo 1); PE = EDC soportado por polímero (usando un procedimiento similar al del ejemplo 21). El tratamiento y purificación se llevó a cabo usando

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los procedimientos apropiados similares a los descritos en los ejemplos anteriores.

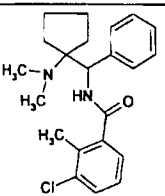
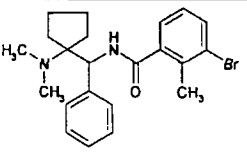
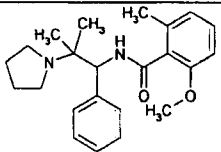
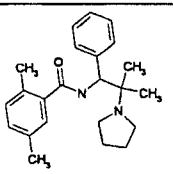
Los materiales de partida de ácido benzoico se obtuvieron
5 comercialmente excepto para el ácido 2,6-dicloro-3-trifluorometilbenzoico
usado en los ejemplos indicados con un #, que se obtuvo mediante el
procedimiento descrito en el documento DE1924766. El ácido 4-cloro-2-metil-
6-(metiltio)benzoico se puede obtener como se describe en F.P. Doyle, J.H.C.
Nayler, H.R.J. Waddington, J.C. Hanson y G.R. Thomas. J.Chem.Soc. 1963,
10 497.

Para los nombres de los compuestos de los ejemplos, los indicados por
(±)- derivan de la amina racémica correspondiente D2, D8, D10, D12, D14,
D16, D18, D20, D22, D24, D26, D29, D36, D38, D40, D42, D43, D46, D48 y
15 aquellos sin ello derivan de las aminas quirales correspondientes D3
enantiómero 2, D6, D31 enantiómero 2. Los tiempos de retención de EMCL se
midieron generalmente usando condiciones de cromatografía analítica CL/EM
del procedimiento A. Los compuestos indicados por * son compuestos
preparados usando formato de secuencia descrito en el ejemplo 23 y se
20 analizaron usando condiciones de cromatografía analítica CL/EM del
procedimiento B.

Tabla 5

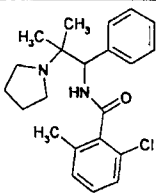
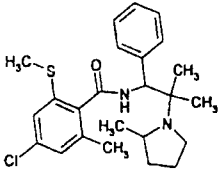
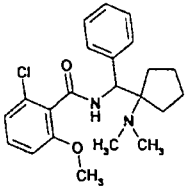
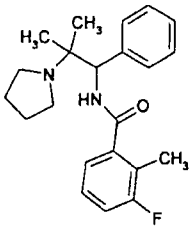
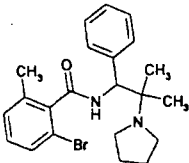
Ej	Estructura	Procedi miento	Espectro de masas	Nombre
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			(Electropulverización CL/EM), IPA ⁺ Tiempo de retención (min)	
36		P	Encontrado 371 (MH ⁺) C ₂₂ H ₂₇ ³⁵ ClN ₂ O requiere 370; 2,08	3-cloro-N-[[1-(dimetilamino)ciclopentil](fenil)metil]-2-metilbenzamida quiral
37		P	Encontrado 415 (MH ⁺) C ₂₂ H ₂₇ ⁷⁹ BrN ₂ O requiere 414; 2,09	3-bromo-N-[[1-(dimetilamino)ciclopentil](fenil)metil]-2-metilbenzamida quiral
38		P	Encontrado 367 (MH ⁺) C ₂₃ H ₃₀ N ₂ O ₂ requiere 366; 1,84	2-metil-6-(metiloxi)-N-[2-metil-1-fenil-2-(1-pirrolidinil)propil]benzamida quiral
39		P	Encontrado 351 (MH ⁺) C ₂₃ H ₃₀ N ₂ O requiere 350; 2,03	(±)-2,5-dimetil-N-[2-metil-1-fenil-2-(1-pirrolidinil)propil]benzamida

40		P	Encontrado 371 (MH ⁺) $C_{22}H_{27}^{35}ClN_2O$ requiere 370; 2,01	2-cloro- <i>N</i> -[[1-(dimetilamino)ciclopentil](fenil)metil]-3-metilbenzamida quiral
41		P	Encontrado 405 (MH ⁺) $C_{23}H_{27}F_3N_2O$ requiere 404; 2,20	<i>N</i> -[[1-(dimetilamino)ciclopentil](fenil)metil]-2-metil-5-(trifluorometil)benzamida quiral
42		P	Encontrado 351 (MH ⁺) $C_{23}H_{30}N_2O$ requiere 350; 2,04	<i>N</i> -[[1-(dimetilamino)ciclopentil](fenil)metil]-2-metil-5-(trifluorometil)benzamida quiral
43		PE	Encontrado 429 (MH ⁺) $C_{23}H_{29}^{79}BrN_2O$ requiere 428; 2,68*	(±)-3-bromo-2-metil- <i>N</i> -[2-metil-2-(2-metil-1-pirrolidinil)-1-fenilpropil]benzamida
44		P	Encontrado 371 (MH ⁺) $C_{22}H_{27}^{35}ClN_2O$ requiere 370; 1,98	(±)-2-cloro-3-metil- <i>N</i> -[2-metil-1-fenil-2-(1-pirrolidinil)propil]benzamida

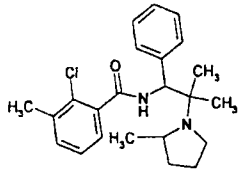
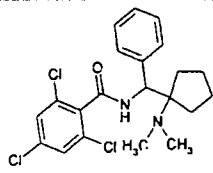
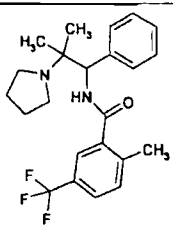
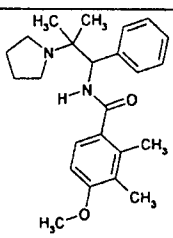
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45		P	Encontrado 371 (MH ⁺) C ₂₂ H ₂₇ ³⁵ ClN ₂ O requiere 370; 1,90	(±)-2-cloro-6-metil-N-[2-metil-1-fenil-2-(1-pirrolidinil)propil]benzamida
46		PE	Encontrado 431 (MH ⁺) C ₂₄ H ₃₁ ³⁵ ClN ₂ OS requiere 430; 2,57*	(±)-4-cloro-2-metil-N-[2-metil-2-(2-metil-1-pirrolidinil)-1-fenilpropil]-6-(metiltio)benzamida
47		P	Encontrado 387 (MH ⁺) C ₂₂ H ₂₇ ³⁵ ClN ₂ O ₂ requiere 386; 1,88	2-cloro-N-[[1-(dimetilamino)ciclopentil](fenil)metil]-6-(metiloxi)benzamida quiral
48		P	Encontrado 355 (MH ⁺) C ₂₂ H ₂₇ FN ₂ O requiere 354; 1,96	(±)-3-fluoro-2-metil-N-[2-metil-1-fenil-2-(1-pirrolidinil)propil]benzamida
49		P	Encontrado 415 (MH ⁺) C ₂₂ H ₂₇ ⁷⁹ BrN ₂ O requiere 414; 1,92	(±)-2-bromo-6-metil-N-[2-metil-1-fenil-2-(1-pirrolidinil)propil]benzamida

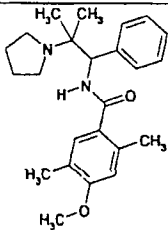
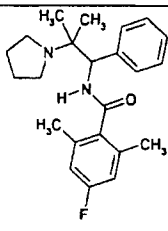
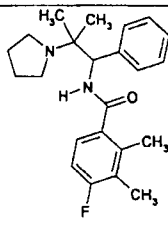
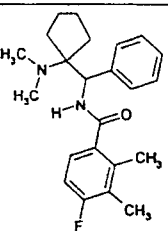
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50		P	Encontrado 371 (MH ⁺) $C_{22}H_{27}^{35}ClN_2O$ requiere 370; 2,08	(±)-3-cloro-2-metil- <i>N</i> -[2-metil-1-fenil-2-(1-pirrolidinil)propil]benzamida
51		P	Encontrado 355 (MH ⁺) $C_{22}H_{27}FN_2O$ requiere 354; 1,97	<i>N</i> -[[1-(dimetilamino)ciclopentil](fenil)metil]-3-fluoro-2-metilbenzamida quiral
52		PE	Encontrado 383 (MH ⁺) $C_{23}H_{30}N_2OS$ requiere 382; 2,62*	(±)- <i>N</i> -[2-metil-2-(2-metil-1-pirrolidinil)-1-fenilpropil]-2-(metiltio)benzamida
53		PE	Encontrado 429 (MH ⁺) $C_{23}H_{29}^{79}BrN_2O$ requiere 428; 2,44*	(±)-2-bromo-6-metil- <i>N</i> -[2-metil-2-(2-metil-1-pirrolidinil)-1-fenilpropil]benzamida
54		P	Encontrado 367 (MH ⁺) $C_{23}H_{30}N_2O_2$ requiere 366; 1,84	(±)-2-metil-6-(metiloxi)- <i>N</i> -[2-metil-1-fenil-2-(1-pirrolidinil)propil]benzamida

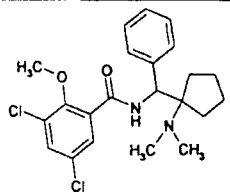
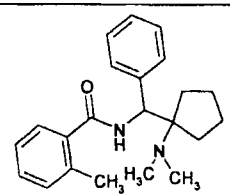
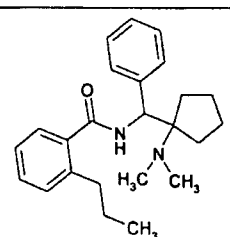
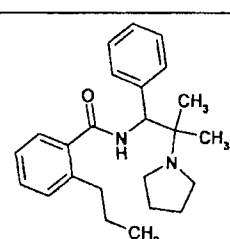
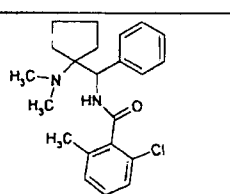
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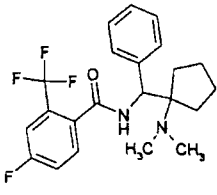
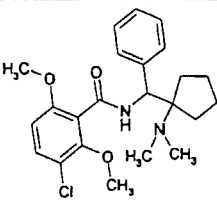
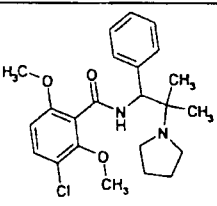
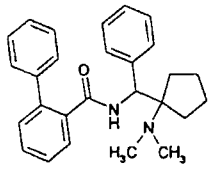
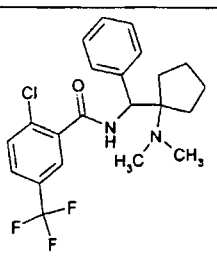
55		PE	Encontrado 385 (MH ⁺) C ₂₃ H ₂₉ ³⁵ ClN ₂ O requiere 384; 2,65*	(±)-2-cloro-3-metil-N-[2-metil-2-(2-metil-1-pirrolidinil)-1-fenilpropil]benzamida
56		P	Encontrado 425 (MH ⁺) C ₂₁ H ₂₃ ³⁵ Cl ₃ N ₂ O requiere 424; 2,08	2,4,6-tricloro-N-[[1-(dimetilamino)ciclopentil](fenil)metil]benzamida quiral
57		P	Encontrado 405 (MH ⁺) C ₂₃ H ₂₇ F ₃ N ₂ O requiere 404; 2,18	(±)-2-metil-N-[2-metil-1-fenil-2-(1-pirrolidinil)propil]-5-(trifluorometil)benzamida
58		P	Encontrado 381 (MH ⁺) C ₂₄ H ₃₂ N ₂ O ₂ requiere 380; 2,10	2,3-Dimetil-4-(metiloxi)-N-[2-metil-1-fenil-2-(1-pirrolidinil)propil]benzamida quiral

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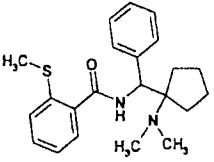
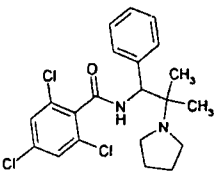
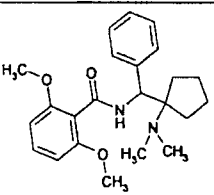
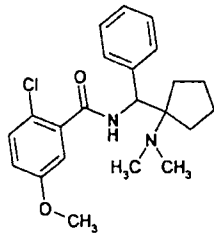
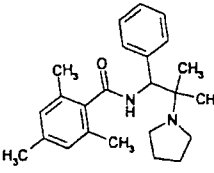
59		P	Encontrado 381 (MH ⁺) C ₂₄ H ₃₂ N ₂ O ₂ requiere 380; 2,14	2,5-Dimetil-4-(metiloxi)-N-[2-metil-1-fenil-2-(1-pirrolidinil)propil] benzamida quiral
60		A	Encontrado 369 (MH ⁺) C ₂₃ H ₂₉ FN ₂ O requiere 368; 2,00	4-Fluoro-2,6-dimetil-N-[2-metil-1-fenil-2-(1-pirrolidinil)propil] benzamida quiral
61		P	Encontrado 369 (MH ⁺) C ₂₃ H ₂₉ FN ₂ O requiere 368; 2,02	4-Fluoro-2,3-dimetil-N-[2-metil-1-fenil-2-(1-pirrolidinil)propil] benzamida quiral
62		P	Encontrado 369 (MH ⁺) C ₂₃ H ₂₉ FN ₂ O requiere 368; 2,05	N-[[1-(Dimetilamino)ciclopentil](fenil)metil]-4-fluoro-2,3-dimetilbenzamida quiral

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63		PE	Encontrado 421 (MH ⁺) C ₂₂ H ₂₆ ³⁵ Cl ₂ N ₂ O ₂ requiere 420; 2,55*	3,5-dicloro-N-[[1-(dimetilamino)ciclopentil](fenil)metil]-2-(metiloxi)benzamida quiral
64		PE	Encontrado 337 (MH ⁺) C ₂₂ H ₂₈ N ₂ O requiere 336; 2,34*	N-[[1-(dimetilamino)ciclopentil](fenil)metil]-2-metilbenzamida quiral
65		PE	Encontrado 365 (MH ⁺) C ₂₄ H ₃₂ N ₂ O requiere 364; 2,48*	N-[[1-(dimetilamino)ciclopentil](fenil)metil]-2-propilbenzamida quiral
66		PE	Encontrado 365 (MH ⁺) C ₂₄ H ₃₂ N ₂ O requiere 364; 2,45*	(±)-N-[2-metil-1-fenil-2-(1-pirrolidinil)propil]-2-propilbenzamida
67		P	Encontrado 371 (MH ⁺) C ₂₂ H ₂₇ ³⁵ ClN ₂ O requiere 370; 1,93	2-cloro-N-[[1-(dimetilamino)ciclopentil](fenil)metil]-6-metilbenzamida quiral

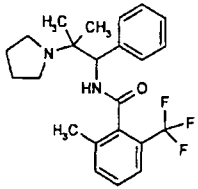
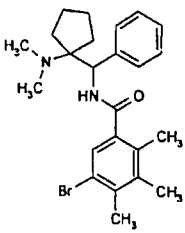
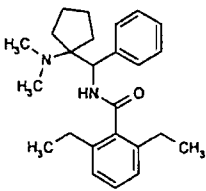
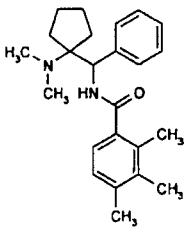
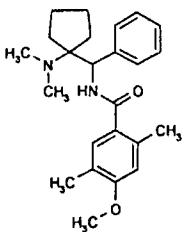
68		PE	Encontrado 409 (MH ⁺) C ₂₂ H ₂₄ F ₄ N ₂ O requiere 408; 2,44*	N-[[1-(dimetilamino)ciclopentil](fenil)metil]-4-fluoro-2-(trifluorometil)benzamida quiral
69		PE	Encontrado 417 (MH ⁺) C ₂₃ H ₂₉ ³⁵ ClN ₂ O ₃ requiere 416; 2,43*	3-cloro-N-[[1-(dimetilamino)ciclopentil](fenil)metil]-2,6-bis(metiloxi)benzamida quiral
70		PE	Encontrado 417 (MH ⁺) C ₂₃ H ₂₉ ³⁵ ClN ₂ O ₃ requiere 416; 2,4*	(±)-3-cloro-2,6-bis(metiloxi)-N-[2-metil-1-(1-pirrolidinil)propil]benzamida
71		PE	Encontrado 399 (MH ⁺) C ₂₇ H ₃₀ N ₂ O requiere 398; 2,51*	N-[[1-(dimetilamino)ciclopentil](fenil)metil]-2-bifenilcarboxamida quiral
72		PE	Encontrado 425 (MH ⁺) C ₂₂ H ₂₄ ³⁵ ClF ₃ N ₂ O requiere 424; 2,48*	2-cloro-N-[[1-(dimetilamino)ciclopentil](fenil)metil]-5-(trifluorometil)benzamida quiral

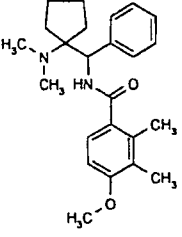
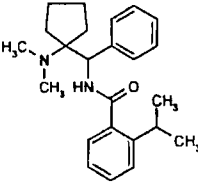
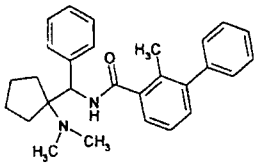
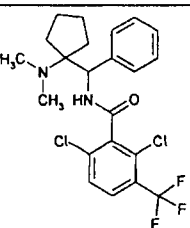
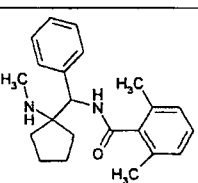
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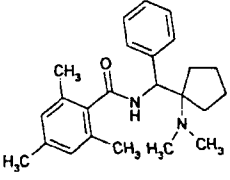
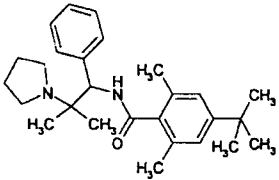
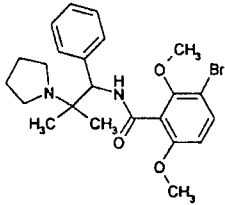
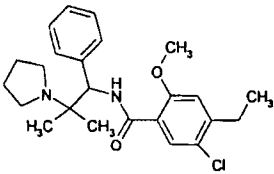
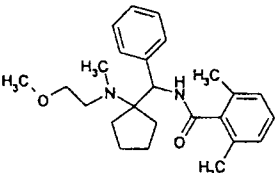
73		PE	Encontrado 369 (MH ⁺) C ₂₂ H ₂₈ N ₂ OS requiere 368; 2,58*	N-[[1-(dimetilamino)ciclopentil](fenil)metil]-2-(metiltio)benzamida quiral
74		PE	Encontrado 425 (MH ⁺) C ₂₁ H ₂₃ ³⁵ Cl ₃ N ₂ O requiere 424; 2,93*	(±)-2,4,6-tricloro-N-[2-metil-1-fenil-2-(1-pirrolidinil)propil]benzamida
75		PE	Encontrado 383 (MH ⁺) C ₂₃ H ₃₀ N ₂ O ₃ requiere 382; 2,88*	N-[[1-(dimetilamino)ciclopentil](fenil)metil]-2,6-bis(metiloxi)benzamida quiral
76		PE	Encontrado 387 (MH ⁺) C ₂₂ H ₂₇ ³⁵ ClN ₂ O ₂ requiere 386; 2,56*	2-cloro-N-[[1-(dimetilamino)ciclopentil](fenil)metil]-5-(metiloxi)benzamida quiral
77		PE	Encontrado 365 (MH ⁺) C ₂₄ H ₃₂ N ₂ O requiere 364; 2,46*	(±)-2,4,6-trimetil-N-[2-metil-1-fenil-2-(1-pirrolidinil)propil]benzamida

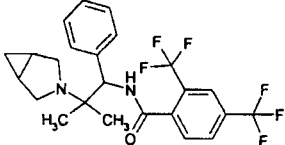
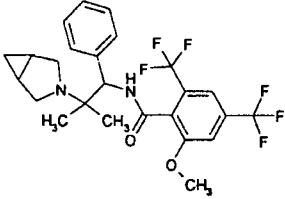
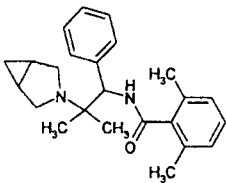
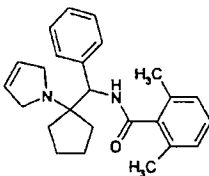
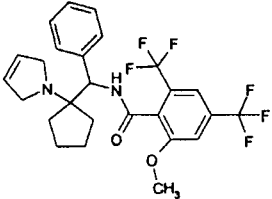
78		PE	Encontrado 375 (MH ⁺) C ₂₁ H ₂₄ ³⁵ ClFN ₂ O requiere 374; 2,99*	2-cloro- <i>N</i> -[[1-(dimetilamino)ciclopentil](fenil)metil]-3-fluorobenzamida quiral
79		PE	Encontrado 351 (MH ⁺) C ₂₃ H ₃₀ N ₂ O requiere 350; 2,96*	<i>N</i> -[[1-(dimetilamino)ciclopentil](fenil)metil]-2,4-dimetilbenzamida quiral
80		E	Encontrado 385 (MH ⁺) C ₂₃ H ₂₉ ³⁵ ClN ₂ O requiere 384; 2,19	4-cloro- <i>N</i> -[[1-(dimetilamino)ciclopentil](fenil)metil]-2,6-dimetilbenzamida quiral
81		E	Encontrado 385 (MH ⁺) C ₂₃ H ₂₉ ³⁵ ClN ₂ O requiere 384; 2,07	4-cloro-2,6-dimetil- <i>N</i> -[2-metil-1-fenil-2-(1-pirrolidinil)propil]benzamida quiral
82		E	Encontrado 405 (MH ⁺) C ₂₃ H ₂₇ F ₃ N ₂ O requiere 404; 1,91	<i>N</i> -[[1-(dimetilamino)ciclopentil](fenil)metil]-2-metil-6-(trifluorometil)benzamida quiral

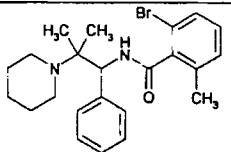
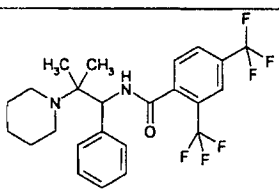
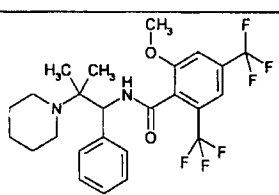
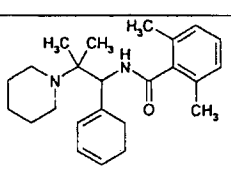
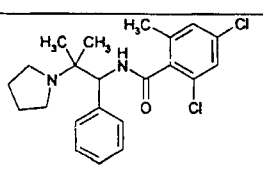
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83		E	Encontrado 405 (MH ⁺) C ₂₃ H ₂₇ F ₃ N ₂ O requiere 404; 1,91	2-metil- <i>N</i> -[2-metil-1-fenil-2-(1-pirrolidinil)propil]-6-(trifluorometil)benzamida quiral
84		A	Encontrado 443 (MH ⁺) C ₂₄ H ₃₁ ⁷⁹ BrN ₂ O requiere 442; 2,27	5-bromo- <i>N</i> -[[1-(dimetilamino)ciclopentil](fenil)metil]-2,3,4-trimetilbenzamida quiral
85		E	Encontrado 379 (MH ⁺) C ₂₅ H ₃₄ N ₂ O requiere 378; 2,07	<i>N</i> -[[1-(dimetilamino)ciclopentil](fenil)metil]-2,6-dietilbenzamida quiral
86		E	Encontrado 365 (MH ⁺) C ₂₄ H ₃₂ N ₂ O requiere 364; 2,06	<i>N</i> -[[1-(dimetilamino)ciclopentil](fenil)metil]-2,3,4-trimetilbenzamida quiral
87		E	Encontrado 381 (MH ⁺) C ₂₄ H ₃₂ N ₂ O ₂ requiere 380; 2,00	<i>N</i> -[[1-(dimetilamino)ciclopentil](fenil)metil]-2,5-dimetil-4-(metiloxi)benzamida quiral

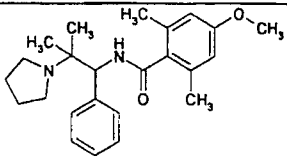
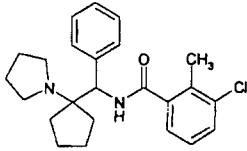
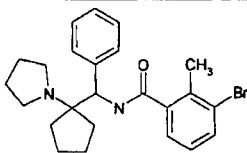
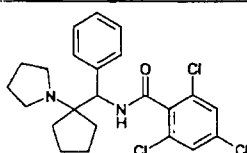
88		E	Encontrado 381 (MH ⁺) C ₂₄ H ₃₂ N ₂ O ₂ requiere 380; 1,96	N-[[1-(dimetilamino)ciclopentil] (fenil)metil]-2,3-dimetil-4- (metiloxi)benzamida quiral
89		E	Encontrado 365 (MH ⁺) C ₂₄ H ₃₂ N ₂ O requiere 364; 2,02	N-[[1-(dimetilamino)ciclopentil] (fenil)metil]-2-(1- metiletil)benzamida quiral
90		P	Encontrado 413 (MH ⁺) C ₂₈ H ₃₂ N ₂ O requiere 412;	(±)-N-[[1-(dimetilamino)ciclopentil] (fenil)metil]-2-metil-3- bifenilcarboxamida
91		P#	Encontrado 459 (MH ⁺) C ₂₂ H ₂₃ ³⁵ Cl ₂ F ₃ N ₂ O requiere 458; 2,11	2,6-dicloro-N-[[1-(dimetilamino)ciclopentil] (fenil)metil]-3- (trifluorometil)benzamida quiral
92		H	Encontrado 337 (MH ⁺) C ₂₂ H ₂₈ N ₂ O requiere 336; 1,88	(±)-2,6-dimetil-N-[[1-(dimetilamino)ciclopentil] (fenil)metil]benzamida

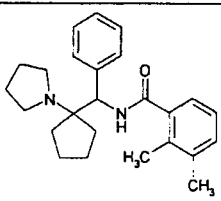
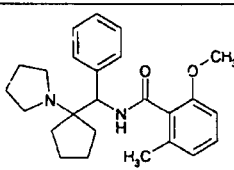
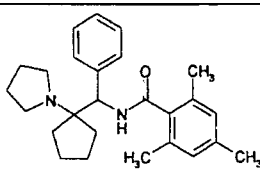
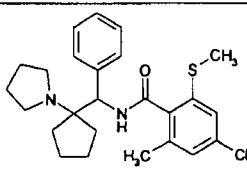
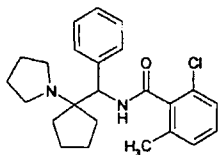
93		P	Encontrado 365 (MH ⁺) C ₂₄ H ₃₂ N ₂ O requiere 364; 1,97	N-[[1-(dimetilamino)ciclopentil](fenil)metil]-2,4,6-trimetilbenzamida quiral
94		P	Encontrado 407 (MH ⁺) C ₂₇ H ₃₈ N ₂ O requiere 406; 2,34	(±)-4-(1,1-dimetiletil)-2,6-dimetil-N-[2-metil-1-fenil-2-(1-pirrolidinil)propil]benzamida
95		P	Encontrado 461 (MH ⁺) C ₂₃ H ₂₉ ⁷⁹ BrN ₂ O ₃ requiere 460; 1,98	(±)-3-bromo-2,6-bis(metiloxi)-N-[2-metil-1-fenil-2-(1-pirrolidinil)propil]benzamida
96		P	Encontrado 415 (MH ⁺) C ₂₄ H ₃₁ ³⁵ ClN ₂ O ₂ requiere 414; 2,36	(±)-5-cloro-4-etil-2-(metiloxi)-N-[2-metil-1-fenil-2-(1-pirrolidinil)propil]benzamida
97		A	Encontrado 395 (MH ⁺) C ₂₅ H ₃₄ N ₂ O ₂ requiere 394; 2,14	(±)-2,6-dimetil-N-[(1-{metil[2-(metiloxi)etil]amino}ciclopentil)(fenil)metil]benzamida

98		A	Encontrado 471 (MH ⁺) C ₂₄ H ₂₄ F ₆ N ₂ O requiere 470; 2,29	(±)-N-[2-(3-azabicyclo[3.1.0]hex-3-il)-2-metil-1-fenilpropil]-2,4-bis(trifluorometil)benzamida
99		H	Encontrado 501 (MH ⁺) C ₂₅ H ₂₆ F ₆ N ₂ O ₂ requiere 500; 2,30	(±)-N-[2-(3-azabicyclo[3.1.0]hex-3-il)-2-metil-1-fenilpropil]-2-(metiloxi)-4,6-bis(trifluorometil)benzamida
100		A	Encontrado 363 (MH ⁺) C ₂₄ H ₃₀ N ₂ O requiere 362; 1,94	(±)-N-[2-(3-azabicyclo[3.1.0]hex-3-il)-2-metil-1-fenilpropil]-2,6-dimetilbenzamida
101		H	Encontrado 375 (MH ⁺) C ₂₅ H ₃₀ N ₂ O requiere 374; 1,94	(±)-N-[[1-(2,5-dihidro-1H-pirrol-1-il)ciclopentil](fenil)metil]-2,6-dimetilbenzamida
102		H	Encontrado 513 (MH ⁺) C ₂₆ H ₂₆ F ₆ N ₂ O ₂ requiere 512;	(±)-N-[[1-(2,5-dihidro-1H-pirrol-1-il)ciclopentil](fenil)metil]-2-(metiloxi)-4,6-

			2,35	bis(trifluorometil) benzamida
103		H	Encontrado 429 (MH ⁺) C ₂₃ H ₂₉ ⁷⁹ BrN ₂ O requiere 428; 2,02	(±)-2-bromo-6-metil-N-[2-metil-1-fenil-2-(1-piperidinil)propil]benzamida
104		H	Encontrado 473 (MH ⁺) C ₂₄ H ₂₆ F ₆ N ₂ O requiere 472; 2,18	(±)-N-[2-metil-1-fenil-2-(1-piperidinil)propil]-2,4-bis(trifluorometil)benzamida
105		H	Encontrado 503 (MH ⁺) C ₂₅ H ₂₈ F ₆ N ₂ O ₂ requiere 502; 2,28	(±)-2-(metiloxi)-N-[2-metil-1-fenil-2-(1-piperidinil)propil]-4,6-bis(trifluorometil)benzamida
106		H	Encontrado 365 (MH ⁺) C ₂₄ H ₃₂ N ₂ O requiere 364; 1,88	(±)-2,6-dimetil-N-[2-metil-1-fenil-2-(1-piperidinil)propil]benzamida
107		H	Encontrado 405 (MH ⁺) C ₂₂ H ₂₆ ³⁵ Cl ₂ N ₂ O	2,4-dicloro-6-metil-N-[2-metil-1-fenil-2-(1-pirrolidinil)propil]benzamida

			requiere 404; 2,10	benzamida quiral
108		H	Encontrado 381 (MH ⁺) C ₂₄ H ₃₂ N ₂ O ₂ requiere 380; 1,89	N-[[1-(dimetilamino)ciclopentil](fenil)metil]-2,6-dimetil-4-(metiloxi)benzamida quiral
109		P	Encontrado 385 (MH ⁺) C ₂₃ H ₂₉ ³⁵ ClN ₂ O requiere 384; 2,11	3-cloro-2,6-dimetil-N-[2-metil-1-fenil-2-(1-pirrolidinil)propil]benzamida quiral
110		P	Encontrado 385 (MH ⁺) C ₂₃ H ₂₉ ³⁵ ClN ₂ O requiere 384; 2,12	3-cloro-N-[[1-(dimetilamino)ciclopentil](fenil)metil]-2,6-dimetilbenzamida quiral
111		H	Encontrado 385 (MH ⁺) C ₂₃ H ₂₉ ³⁵ ClN ₂ O requiere 384; 2,02	(±)-3-cloro-2,6-dimetil-N-[2-metil-1-fenil-2-(1-pirrolidinil)propil]benzamida
112		H	Encontrado 421 (MH ⁺) C ₂₂ H ₂₆ ³⁵ Cl ₂ N ₂ O ₂	(±)-3,6-dicloro-2-(metiloxi)-N-[2-metil-1-fenil-2-(1-pirrolidinil)propil]benzamida

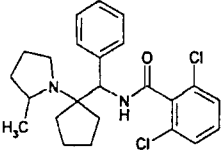
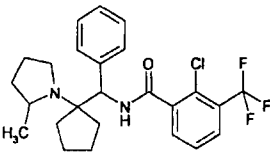
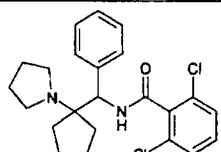
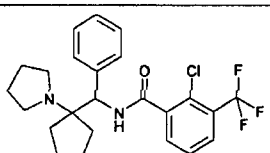
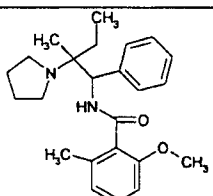
			requiere 420; 2,02	benzamida
113		H	Encontrado 381 (MH ⁺) C ₂₄ H ₃₂ N ₂ O ₂ requiere 380; 1,86	(±)-2,6-dimetil-4-(metiloxi)- N-[2-metil-1-fenil-2-(1- pirrolidinil)propil] benzamida
114		H	Encontrado 397 (MH ⁺) C ₂₄ H ₂₉ ³⁵ ClN ₂ O requiere 396; 2,13	(±)-3-cloro-2-metil-N- {fenil[1-(1- pirrolidinil)ciclopentil]metil} benzamida
115		H	Encontrado 441 (MH ⁺) C ₂₄ H ₂₉ ⁷⁹ BrN ₂ O requiere 440; 2,15	(±)-3-bromo-2-metil-N- {fenil[1-(1- pirrolidinil)ciclopentil]metil} benzamida
116		H	Encontrado 451 (MH ⁺) C ₂₃ H ₂₅ ³⁵ Cl ₃ N ₂ O requiere 450; 2,14	(±)-2,4,6-tricloro-N-{fenil[1- (1- pirrolidinil)ciclopentil]metil} benzamida

117		H	Encontrado 377 (MH ⁺) C ₂₅ H ₃₂ N ₂ O requiere 376; 2,02	(±)-2,3-dimetil- <i>N</i> -{fenil[1-(1-pirrolidinil)ciclopentil]metil}benzamida
118		H	Encontrado 393 (MH ⁺) C ₂₅ H ₃₂ N ₂ O ₂ requiere 392; 1,95	(±)-2-metil-6-(metiloxi)- <i>N</i> -{fenil[1-(1-pirrolidinil)ciclopentil]metil}benzamida
119		H	Encontrado 391 (MH ⁺) C ₂₆ H ₃₄ N ₂ O requiere 390; 2,08	(±)-2,4,6-trimetil- <i>N</i> -{fenil[1-(1-pirrolidinil)ciclopentil]metil}benzamida
120		H	Encontrado 443 (MH ⁺) C ₂₅ H ₃₁ ³⁵ ClN ₂ OS requiere 442; 2,18	(±)-4-cloro-2-metil-6-(metiltio)- <i>N</i> -{fenil[1-(1-pirrolidinil)ciclopentil]metil}benzamida
121		H	Encontrado 397 (MH ⁺) C ₂₄ H ₂₉ ³⁵ ClN ₂ O requiere 396; 2,08	(±)-2-cloro-6-metil- <i>N</i> -{fenil[1-(1-pirrolidinil)ciclopentil]metil}benzamida

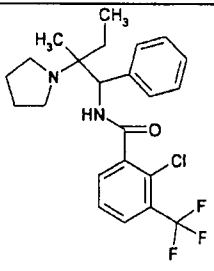
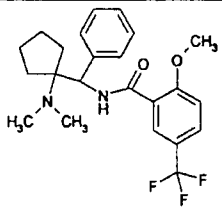
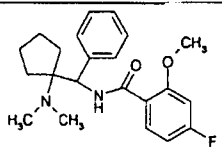
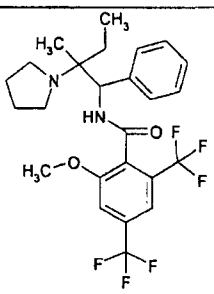
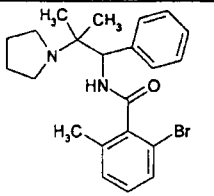
122		H	Encontrado 413 (MH ⁺) $C_{24}H_{29}^{35}ClN_2O_2$ requiere 412; 1,92	(±)-2-cloro-6-(metiloxi)-N- {fenil[1-(1- pirrolidinil)ciclopentil]metil} benzamida
123		H	Encontrado 441 (MH ⁺) $C_{24}H_{29}^{79}BrN_2O$ requiere 440; 1,97	(±)-2-bromo-6-metil-N- {fenil[1-(1- pirrolidinil)ciclopentil]metil} benzamida
124		H	Encontrado 379 (MH ⁺) $C_{24}H_{30}N_2O_2$ requiere 378; 1,97	(±)-N-[[1-(1- azetidínil)ciclopentil](fenil) metil]-2-metil-6- (metiloxi)benzamida
125		A	Encontrado 363 (MH ⁺) $C_{24}H_{30}N_2O$ requiere 362; 1,99	(±)-N-[[1-(1- azetidínil)ciclopentil](fenil) metil]-2,3- dimetilbenzamida
126		A	Encontrado 363 (MH ⁺) $C_{24}H_{30}N_2O$ requiere 362; 1,90	(±)-N-[[1-(1- azetidínil)ciclopentil](fenil) metil]-2,6- dimetilbenzamida

127		A	Encontrado 391 (MH ⁺) C ₂₆ H ₃₄ N ₂ O requiere 390; 2,06	(±)-2,6-dimetil- <i>N</i> -[[1-(2-metil-1-pirrolidinil)ciclopentil](fenil)metil]benzamida
128		A	Encontrado 379 (MH ⁺) C ₂₅ H ₃₄ N ₂ O requiere 378; 2,04	(±)- <i>N</i> -[[1-(dietilamino)ciclopentil](fenil)metil]-2,6-dimetilbenzamida
129		A	Encontrado 377 (MH ⁺) C ₂₅ H ₃₂ N ₂ O requiere 376; 1,90	(±)-2,6-dimetil- <i>N</i> -{fenil[1-(1-pirrolidinil)ciclopentil]metil}benzamida
130		H	Encontrado 419 (MH ⁺) C ₂₃ H ₂₈ ³⁵ Cl ₂ N ₂ O requiere 418; 2,15	(±)-2,6-dicloro- <i>N</i> -[[1-(dietilamino)ciclopentil](fenil)metil]benzamida
131		H	Encontrado 453 (MH ⁺) C ₂₄ H ₂₈ ³⁵ ClF ₃ N ₂ O requiere 452;	(±)-2-cloro- <i>N</i> -[[1-(dietilamino)ciclopentil](fenil)metil]-3-(trifluorometil)benzamida

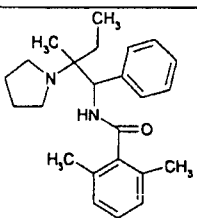
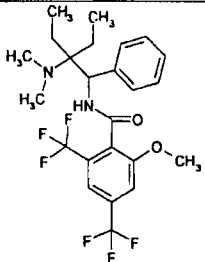
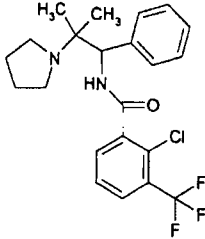
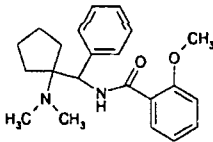
299

			2,25	
132		H	Encontrado 431 (MH ⁺) C ₂₄ H ₂₈ ³⁵ Cl ₂ N ₂ O requiere 430; 1,93	(±)-2,6-dicloro- <i>N</i> -[[1-(2-metil-1-pirrolidinil)ciclopentil](fenil)metil]benzamida
133		H	Encontrado 465 (MH ⁺) C ₂₅ H ₂₈ ³⁵ ClF ₃ N ₂ O requiere 464; 2,15	(±)-2-cloro- <i>N</i> -[[1-(2-metil-1-pirrolidinil)ciclopentil](fenil)metil]-3-(trifluorometil)benzamida
134		H	Encontrado 417 (MH ⁺) C ₂₃ H ₂₆ ³⁵ Cl ₂ N ₂ O requiere 416; 1,99	(±)-2,6-dicloro- <i>N</i> -{fenil[1-(1-pirrolidinil)ciclopentil]metil}benzamida
135		H	Encontrado 451 (MH ⁺) C ₂₄ H ₂₆ ³⁵ ClF ₃ N ₂ O requiere 450	(±)-2-cloro- <i>N</i> -{fenil[1-(1-pirrolidinil)ciclopentil]metil}-3-(trifluorometil)benzamida
136		E	Encontrado 381 (MH ⁺) C ₂₄ H ₃₂ N ₂ O ₂ requiere 380; 1,83 y 1,87	(±)-2-metil-6-(metiloxi)- <i>N</i> -[2-metil-1-fenil-2-(1-pirrolidinil)butil]benzamida

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137		A	Encontrado 439 (MH ⁺) C ₂₃ H ₂₆ ³⁵ ClF ₃ N ₂ O requiere 438; 2,11 y 2,17,	(±)-2-cloro-N-[2-metil-1-fenil-2-(1-pirrolidinil)butil]-3-(trifluorometil)benzamida
138		P	Encontrado 421 (MH ⁺) C ₂₃ H ₂₇ F ₃ N ₂ O ₂ requiere 420; 2,19,	(±)-N-[[1-(dimetilamino)ciclopentil](fenil)metil]-2-(metiloxi)-5-(trifluorometil)benzamida
139		P	Encontrado 371 (MH ⁺) C ₂₂ H ₂₇ FN ₂ O ₂ requiere 370; 1,99,	(±)-N-[[1-(dimetilamino)ciclopentil](fenil)metil]-4-fluoro-2-(metiloxi)benzamida
140		E	Encontrado 503 (MH ⁺) C ₂₅ H ₂₈ F ₆ N ₂ O ₂ requiere 502; 2,23 y 2,27,	(±)-2-(metiloxi)-N-[2-metil-1-fenil-2-(1-pirrolidinil)butil]-4,6-bis(trifluorometil)benzamida
141		E	Encontrado 415 (MH ⁺) C ₂₂ H ₂₇ ⁷⁹ BrN ₂ O	2-bromo-6-metil-N-[2-metil-1-fenil-2-(1-pirrolidinil)propil]

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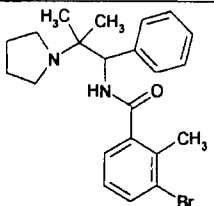
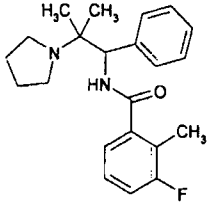
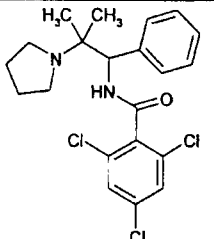
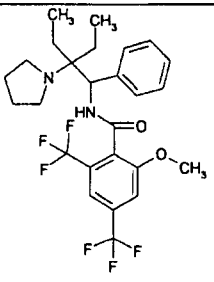
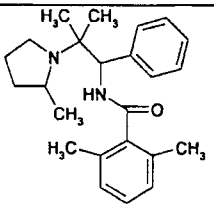
			requiere 414; 1,84,	benzamida quiral
142		A	Encontrado 365 (MH ⁺) C ₂₄ H ₃₂ N ₂ O requiere 364; 1,86 y 1,94,	(±)-2,6-dimetil- <i>N</i> -[2-metil-1-fenil-2-(1-pirrolidinil)butil]benzamida
143		E	Encontrado 491 (MH ⁺) C ₂₄ H ₂₈ F ₆ N ₂ O ₂ requiere 490; 2,26,	(±)- <i>N</i> -[2-(dimetilamino)-2-etil-1-fenilbutil]-2-(metiloxi)-4,6-bis(trifluorometil)benzamida
144		P	Encontrado 425 (MH ⁺) C ₂₂ H ₂₄ ³⁵ ClF ₃ N ₂ O requiere 424; 2,0,	(±)-2-cloro- <i>N</i> -[2-metil-1-fenil-2-(1-pirrolidinil)propil]-3-(trifluorometil)benzamida
145		P	Encontrado 353 (MH ⁺) C ₂₂ H ₂₈ N ₂ O ₂ requiere 352; 1,93 ,	(±)- <i>N</i> -[[1-(dimetilamino)ciclopentil](fenil)metil]-2-(metiloxi)benzamida

146		E	Encontrado 371 (MH ⁺) C ₂₂ H ₂₇ ³⁵ ClN ₂ O requiere 370; 1,98 ,	3-cloro-2-metil- <i>N</i> -[2-metil-1-fenil-2-(1-pirrolidinil)propil]benzamid a quiral
147		E	Encontrado 351 (MH ⁺) C ₂₃ H ₃₀ N ₂ O requiere 350; 1,89 ,	2,6-dimetil- <i>N</i> -[2-metil-1-fenil-2-(1-pirrolidinil)propil]benzamida quiral
148		P	Encontrado 429 (MH ⁺) C ₂₈ H ₃₂ N ₂ O ₂ requiere 428; 2,32 ,	(±)- <i>N</i> -[[1-(dimetilamino)ciclopentil](fenil)metil]-4-(metiloxi)-3-bifenilcarboxamida
149		E	Encontrado 351 (MH ⁺) C ₂₃ H ₃₀ N ₂ O requiere 350; 1,94 ,	2,5-dimetil- <i>N</i> -[2-metil-1-fenil-2-(1-pirrolidinil)propil]benzamida quiral
150		P	Encontrado 351 (MH ⁺) C ₂₃ H ₃₀ N ₂ O requiere 350 1,80 ,	(±)-2,6-dimetil- <i>N</i> -[2-metil-1-fenil-2-(1-pirrolidinil)propil]benzamida

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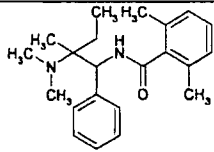
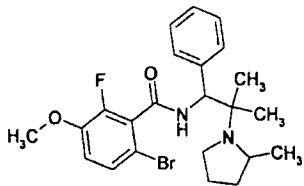
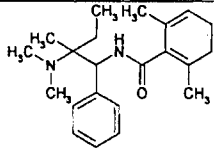
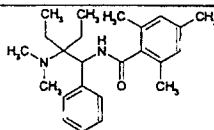
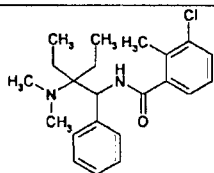
151		E	Encontrado 365 (MH ⁺) C ₂₄ H ₃₂ N ₂ O requiere 364; 1,88 ,	2,4,6-trimetil-N-[2-metil-1-fenil-2-(1-pirrolidinil)propil]benzamida quiral
152		E	Encontrado 387 (MH ⁺) C ₂₂ H ₂₇ ³⁵ ClN ₂ O ₂ requiere 386; 1,84 ,	2-cloro-6-(metiloxi)-N-[2-metil-1-fenil-2-(1-pirrolidinil)propil]benzamida quiral
153		E	Encontrado 499 (MH ⁺) C ₂₃ H ₂₆ ⁷⁹ BrF ₃ N ₂ O ₂ requiere 498; 2,28 ,	3-bromo-2-(metiloxi)-N-[2-metil-1-fenil-2-(1-pirrolidinil)propil]-5-(trifluorometil)benzamida quiral
154		E	Encontrado 365 (MH ⁺) C ₂₄ H ₃₂ N ₂ O requiere 364; 2,00 ,	(±)-2,6-dimetil-N-[2-metil-1-fenil-2-(2-metil-1-pirrolidinil)-1-fenilpropil]benzamida
155		E	Encontrado 405 (MH ⁺) C ₂₃ H ₂₇ F ₃ N ₂ O requiere 404; 2,19 ,	2-metil-N-[2-metil-1-fenil-2-(1-pirrolidinil)propil]-5-(trifluorometil)benzamida quiral

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156		E	Encontrado 415 (MH ⁺) C ₂₂ H ₂₇ ⁷⁹ BrN ₂ O requiere 414; 2,12	3-bromo-2-metil-N-[2-metil-1-fenil-2-(1-pirrolidinil)propil]benzamida quiral
157		E	Encontrado 355 (MH ⁺) C ₂₂ H ₂₇ FN ₂ O requiere 354; 1,96 ,	3-fluoro-2-metil-N-[2-metil-1-fenil-2-(1-pirrolidinil)propil]benzamida quiral
158		E	Encontrado 425 (MH ⁺) C ₂₁ H ₂₃ ³⁵ Cl ₃ N ₂ O requiere 424; 2,11 ,	2,4,6-tricloro-N-[2-metil-1-fenil-2-(1-pirrolidinil)propil]benzamida quiral
159		E	Encontrado 517 (MH ⁺) C ₂₆ H ₃₀ F ₆ N ₂ O ₂ requiere 516; 2,32 ,	(±)-N-[2-etil-1-fenil-2-(1-pirrolidinil)butil]-2-(metiloxi)-4,6-bis(trifluorometil)benzamida
160		E	Encontrado 365(MH ⁺) C ₂₄ H ₃₂ N ₂ O requiere 364; 1,96 ,	(±)-2,6-dimetil-N-[2-metil-2-(2-metil-1-pirrolidinil)-1-fenilpropil]benzamida

161		E	Encontrado 371 (MH ⁺) $C_{22}H_{27}^{35}ClN_2O$ requiere 370; 1,89 ,	2-cloro-3-metil- <i>N</i> -[2-metil-1-fenil-2-(1-pirrolidinil)propil]benzamida quiral
162		E	Encontrado 445 (MH ⁺) $C_{23}H_{29}^{79}BrN_2O_2$ requiere 444; 2,15	5-bromo-3-metil-2-(metiloxi)- <i>N</i> -[2-metil-1-fenil-2-(1-pirrolidinil)propil]benzamida quiral
163		P	Encontrado 407 (MH ⁺) $C_{22}H_{25}F_3N_2O_2$ requiere 406; 2,05 ,	(±)- <i>N</i> -[[1-(dimetilamino)ciclopentil](fenil)metil]-2-[(trifluorometil)oxi]benzamida
164		P	Encontrado 387 (MH ⁺) $C_{22}H_{27}^{35}ClN_2O_2$ requiere 386; 2,10 ,	(±)-4-cloro- <i>N</i> -[[1-(dimetilamino)ciclopentil](fenil)metil]-2-(metiloxi)benzamida
165		E	Encontrado 503 (MH ⁺) $C_{25}H_{28}F_6N_2O_2$ requiere 502; 2,21 ,	2-(etiloxi)- <i>N</i> -[2-metil-1-fenil-2-(1-pirrolidinil)propil]-4,6-bis(trifluorometil)benzamida quiral

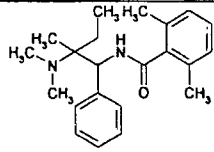
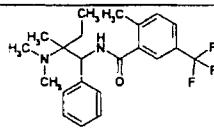
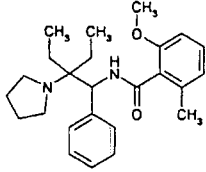
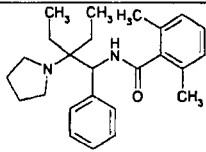
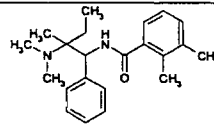
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166		A	Encontrado 339 (MH ⁺) C ₂₂ H ₃₀ N ₂ O requiere 338; 1,75 ,	(±)-N-[2-(dimetilamino)-2-metil-1-fenilbutil]-2,6-dimetilbenzamida
167		PE	Encontrado 463 (MH ⁺) C ₂₃ H ₂₈ ⁷⁹ BrFN ₂ O ₂ requiere 462; 2,44* ,	(±)-6-bromo-2-fluoro-N-[2-metil-2-(2-metil-1-pirrolidinil)-1-fenilpropil]-3-(metiloxi)benzamida
168		P	Encontrado 339 (MH ⁺) C ₂₂ H ₃₀ N ₂ O requiere 338; 1,71 y 1,76 ,	(±)-N-[2-(dimetilamino)-2-metil-1-fenilbutil]-2,6-dimetilbenzamida
169		E	Encontrado 367 (MH ⁺) C ₂₄ H ₃₄ N ₂ O requiere 366; 1,87 ,	(±)-N-[2-(dimetilamino)-2-etil-1-fenilbutil]-2,4,6-trimetilbenzamida
170		E	Encontrado 373 (MH ⁺) C ₂₂ H ₂₉ ³⁵ ClN ₂ O requiere 372; 1,85 ,	(±)-3-cloro-N-[2-(dimetilamino)-2-etil-1-fenilbutil]-2-metilbenzamida

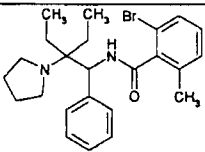
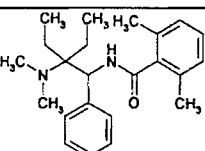
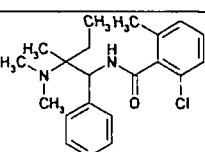
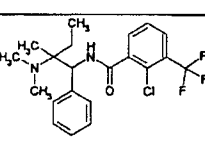
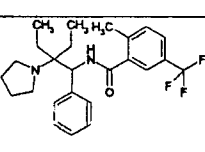
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171		E	Encontrado 393 (MH ⁺) C ₂₆ H ₃₆ N ₂ O requiere 392; 2,02 ,	(±)-N-[2-etil-1-fenil-2-(1-pirrolidinil)butil]-2,4,6-trimetilbenzamida
172		E	Encontrado 425 (MH ⁺) C ₂₁ H ₂₃ ³⁵ Cl ₃ N ₂ O requiere 424; 2,25 ,	(±)-2,3,6-tricloro-N-[[1-(dimetilamino)ciclopentil](fenil)metil]benzamida
173		E	Encontrado 503 (MH ⁺) C ₂₅ H ₂₈ F ₆ N ₂ O ₂ requiere 502; 2,18 ,	N-[[1-(dimetilamino)ciclopentil](fenil)metil]-2-(etiloxi)-4,6-bis(trifluorometil)benzamida quiral
174		E	Encontrado 399 (MH ⁺) C ₂₄ H ₃₁ ³⁵ ClN ₂ O requiere 398; 2,12 ,	(±)-3-cloro-N-[2-etil-1-fenil-2-(1-pirrolidinil)butil]-2-metilbenzamida
175		E	Encontrado 417 (MH ⁺) C ₂₂ H ₂₉ ⁷⁹ BrN ₂ O requiere 416; 1,81 ,	(±)-2-bromo-N-[2-(dimetilamino)-2-etil-1-fenilbutil]-6-metilbenzamida

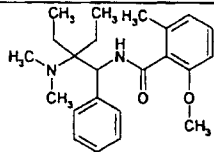
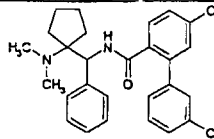
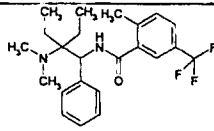
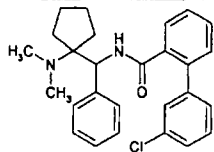
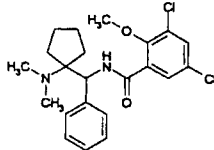
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176		A	Encontrado 339 (MH ⁺) C ₂₂ H ₃₀ N ₂ O requiere 338; 1,63 ,	(±)-N-[2-(dimetilamino)-2-metil-1-fenilbutil]-2,6-dimetilbenzamida
177		P	Encontrado 393 (MH ⁺) C ₂₂ H ₂₇ F ₃ N ₂ O requiere 392; 1,95 y 2,03 ,	(±)-N-[2-(dimetilamino)-2-metil-1-fenilbutil]-2-metil-5-(trifluorometil)benzamida
178		E	Encontrado 395 (MH ⁺) C ₂₅ H ₃₄ N ₂ O ₂ requiere 394; 1,86 ,	(±)-N-[2-etil-1-fenil-2-(1-pirrolidinil)butil]-2-metil-6-(metiloxi)benzamida
179		A	Encontrado 379 (MH ⁺) C ₂₅ H ₃₄ N ₂ O requiere 378; 1,89 ,	(±)-N-[2-etil-1-fenil-2-(1-pirrolidinil)butil]-2,6-dimetilbenzamida
180		P	Encontrado 339 (MH ⁺) C ₂₂ H ₃₀ N ₂ O requiere 388; 1,90 ,	N-[2-(dimetilamino)-2-metil-1-fenilbutil]-2,3-dimetilbenzamida quiral

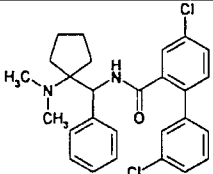
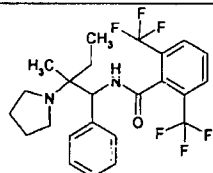
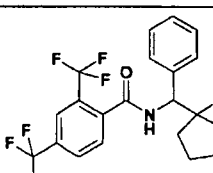
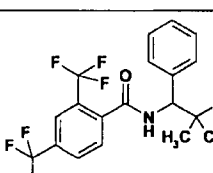
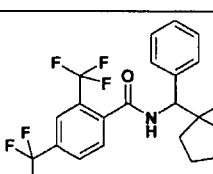
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181		E	Encontrado 443 (MH ⁺) C ₂₄ H ₃₁ ⁷⁹ BrN ₂ O requiere 442; 2,00 ,	(±)-2-bromo- <i>N</i> -[2-etil-1-fenil-2-(1-pirrolidinil)butil]-6-metilbenzamida
182		A	Encontrado 353 (MH ⁺) C ₂₃ H ₃₂ N ₂ O requiere 352; 1,82 ,	(±)- <i>N</i> -[2-(dimetilamino)-2-etil-1-fenilbutil]-2,6-dimetilbenzamida
183		P	Encontrado 359 (MH ⁺) C ₂₁ H ₂₇ ³⁵ ClN ₂ O requiere 358; 1,88 y 1,91,	(±)-2-cloro- <i>N</i> -[2-(dimetilamino)-2-metil-1-fenilbutil]-6-metilbenzamida
184		P	Encontrado 413 (MH ⁺) C ₂₁ H ₂₄ ³⁵ ClF ₃ N ₂ O requiere 412; 2,09 y 2,21,	(±)-2-cloro- <i>N</i> -[2-(dimetilamino)-2-metil-1-fenilbutil]-3-(trifluorometil)benzamida
185		E	Encontrado 433 (MH ⁺) C ₂₅ H ₃₁ F ₃ N ₂ O requiere 432; 2,20 ,	(±)- <i>N</i> -[2-etil-1-fenil-2-(1-pirrolidinil)butil]-2-metil-5-(trifluorometil)benzamida

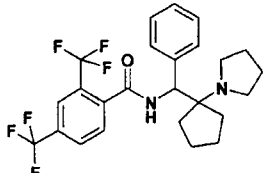
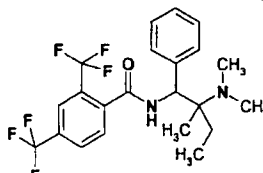
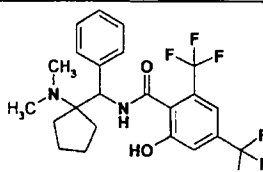
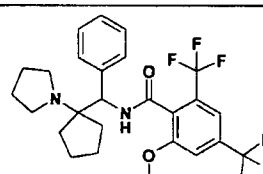
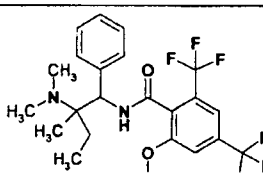
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186		E	Encontrado 369 (MH ⁺) C ₂₃ H ₃₂ N ₂ O ₂ requiere 368; 1,74 ,	(±)-N-[2-(dimetilamino)-2-etil-1-fenilbutil]-2-metil-6-(metiloxi)benzamida
187		P	Encontrado 467 (MH ⁺) C ₂₇ H ₂₈ ³⁵ Cl ₂ N ₂ O requiere 466; 2,3	(±)-3',5-dicloro-N-[[1-(dimetilamino)ciclopentil](fenil)metil]-2-bifenilcarboxamida
188		E	Encontrado 407 (MH ⁺) C ₂₃ H ₂₉ F ₃ N ₂ O requiere 406; 2,08 ,	(±)-N-[2-(dimetilamino)-2-etil-1-fenilbutil]-2-metil-5-(trifluorometil)benzamida
189		P	Encontrado 433 (MH ⁺) C ₂₇ H ₂₉ ³⁵ ClN ₂ O requiere 432; 2,0	(±)-3'-cloro-N-[[1-(dimetilamino)ciclopentil](fenil)metil]-2-bifenilcarboxamida
190		P	Encontrado 421 (MH ⁺) C ₂₂ H ₂₆ ³⁵ Cl ₂ N ₂ O ₂ requiere 420; 2,12	(±)-3,5-dicloro-N-[[1-(dimetilamino)ciclopentil](fenil)metil]-2-(metiloxi)benzamida

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191		P	Encontrado 468 (MH ⁺) C ₂₇ H ₂₈ ³⁵ Cl ₂ N ₂ O requiere 467; 2,3	(±)-3',4-dicloro-N-[[1-(dimetilamino)ciclopentil](fenil)metil]-2-bifenilcarboxamida
192		A	Encontrado 473 (MH ⁺) C ₂₄ H ₂₆ F ₆ N ₂ O requiere 472; 1,97 ,	(±)-N-[2-metil-1-fenil-2-(1-pirrolidinil)butil]-2,6-bis(trifluorometil)benzamida
193		A	Encontrado 459(MH ⁺) C ₂₃ H ₂₄ F ₆ N ₂ O Requiere 458; 2,20	N-[[1-(dimetilamino)ciclopentil](fenil)metil]-2,4-bis(trifluorometil)benzamida quiral
194		A	Encontrado 459(MH ⁺) C ₂₃ H ₂₄ F ₆ N ₂ O Requiere 458; 2,21	N-[2-metil-1-fenil-2-(1-pirrolidinil)propil]-2,4-bis(trifluorometil)benzamida quiral
195		A	Encontrado 471(MH ⁺) C ₂₄ H ₂₄ F ₆ N ₂ O Requiere 470; 2,24	(±)-N-[[1-(1-azetidil)ciclopentil](fenil)metil]-2,4-bis(trifluorometil)benzamida

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196		A	Encontrado 485(MH ⁺) C ₂₅ H ₂₆ F ₆ N ₂ O Requiere 484; 2,28	(±)-N-{fenil[1-(1-pirrolidinil)ciclopentil]metil} -2,4-bis(trifluorometil) benzamida
197		A	Encontrado 447(MH ⁺) C ₂₂ H ₂₄ F ₆ N ₂ O Requiere 446; 2,16	(±)-N-[2-(dimetilamino)-2-metil-1-fenilbutil]-2,4-bis(trifluorometil) benzamida
198		A	Encontrado 475(MH ⁺) C ₂₃ H ₂₄ F ₆ N ₂ O ₂ Requiere 475; 1,97	N-[[1-(dimetilamino)ciclopentil](fenil)metil]-2-hidroxi-4,6-bis(trifluorometil) benzamida quiral
199		P	Encontrado 515(MH ⁺) C ₂₆ H ₂₈ F ₆ N ₂ O ₂ Requiere 514; 2,33	(±)-2-(metiloxi)-N-{fenil[1-(1-pirrolidinil)ciclopentil]metil}-4,6-bis(trifluorometil) benzamida
200		P	Encontrado 477(MH ⁺) C ₂₃ H ₂₆ F ₆ N ₂ O ₂ Requiere 476; 2,21	(±)-N-[2-(dimetilamino)-2-metil-1-fenilbutil]-2-(metiloxi)-4,6-bis(trifluorometil) benzamida

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201		P	Encontrado 439 (MH ⁺) C ₂₃ H ₂₆ ³⁵ ClF ₃ N ₂ O requiere 438; 2,16,	(±)-2-cloro- <i>N</i> -[[1-(dimetilamino)ciclohexil](fenil)metil]-3-(trifluorometil)benzamida
202		P	Encontrado 405 (MH ⁺) C ₂₂ H ₂₆ ³⁵ Cl ₂ N ₂ O requiere 404; 1,90,	(±)-2,6-dicloro- <i>N</i> -[[1-(dimetilamino)ciclohexil](fenil)metil]benzamida
203		P	Encontrado 353 (MH ⁺) C ₂₂ H ₂₈ N ₂ O ₂ requiere 352; 1,70 y 1,72,	(±)- <i>N</i> -[[3-(dimetilamino)tetrahidro-3-furanil](fenil)metil]-2,6-dimetilbenzamida
204		P	Encontrado 369 (MH ⁺) C ₂₂ H ₂₈ N ₂ O ₃ requiere 368; 1,75 y 1,77,	(±)- <i>N</i> -[[3-(dimetilamino)tetrahidro-3-furanil](fenil)metil]-2-metil-6-(metiloxi)benzamida
205		P	Encontrado 427 (MH ⁺) C ₂₁ H ₂₂ ³⁵ ClF ₃ N ₂ O ₂ requiere 426; 1,94 y 1,96,	(±)-2-cloro- <i>N</i> -[[3-(dimetilamino)tetrahidro-3-furanil](fenil)metil]-3-(trifluorometil)benzamida

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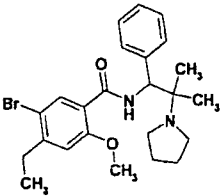
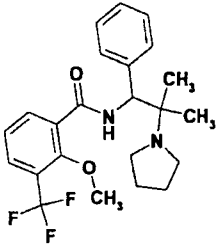
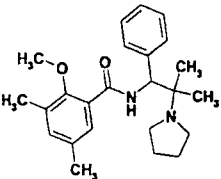
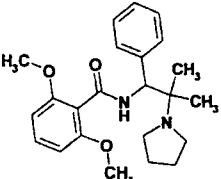
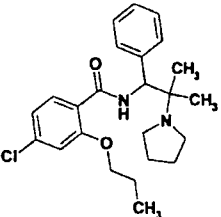
206		P	Encontrado 353 (MH ⁺) C ₂₂ H ₂₈ N ₂ O ₂ requiere 352; 1,74 y 1,76,	(±)-N-[[3-(dimetilamino)tetrahydro-3-furanil](fenil)metil]-2,3-dimetilbenzamida
207		A	Encontrado 459 (MH ⁺) C ₂₃ H ₂₄ F ₆ N ₂ O requiere 458; 1,97 ,	N-[[1-(dimetilamino)ciclopentil](fenil)metil]-2,6-bis(trifluorometil)benzamida quiral
208		A	Encontrado 459 (MH ⁺) C ₂₃ H ₂₄ F ₆ N ₂ O requiere 458; 1,92 ,	N-[2-metil-1-fenil-2-(1-pirrolidinil)propil]-2,6-bis(trifluorometil)benzamida quiral
209		A	Encontrado 473 (MH ⁺) C ₂₄ H ₂₆ F ₆ N ₂ O requiere 472; 2,05 y 2,09,	(±)-N-[2-metil-1-fenil-2-(1-pirrolidinil)butil]-2,6-bis(trifluorometil)benzamida

210		PE	Encontrado 421 (MH ⁺) $C_{22}H_{26}^{35}Cl_2N_2O_2$ requiere 420; 2,53*,	(±)-3,5-dicloro-2-(metiloxi)- <i>N</i> -[2-metil-1-fenil-2-(1- pirrolidinil)propil] benzamida
211		PE	Encontrado 431 (MH ⁺) $C_{22}H_{27}^{79}BrN_2O_2$ requiere 430; 2,57*,	(±)-5-bromo-2-(metiloxi)- <i>N</i> -[2-metil-1-fenil-2-(1- pirrolidinil)propil] benzamida
212		PE	Encontrado 399 (MH ⁺) $C_{27}H_{30}N_2O$ requiere 398; 2,47*,	(±)- <i>N</i> -[2-metil-1-fenil-2-(1- pirrolidinil)propil]-2- bifenilcarboxamida
213		PE	Encontrado 387 (MH ⁺) $C_{22}H_{27}^{35}ClN_2O_2$ requiere 386; 2,49*,	(±)-4-cloro-2-(metiloxi)- <i>N</i> - [2-metil-1-fenil-2-(1- pirrolidinil)propil] benzamida
214		PE	Encontrado 425 (MH ⁺) $C_{22}H_{24}^{35}ClF_3N_2O$ requiere 424; 2,45*,	(±)-2-cloro- <i>N</i> -[2-metil-1- fenil-2-(1- pirrolidinil)propil]-5- (trifluorometil)benzamida

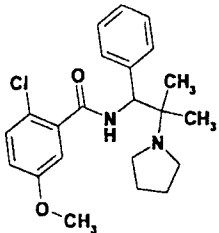
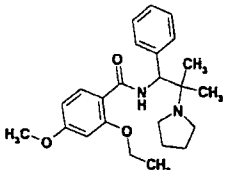
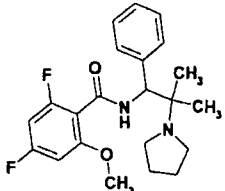
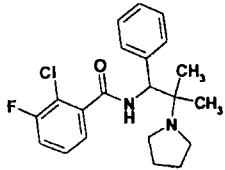
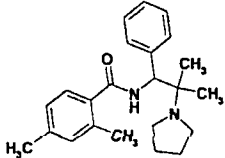
m6

215		PE	Encontrado 409 (MH ⁺) C ₂₂ H ₂₄ F ₄ N ₂ O requiere 408; 2,39*,	(±)-4-fluoro- <i>N</i> -[2-metil-1-fenil-2-(1-pirrolidinil)propil]-2-(trifluorometil)benzamida
216		PE	Encontrado 409 (MH ⁺) C ₂₂ H ₂₄ F ₄ N ₂ O requiere 408; 2,56*,	(±)-2-fluoro- <i>N</i> -[2-metil-1-fenil-2-(1-pirrolidinil)propil]-6-(trifluorometil)benzamida
217		PE	Encontrado 431 (MH ⁺) C ₂₂ H ₂₇ ⁷⁹ BrN ₂ O ₂ requiere 430; 2,54*,	5-bromo- <i>N</i> -[[1-(dimetilamino)ciclopentil](fenil)metil]-2-(metiloxi)benzamida quiral
218		PE	Encontrado 387 (MH ⁺) C ₂₂ H ₂₇ ³⁵ ClN ₂ O ₂ requiere 386; 2,54*,	4-cloro- <i>N</i> -[[1-(dimetilamino)ciclopentil](fenil)metil]-2-(metiloxi)benzamida quiral
219		PE	Encontrado 409 (MH ⁺) C ₂₂ H ₂₄ F ₄ N ₂ O requiere 408; 2,47*,	<i>N</i> -[[1-(dimetilamino)ciclopentil](fenil)metil]-2-fluoro-6-(trifluorometil)benzamida quiral

317

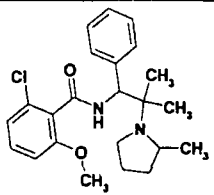
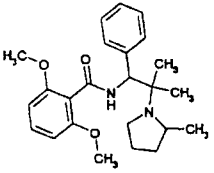
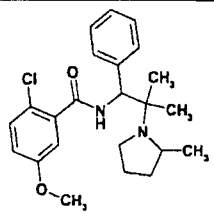
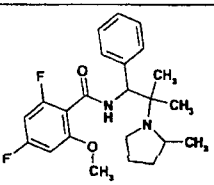
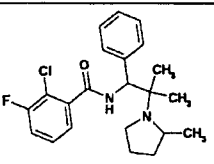
220		PE	Encontrado 459 (MH ⁺) C ₂₄ H ₃₁ ⁷⁹ BrN ₂ O ₂ requiere 458; 2,81*,	(±)-5-bromo-4-etil-2-(metiloxi)- <i>N</i> -[2-metil-1-fenil-2-(1-pirrolidinil)propil]benzamida
221		PE	Encontrado 421 (MH ⁺) C ₂₃ H ₂₇ F ₃ N ₂ O ₂ requiere 420; 2,63*,	(±)-2-(metiloxi)- <i>N</i> -[2-metil-1-fenil-2-(1-pirrolidinil)propil]-3-(trifluorometil)benzamida
222		PE	Encontrado 381 (MH ⁺) C ₂₄ H ₃₂ N ₂ O ₂ requiere 380; 2,52*,	(±)-3,5-dimetil-2-(metiloxi)- <i>N</i> -[2-metil-1-fenil-2-(1-pirrolidinil)propil]benzamida
223		PE	Encontrado 383 (MH ⁺) C ₂₃ H ₃₀ N ₂ O ₃ requiere 382; 2,77*,	(±)-2,6-bis(metiloxi)- <i>N</i> -[2-metil-1-fenil-2-(1-pirrolidinil)propil]benzamida
224		PE	Encontrado 415 (MH ⁺) C ₂₄ H ₃₁ ³⁵ ClN ₂ O ₂ requiere 414; 3,05*,	(±)-4-cloro- <i>N</i> -[2-metil-1-fenil-2-(1-pirrolidinil)propil]-2-(propiloxi)benzamida

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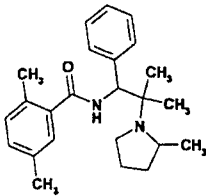
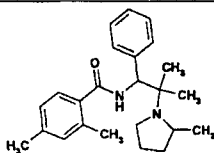
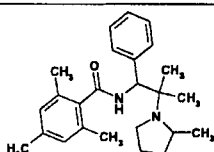
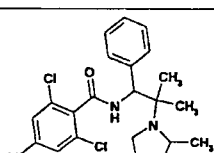
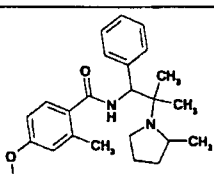
225		PE	Encontrado 387 (MH ⁺) C ₂₂ H ₂₇ ³⁵ ClN ₂ O ₂ requiere 386; 2,53*,	(±)-2-cloro-5-(metiloxi)-N-[2-metil-1-fenil-2-(1-pirrolidinil)propil] benzamida
226		PE	Encontrado 397 (MH ⁺) C ₂₄ H ₃₂ N ₂ O ₃ requiere 396; 2,58*,	(±)-2-(etiloxi)-4-(metiloxi)-N-[2-metil-1-fenil-2-(1-pirrolidinil)propil] benzamida
227		PE	Encontrado 389 (MH ⁺) C ₂₂ H ₂₆ F ₂ N ₂ O ₂ requiere 388; 2,47*,	(±)-2,4-difluoro-6-(metiloxi)-N-[2-metil-1-fenil-2-(1-pirrolidinil)propil] benzamida
228		PE	Encontrado 375 (MH ⁺) C ₂₁ H ₂₄ ³⁵ ClFN ₂ O requiere 374; 2,86*,	(±)-2-cloro-3-fluoro-N-[2-metil-1-fenil-2-(1-pirrolidinil)propil] benzamida
229		PE	Encontrado 351 (MH ⁺) C ₂₃ H ₃₀ N ₂ O requiere 350; 2,84*,	(±)-2,4-dimetil-N-[2-metil-1-fenil-2-(1-pirrolidinil)propil] benzamida

230		PE	Encontrado 449 (MH ⁺) C ₂₂ H ₂₆ ⁷⁹ BrFN ₂ O ₂ requiere 448; 2,45*	6-bromo-N-[[1-(dimetilamino)ciclopentil](fenil)metil]-2-fluoro-3-(metiloxi)benzamida quiral
231		PE	Encontrado 443 (MH ⁺) C ₂₂ H ₂₃ ³⁵ ClF ₄ N ₂ O requiere 442; 2,94*,	(±)-3-cloro-2-fluoro-N-[2-metil-1-fenil-2-(1-pirrolidinil)propil]-6-(trifluorometil)benzamida
232		P	Encontrado 337 (MH ⁺) C ₂₂ H ₂₈ N ₂ O requiere 336; 1,86,	(±)-N-[[1-(dimetilamino)ciclopentil](fenil)metil]-2-metilbenzamida
233		A	Encontrado 517 (MH ⁺) C ₂₆ H ₃₀ F ₆ N ₂ O ₂ requiere 516; 2,32,	(±)-N-[2-(hexahidro-1H-azepin-1-il)-2-metil-1-fenilpropil]-2-(metiloxi)-4,6-bis(trifluorometil)benzamida
234		A	Encontrado 453 (MH ⁺) C ₂₄ H ₂₈ ³⁵ ClF ₃ N ₂ O requiere 452; 2,21,	(±)-2-cloro-N-[2-(hexahidro-1H-azepin-1-il)-2-metil-1-fenilpropil]-3-(trifluorometil)benzamida

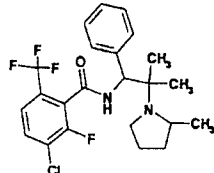
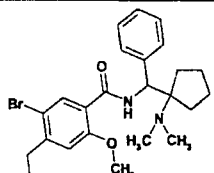
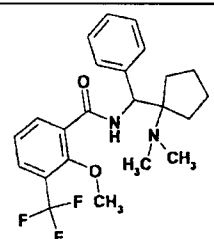
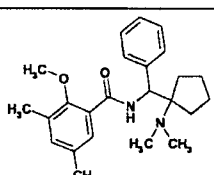
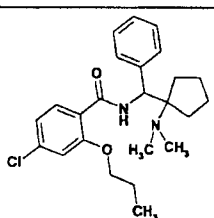
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235		PE	Encontrado 401 (MH ⁺) C ₂₃ H ₂₉ ³⁵ ClN ₂ O ₂ requiere 400; 2,48*,	(±)-2-cloro- <i>N</i> -[2-metil-2-(2-metil-1-pirrolidinil)-1-fenilpropil]-6-(metiloxi)benzamida
236		PE	Encontrado 397 (MH ⁺) C ₂₄ H ₃₂ N ₂ O ₃ requiere 396; 2,79*,	(±)- <i>N</i> -[2-metil-2-(2-metil-1-pirrolidinil)-1-fenilpropil]-2,6-bis(metiloxi)benzamida
237		PE	Encontrado 401 (MH ⁺) C ₂₃ H ₂₉ ³⁵ ClN ₂ O ₂ requiere 400; 2,53*,	(±)-2-cloro- <i>N</i> -[2-metil-2-(2-metil-1-pirrolidinil)-1-fenilpropil]-5-(metiloxi)benzamida
238		PE	Encontrado 403 (MH ⁺) C ₂₃ H ₂₈ F ₂ N ₂ O ₂ requiere 402; 2,52*,	(±)-2,4-difluoro- <i>N</i> -[2-metil-2-(2-metil-1-pirrolidinil)-1-fenilpropil]-6-(metiloxi)benzamida
239		PE	Encontrado 389 (MH ⁺) C ₂₂ H ₂₆ ³⁵ ClFN ₂ O requiere 388; 2,89*,	(±)-2-cloro-3-fluoro- <i>N</i> -[2-metil-2-(2-metil-1-pirrolidinil)-1-fenilpropil]benzamida

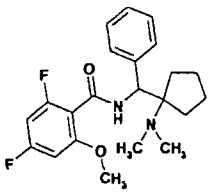
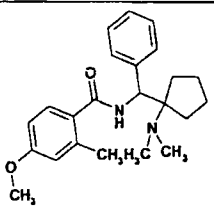
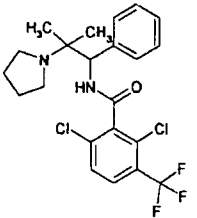
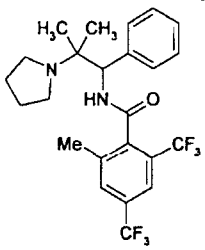
321

240		PE	Encontrado 365 (MH ⁺) C ₂₄ H ₃₂ N ₂ O requiere 364; 2,66*,	(±)-2,5-dimetil-N-[2-metil-2-(2-metil-1-pirrolidinil)-1-fenilpropil]benzamida
241		PE	Encontrado 365 (MH ⁺) C ₂₄ H ₃₂ N ₂ O requiere 364; 2,94*,	(±)-2,4-dimetil-N-[2-metil-2-(2-metil-1-pirrolidinil)-1-fenilpropil]benzamida
242		PE	Encontrado 379 (MH ⁺) C ₂₅ H ₃₄ N ₂ O requiere 378; 2,5*,	(±)-2,4,6-trimetil-N-[2-metil-2-(2-metil-1-pirrolidinil)-1-fenilpropil]benzamida
243		PE	Encontrado 439 (MH ⁺) C ₂₂ H ₂₅ ³⁵ Cl ₃ N ₂ O requiere 438; 2,91*,	(±)-2,4,6-tricloro-N-[2-metil-2-(2-metil-1-pirrolidinil)-1-fenilpropil]benzamida
244		PE	Encontrado 381 (MH ⁺) C ₂₄ H ₃₂ N ₂ O ₂ requiere 380; 2,84*,	(±)-2-metil-N-[2-metil-2-(2-metil-1-pirrolidinil)-1-fenilpropil]-4-(metiloxi)benzamida

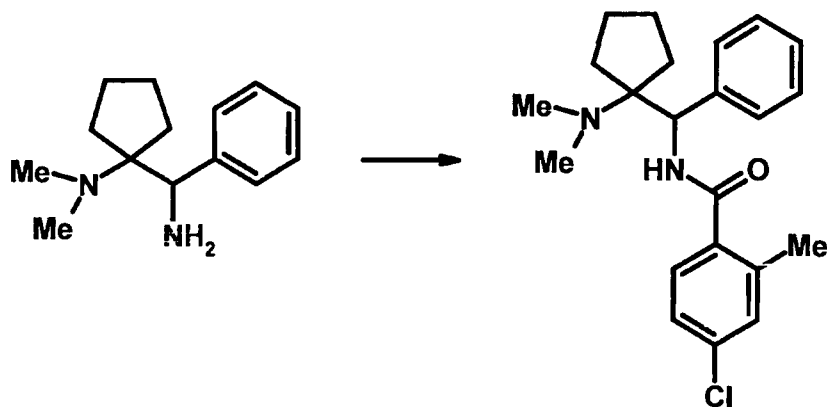
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245		PE	Encontrado 457 (MH ⁺) $C_{23}H_{25}^{35}ClF_4N_2O$ requiere 456; 2,97*,	(±)-3-cloro-2-fluoro- <i>N</i> -[2-metil-2-(2-metil-1-pirrolidinil)-1-fenilpropil]-6-(trifluorometil)benzamida
246		PE	Encontrado 459 (MH ⁺) $C_{24}H_{31}^{79}BrN_2O_2$ requiere 458; 2,84*,	5-bromo- <i>N</i> -[[1-(dimetilamino)ciclopentil](fenil)metil]-4-etil-2-(metiloxi)benzamida quiral
247		PE	Encontrado 421 (MH ⁺) $C_{23}H_{27}F_3N_2O_2$ requiere 420; 2,67*,	<i>N</i> -[[1-(dimetilamino)ciclopentil](fenil)metil]-2-(metiloxi)-3-(trifluorometil)benzamida quiral
248		PE	Encontrado 381 (MH ⁺) $C_{24}H_{32}N_2O_2$ requiere 380; 2,54*,	<i>N</i> -[[1-(dimetilamino)ciclopentil](fenil)metil]-3,5-dimetil-2-(metiloxi)benzamida quiral
249		PE	Encontrado 415 (MH ⁺) $C_{24}H_{31}^{35}ClN_2O_2$ requiere 414; 3,21*,	4-cloro- <i>N</i> -[[1-(dimetilamino)ciclopentil](fenil)metil]-2-(propiloxi)benzamida quiral

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250		PE	Encontrado 389 (MH ⁺) C ₂₂ H ₂₆ F ₂ N ₂ O ₂ requiere 388; 2,51*,	N-[[1-(dimetilamino)ciclopentil](fenil)metil]-2,4-difluoro-6-(metiloxi)benzamida quiral
251		PE	Encontrado 367 (MH ⁺) C ₂₃ H ₃₀ N ₂ O ₂ requiere 366; 2,98*,	N-[[1-(dimetilamino)ciclopentil](fenil)metil]-2-metil-4-(metiloxi)benzamida quiral
252		P#	Encontrado 459 (MH ⁺) C ₂₂ H ₂₃ ³⁵ Cl ₂ F ₃ N ₂ O requiere 458; 2,07	2,6-dicloro-N-[2-metil-1-(1-pirrolidinil)propil]-3-(trifluorometil)benzamida quiral
253		A	Encontrado 473 (MH ⁺) C ₂₄ H ₂₆ F ₆ N ₂ O requiere 472; 2,22,	2-metil-N-[2-metil-1-(1-pirrolidinil)propil]-4,6-bis-(trifluorometil)benzamida quiral

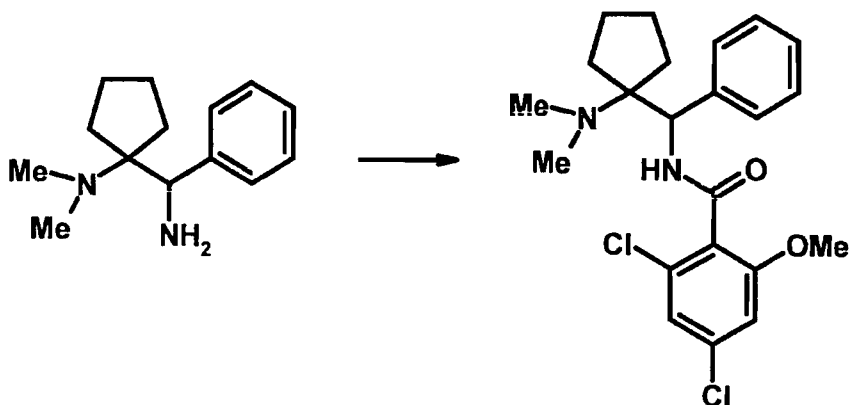
Ejemplo 254: 4-Cloro-N-[[1-(dimetilamino)ciclopentil](fenil) metil] -2-metilbenzamida quiral



- 5 Una mezcla de {1-[amino(fenil)metil]ciclopentil}dimetilamina D3 enantiómero 2 (80 mg, 0,37 mmoles), ácido 4-cloro-2-metilbenzoico (68 mg; 0,40 mmoles), HOBt (61 mg; 0,40 mmoles) y PS-DCC (310 mg de carga 1,3 mmoles/g, 0,40 mmoles) en DCM (4 ml) se agitó durante toda una noche. Se añadió bicarbonato sódico acuoso saturado y la mezcla se separó con un
- 10 cartucho de separación de fases y los extractos orgánicos se aplicaron directamente a una resina SCX. La elución con DCM, metanol y después amoníaco 1 M en metanol, seguido de cromatografía eluyendo con acetato de etilo al 12 - 100% - pentano (SP4 Biotage) produjo el producto del título (64 mg; 43%). ¹H RMN (CDCl₃) δ: 0,9 - 1,0 (1H, m), 1,25 - 1,40 (1H, m), 1,4 - 1,6 (2H, m), 1,6 - 1,75 (2H, m), 1,8 - 1,9 (2H, m), 2,22 (6H, s), 2,41 (3H, s), 5,09 (1H, d, J = 5Hz), 7,07 (1H, d, J = 5Hz), 7,2 - 7,4 (8H, m), Espectro de masas (Electropulverización CL/EM); Encontrado 371 (MH⁺). C₂₂H₂₇³⁵ClN₂O requiere 370. Tiempo de retención 2,26 min. El producto del título se convirtió en su correspondiente sal clorhidrato.

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Ejemplo 255: 2,4-Dicloro-*N*-[[1-(dimetilamino)ciclopentil](fenil)metil]-6-(metiloxi)benzamida quiral



5 Una mezcla de {1-[amino(fenil)metil]ciclopentil}dimetilamina D3 enantiómero 2 (80 mg, 0,37 mmoles), ácido 2,4-dicloro-6-(metiloxi)benzoico (88 mg; 0,40 mmoles), HOBt (61 mg; 0,40 mmoles) y PS-DCC (310 mg de carga 1,3 mmol/g, 0,40 mmoles) en DCM (4 ml) se agitó durante toda una noche. Se

añadió bicarbonato sódico acuoso saturado y la mezcla se separó con un

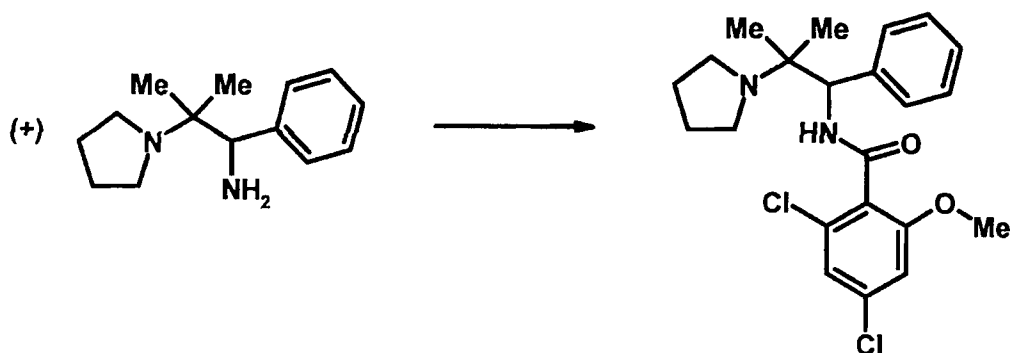
10 cartucho de separación de fases y los extractos orgánicos se aplicaron directamente a una resina de SCX. La elución con DCM, metanol y después amoníaco 1 M en metanol, seguido de cromatografía eluyendo con acetato de etilo al 12 - 100% - pentano (SP4 Biotage) produjo el producto del título (133 mg; 79%). ¹H RMN (CDCl₃) δ: 0,95 - 1,10 (1H, m), 1,25 - 1,35 (1H, m), 1,40 -

15 1,60 (2H, m), 1,60 - 1,75 (2H, m), 1,80 - 1,90 (2H, m), 2,22 (6H, s), 3,82 (3H, s), 5,08 (1H, d, J = 5Hz), 6,82 (1H, d, J = 2Hz), 7,02 (1H, d, J = 2Hz), 7,07 (1H, m), 7,22 - 7,33 (3H, m), 7,44 - 7,46 (2H, m). Espectro de masas (Elecropulverización CL/EM); Encontrado 421 (MH⁺). C₂₂H₂₆³⁵Cl₂N₂O₂ requiere 420. Tiempo de retención 2,34 min. El producto del título se convirtió en su

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correspondiente sal clorhidrato. El ácido 2,4-Dicloro-6-(metiloxi)benzoico se puede preparar como se describe por G. E. Stokker, A. W. Alberts, P. S. Anderson, E. J. Cragoe Jr., A. A. Deana, J. L. Gilfillan, J. Hirshfield, W. J. Holtz, W. F. Hoffman, J.W. Huff, T.J. Lee, F.C. Novello, J.D. Prugh, C.S. Rooney, R.L. Smith, A.K. Willard J Med Chem, 1986, 29(2), 170.

Ejemplo 256: 2,4-Dicloro-6-(metiloxi)-N-[2-metil-1-fenil-2-(1-pirrolidinil)propil]benzamida quiral



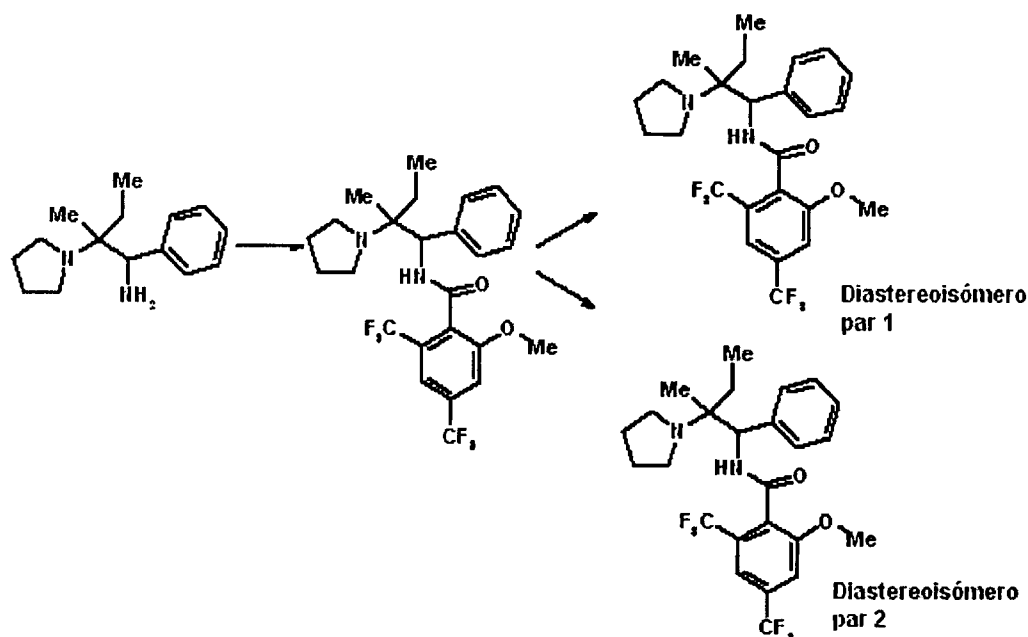
10 A una solución de (+)-[2-metil-1-fenil-2-(1-pirrolidinil)propil]amina D6 (0,10 g; 0,459 mmoles) y trietilamina (0,15 ml; 1 mmol) en DCM (3 ml) se le añadió una solución de cloruro de 2,4-dicloro-6-metiloxibenzoílo (0,13 g; 0,540 mmoles) en DCM (2 ml). Después de una hora se añadió carbonato ácido de sodio acuoso saturado (8 ml) y la mezcla se agitó durante 2 minutos. La fase
15 orgánica se pasó a través de un cartucho de separación de fases y el disolvente se retiró a presión reducida. El residuo se disolvió en una cantidad mínima de DCM y se aplicó a una columna de gel de sílice de 10 g. La elución con gradiente de acetato de etilo al 0 - 100% en pentano y la retirada del disolvente a presión reducida produjo el compuesto del título en forma de una
20 goma incolora (0,14 g; 72%). ^1H RMN (CDCl_3) δ : 0,91 (3H, s), 0,96 (3H, s),

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1,60-1,80 (4H, m), 2,55-2,75 (4H, m), 3,82 (3H, s), 4,76 (1H, d, $J = 2,4\text{Hz}$), 6,81 (1H, d, $J = 1,6\text{Hz}$), 7,02 (1H, d, $J = 1,6\text{Hz}$), 7,20-7,50 (6H, m). Espectro de masas (Electropulverización CL/EM). Encontrado 421 (MH^+). $\text{C}_{22}\text{H}_{26}^{35}\text{Cl}_2\text{N}_2\text{O}_2$ requiere 420. Tiempo de retención: 1,97 min.

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Ejemplos 257: ($\pm$)-2-(Metiloxi)-N-[2-metil-1-fenil-2-(1-pirrolidinil)butil]-4,6-bis(trifluorometil)benzamida Par Diastereoisómero 1 y Par Diastereoisómero 2



10 A una solución agitada de ($\pm$)-[2-metil-1-fenil-2-(1-pirrolidinil)butil]amina D22 (2,32 g; 10 mmoles) y trietilamina (2,78 ml; 20 mmoles) en DCM (75 ml) a temperatura ambiente se añadió una solución de cloruro de 2-(metiloxi)-4,6-bis(trifluorometil)benzoilo (3,10 g; 10 mmoles) en DCM (25 ml) gota a gota durante 10 minutos. Después de 20 horas se añadió carbonato ácido de sodio
15 acuoso saturado (100 ml) y se continuó la agitación durante 0,5 horas. Se

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separaron las fases y la fase acuosa se extrajo con DCM (150 ml). Los extractos orgánicos combinados se secaron (Na_2SO_4), se filtraron y el disolvente se retiró a presión reducida proporcionando una espuma de color naranja pálido (4,8 g). La muestra se disolvió en una cantidad mínima de DCM y una mitad de la solución se aplicó a una columna de sílice 40 M. La elución con MeOH al 2% en DCM (2,5 l) después MeOH al 3% en DCM (2,4 l) produjo el par diastereoisómero 1 del compuesto del título (0,16 g) ^1H RMN (CDCl_3) δ : 0,97 (3H, s), 1,01 (3H, t, $J = 7,6\text{Hz}$), 1,25 - 1,35 (2H, c, $J = 8\text{Hz}$), 1,55 - 1,75 (4H, m), 2,55 - 2,70 (4H, m), 3,93 (3H, s), 4,84 (1H, d, $J = 0,9\text{Hz}$), 7,20 - 7,45 (7H, m), 7,54 (1H, s). Espectro de masas (Electropulverización CL/EM). Encontrado 503 (MH^+). $\text{C}_{25}\text{H}_{28}\text{F}_6\text{N}_2\text{O}_2$ requiere 502. Tiempo de retención: 2,27 min.

La elución adicional con MeOH al 5% en DCM produjo el par diastereoisómero 2 del compuesto del título (0,36g). ^1H RMN (CDCl_3) δ : 0,75 - 0,85 (3H, t), 1,03 (3H, s), 1,35 - 1,55 (1H, m), 1,60 - 1,72 (4H, m), 1,72 - 1,90 (1H, m), 2,70 - 2,85 (4H, m), 3,92 (3H, s), 4,83 (1H, d, $J = 3,6\text{Hz}$), 7,20 - 7,40 (7H, m), 7,53 (1H, s). Espectro de masas (Electropulverización CL/EM). Encontrado 503 (MH^+). $\text{C}_{25}\text{H}_{28}\text{F}_6\text{N}_2\text{O}_2$ requiere 502. Tiempo de retención: 2,30 min.

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Los compuestos de los ejemplos anteriores se pueden convertir en sus correspondientes sales clorhidrato disolviendo la base libre precursora en DCM o mezclas de DCM / metanol y añadiendo cloruro de hidrógeno 1 M en éter, seguido de la evaporación y secando a vacío. Los compuestos purificados mediante autopurificación dirigida por masas se aislaron en forma de la sal

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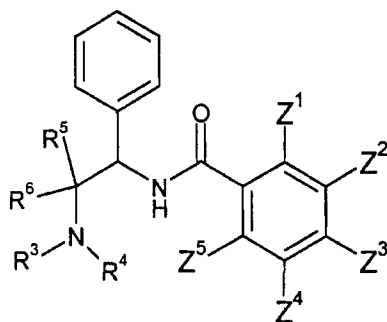
formiato que se podría convertir en la base libre mediante una columna de SCX y en la sal clorhidrato correspondiente mediante reacción con cloruro de hidrógeno 1 M en éter como se ha descrito anteriormente.

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REIVINDICACIONES

Habiendo así especialmente descrito y determinado la naturaleza de la presente invención y la forma como la misma ha de ser llevada a la práctica, se declara reivindicar como de propiedad y de derecho exclusivo:

- 5 1. Un compuesto de fórmula (I) o una sal o solvato del mismo:



(I)

- 10 en la que

Z¹ se selecciona entre el grupo constituido por alquilo C₁₋₄, cicloalquilo C₃₋₆, alcoxi C₁₋₄, alquil C₁₋₄ tio, haloalquilo C₁₋₄, fenilo, haloalcoxi C₁₋₄, halofenilo, alquil C₁₋₄ sulfoxi, alquil C₁₋₄ sulfonilo, bromo y cloro;

- 15 Z² se selecciona entre el grupo constituido por hidrógeno, halógeno, ciano, alquilo C₁₋₄, fenilo, haloalquilo C₁₋₄, haloalcoxi C₁₋₄, halofenilo, alcoxi C₁₋₄ alquilo C₁₋₄ y cicloalquilo C₃₋₆;

Z³ se selecciona entre el grupo constituido por hidrógeno, halógeno, alquilo C₁₋

- 20 4, alcoxi C₁₋₄, alquil C₁₋₄ tio, haloalquilo C₁₋₄, haloalcoxi C₁₋₄, y cicloalquilo C₃₋₆;

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Z^4 se selecciona entre el grupo constituido por hidrógeno, halógeno, alquilo C_{1-3} , haloalquilo C_{1-4} , alcoxi C_{1-4} , alquil C_{1-4} tio, fenilo, haloalcoxi C_{1-4} , halofenilo, alcoxi C_{1-4} alquilo C_{1-4} y cicloalquilo C_{3-6} ;

- 5 Z^5 se selecciona entre el grupo constituido por hidrógeno, fluoro, cloro, bromo, yodo, hidroxí, alquilo C_{1-4} , alcoxi C_{1-4} , alquil C_{1-4} tio, fenilo, haloalquilo C_{1-4} , haloalcoxi C_{1-4} , halofenilo, alcoxi C_{1-4} alquilo C_{1-4} y cicloalquilo C_{3-6} ;

en la que si más de uno de Z^1 a Z^5 es metoxi, entonces solamente Z^1 y Z^5 son
10 metoxi

- R^3 y R^4 son independientemente hidrógeno, alquilo C_{1-4} , opcionalmente sustituido con uno o más grupos Y; o R^3 y R^4 junto con el átomo de nitrógeno al que están unidos forman un anillo carbocíclico saturado o parcialmente
15 insaturado de 4-, 5-, 6- ó 7-miembros opcionalmente sustituido con un grupo Y';

Y se selecciona entre el grupo constituido por alcoxi C_{1-4} , hidroxí, haloalcoxi C_{1-4} y cicloalquilo C_{3-5} ;

- 20 Y' se selecciona entre el grupo constituido por alquilo C_{1-4} , alcoxi C_{1-4} , halógeno, hidroxí, haloalcoxi C_{1-4} , cicloalquilo C_{3-5} y arilo C_{5-10} o Y' forma un puente $-CH_2-$ o $-CH_2-CH_2-$ entre dos átomos sobre el anillo carbocíclico de 4-, 5-, 6- ó 7-miembros;

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R⁵ y R⁶ son independientemente alquilo C₁₋₄, opcionalmente sustituido con uno o más grupos X; o R⁵ y R⁶ junto con el átomo de carbono al que están unidos forman un anillo carbocíclico saturado de 5- ó 6- miembros opcionalmente sustituido con uno o más grupos X', en el caso de que R⁵ y R⁶ junto con el
5 átomo de carbono al que están unidos formen un anillo carbocíclico saturado de 5- miembros, ese anillo puede opcionalmente adicionalmente comprender un grupo heteroátomo adicional seleccionado entre O, N y S(O)_m; donde m = 0, 1 ó 2.

10 X se selecciona entre el grupo constituido por halógeno, hidroxilo, alcoxi C₁₋₄, haloalquilo C₁₋₄, haloalcoxi C₁₋₄ y arilo C₅₋₁₀; y

X' se selecciona entre el grupo constituido por halógeno, hidroxilo, alquilo C₁₋₄, alcoxi C₁₋₄, haloalquilo C₁₋₄, haloalcoxi C₁₋₄ y arilo C₅₋₁₀;

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en la que R³, R⁴, R⁵ y R⁶ no son todos simultáneamente metilo no sustituido;

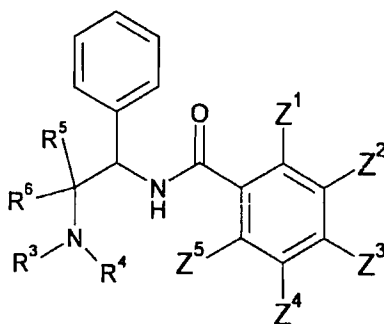
con la condición de que

- cuando simultáneamente Z1 es propilo, Z3 es cloro, Z2 = Z4 = Z5 = H,
20 y R5 y R6 son ambos metilo, entonces R³ y R⁴ junto con el átomo de nitrógeno al que están unidos no forman un grupo 2-metilpirrolidina;
- cuando simultáneamente Z1 es metilo, Z3 es metoxi, Z2 = Z4 = Z5 = H, y R5 y R6 son ambos metilo, entonces R³ y R⁴ junto con el átomo de nitrógeno al que están unidos no forman un grupo pirrolidina.

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2. Un compuesto según la reivindicación 1 que es un compuesto de fórmula (Ia) o una sal o solvato del mismo:



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(Ia)

en la que

Z^1 se selecciona entre el grupo constituido por alquilo C_{1-4} , alcoxi C_{1-2} , alquil C_{1-4} tio, haloalquilo C_{1-4} , y cloro;

Z^2 se selecciona entre el grupo constituido por hidrógeno, halógeno, haloalquilo C_{1-4} , y alquilo C_{1-4} ;

15 Z^3 se selecciona entre el grupo constituido por hidrógeno, halógeno, haloalquilo C_{1-4} y alquilo C_{1-4} ;

Z^4 se selecciona entre el grupo constituido por hidrógeno y halógeno;

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Z⁵ se selecciona entre el grupo constituido por bromo, alquilo C₁₋₄, alcoxi C₁₋₄ y haloalquilo C₁₋₄;

R³ y R⁴ son independientemente metilo o etilo no sustituido, o R³ y R⁴ junto con el átomo de nitrógeno al que están unidos forman un anillo carbocíclico saturado de 5- ó 6-miembros;

R⁵ y R⁶ son independientemente metilo o etilo, o R⁵ y R⁶ junto con el átomo de carbono al que están unidos forman un anillo carbocíclico saturado de 5- miembros;

y al menos uno de los pares de grupos R³ / R⁴ y R⁵ / R⁶ forma un grupo cíclico con el átomo de nitrógeno o carbono al que están unidos respectivamente.

3. Un compuesto según la reivindicación 1 ó reivindicación 2 que es cualquiera de los ejemplos 1 a 252 o una sal o solvato del mismo.

4. Un compuesto según una cualquiera de las reivindicaciones 1 a 3 para uso en terapia.

5. Un compuesto según la reivindicación 4 para uso en el tratamiento de un trastorno mediado por GlyT1.

6. Un compuesto según la reivindicación 4, en el que el trastorno es psicosis, incluyendo esquizofrenia, demencia o trastorno de déficit de atención.

7. Un procedimiento de tratamiento de un mamífero, incluyendo un ser humano, que sufre de o es susceptible a un trastorno mediado por GlyT1, que comprende la administración de una cantidad eficaz de un compuesto según la
5 reivindicación 4.

8. Un procedimiento según la reivindicación 7, en el que el trastorno es psicosis, incluyendo esquizofrenia, demencia o trastorno de déficit de atención.

10 9. Uso de un compuesto según la reivindicación 1 en la preparación de un medicamento para el tratamiento de un trastorno mediado por GlyT1.

10. Uso según la reivindicación 9, en el que el trastorno es psicosis, incluyendo esquizofrenia, demencia o trastorno de déficit de atención.

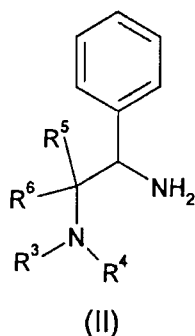
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11. Una composición farmacéutica que comprende un compuesto según la reivindicación 4, y al menos un vehículo, diluyente o excipiente farmacéuticamente aceptable.

20 12. Una composición farmacéutica según la reivindicación 11 que comprende además uno o más agentes terapéuticos distintos, seleccionados entre agentes antidepresivos seleccionados entre antagonistas de 5HT₃, agonistas de serotonina, antagonistas de NK-1, inhibidores selectivos de la recaptación de serotonina (SSRI), inhibidores de la recaptación de
25 noradrenalina (SNRI), antidepresivos tricíclicos, antidepresivos

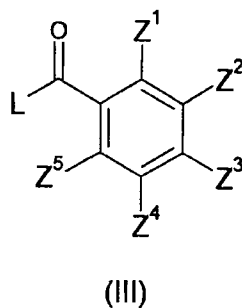
dopaminérgicos, antagonistas de H3, antagonistas de 5HT1A, antagonistas de 5HT1B, antagonistas de 5HT1D, agonistas de D1, agonistas de M1, agentes anticonvulsivos; fármacos antipsicóticos atípicos y potenciadores cognitivos

- 5 13. Un procedimiento de preparación de un compuesto como se ha definido en una cualquiera de las reivindicaciones 1 a 3, que comprende la etapa de: hacer reaccionar un compuesto de fórmula (II):



10

en la que R^3 , R^4 , R^5 y R^6 son como se han definido en la fórmula (I), con un compuesto de fórmula (III):



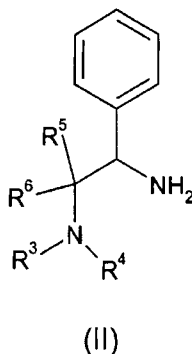
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en la que Z^1 , Z^2 , Z^3 , Z^4 y Z^5 son como se han definido en la fórmula (I) y L representa un grupo saliente adecuado;

y después opcionalmente:

- 5
- retirar cualesquiera grupos protectores y/o
 - convertir un compuesto de fórmula (I) en otro compuesto de fórmula (I) y/o
 - formar una sal o solvato.

14. Un compuesto de fórmula (II):



10

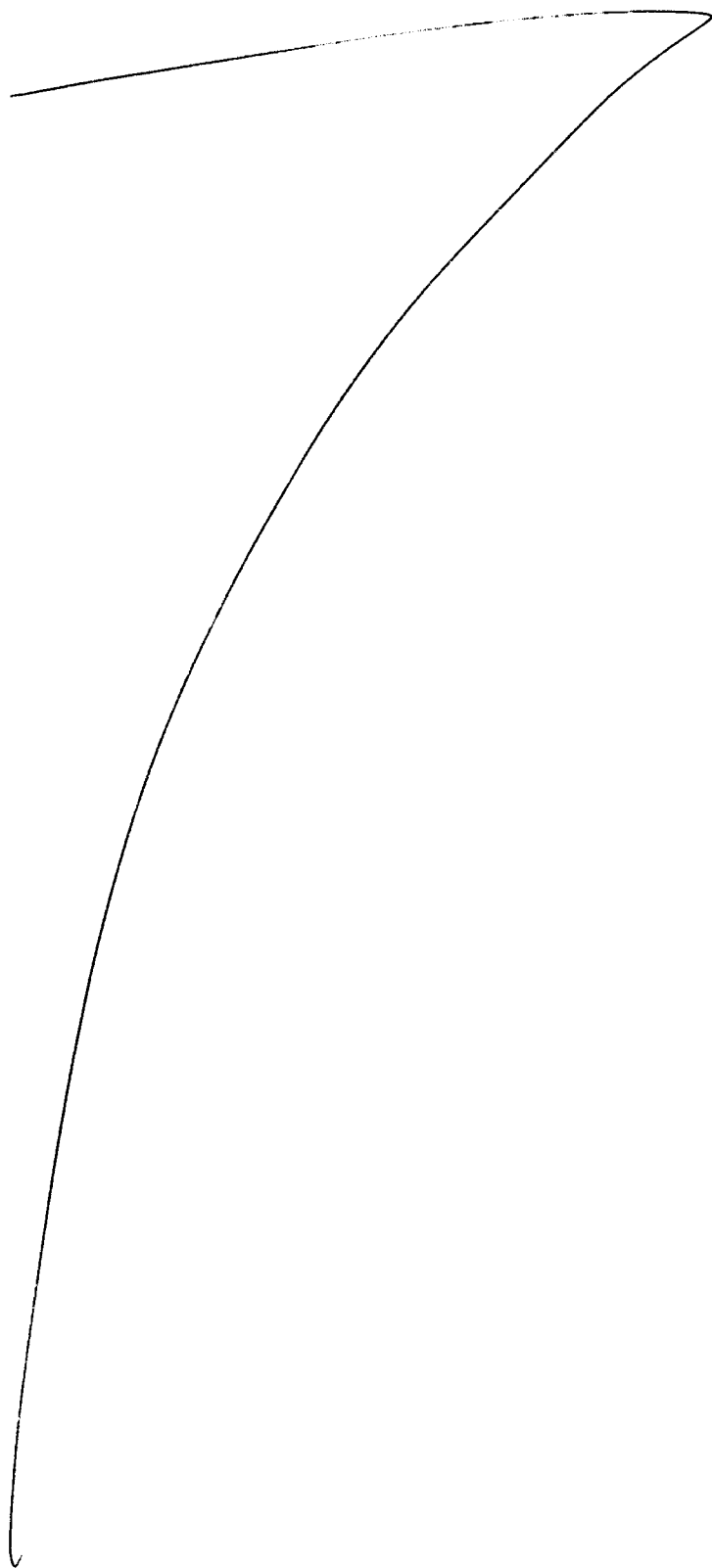
en la que R^2 , R^3 , R^4 , R^5 y R^6 son como se han definido en la fórmula (I) en una cualquiera de las reivindicaciones 1 a 3 en la que el compuesto (II) no es el

15

compuesto en el que simultáneamente R^3 y R^4 junto con el átomo de nitrógeno al que están unidos forman un anillo de piperidina no sustituido y R^5 y R^6 junto con el átomo de carbono al que están unidos forman un anillo ciclopentilo no sustituido.

p.: GLAXO GROUP LIMITED

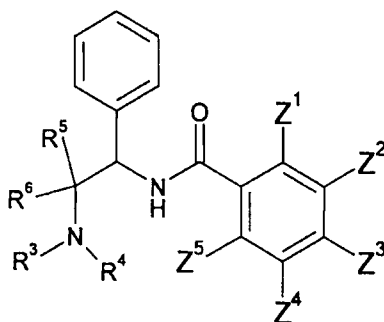
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RESUMEN

La presente invención se refiere a compuestos de fórmula (I), o a las sales o solvatos de los mismos, a su uso en la fabricación de medicamentos para tratar trastornos neurológicos y neuropsiquiátricos, en particular psicosis, demencia o trastorno de déficit de atención. La invención comprende adicionalmente procedimientos para preparar estos compuestos y las formulaciones farmacéuticas de los mismos.



(I)

PATENT COOPERATION TREATY

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From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

KONDO, Rienthony, Christopher
GlaxoSmithKline
Corporate Intellectual Property (CN)
980 Great West Road
Middlesex TW8 9GS
GRANDE BRETAGNE

GlaxoSmithKline Corporate IP	
Received BRENTFORD	
- 2 JAN 2007	
ATTY: <i>RQK</i>	ADMIN: <i>SM</i>
☒ PM : N/A ☐ ON ☐ UPDATED ON:	
ATTY CHECKED/FILE <i>RE</i> Date of mailing (day/month/year)	

PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL PRELIMINARY
REPORT ON PATENTABILITY

(PCT Rule 71.1)

15.12.2006

Applicant's or agent's file reference
PAB/PB61205

IMPORTANT NOTIFICATION

International application No.
PCT/GB2005/004951

International filing date (day/month/year)
21.12.2005

Priority date (day/month/year)
23.12.2004

Applicant
GLAXO GROUP LIMITED

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

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

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

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

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

Name and mailing address of the international
preliminary examining authority:



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

Authorized Officer

Oberhauser, Andrea

Tel. +49 89 2399-8139



PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

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Applicant's or agent's file reference PAB/PB61205		FOR FURTHER ACTION	See Form PCT/PEA/416
International application No. PCT/GB2005/004951	International filing date (day/month/year) 21.12.2005	Priority date (day/month/year) 23.12.2004	
International Patent Classification (IPC) or national classification and IPC INV. C07C233/78 A61K31/166 C07C211/36			
Applicant GLAXO GROUP LIMITED			
1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36. 2. This REPORT consists of a total of 6 sheets, including this cover sheet. 3. This report is also accompanied by ANNEXES, comprising: a. ☒ sent to the applicant and to the International Bureau a total of 1 sheets, as follows: ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions). ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box. b. ☐ (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).			
4. This report contains indications relating to the following items: ☒ Box No. I Basis of the report ☐ Box No. II Priority ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability ☐ Box No. IV Lack of unity of invention ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement ☐ Box No. VI Certain documents cited ☐ Box No. VII Certain defects in the international application ☐ Box No. VIII Certain observations on the international application			
Date of submission of the demand 01.08.2006		Date of completion of this report 15.12.2006	
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465		Authorized officer Bueno Torres, Pilar Telephone No. +49 89 2399-8290 	

**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/GB2005/004951

2A2

Box No. I Basis of the report

1. With regard to the **language**, this report is based on

- ☒ the international application in the language in which it was filed
- ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of:
- ☐ international search (under Rules 12.3(a) and 23.1(b))
 - ☐ publication of the international application (under Rule 12.4(a))
 - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-127 as originally filed

Claims, Numbers

1-12 as originally filed

13 received on 03.08.2006 with letter of 01.08.2006

- ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:

- ☐ the description, pages
- ☐ the claims, Nos.
- ☐ the drawings, sheets/figs
- ☐ the sequence listing (*specify*):
- ☐ any table(s) related to sequence listing (*specify*):

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

- ☐ the description, pages
- ☐ the claims, Nos.
- ☐ the drawings, sheets/figs
- ☐ the sequence listing (*specify*):
- ☐ any table(s) related to sequence listing (*specify*):

* If item 4 applies, some or all of these sheets may be marked "superseded."

**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No. 
PCT/GB2005/004951

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

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

☐ the entire international application,

☒ claims Nos. 3, 7-8

because:

☒ the said international application, or the said claims Nos. 7-8 relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 3 are so unclear that no meaningful opinion could be formed (*specify*):

see separate sheet

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed (*specify*).

☐ no international search report has been established for the said claims Nos.

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13ter.1(a) or (b) and 13ter.2.

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-bis of the Administrative Instructions, and such tables were not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.

☐ See separate sheet for further details

**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
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Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1, 2, 4-13
	No: Claims	
Inventive step (IS)	Yes: Claims	1,2, 4-13
	No: Claims	
Industrial applicability (IA)	Yes: Claims	1-2, 4-6, 9-13
	No: Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

**INTERNATIONAL PRELIMINARY
REPORT ON PATENTABILITY
(SEPARATE SHEET)**

International application No.

PCT/GB2005/004951

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Re Item III

- a) Claim 3 contains a reference to the description. According to Rule 6.2(a) PCT, claims should not contain such references except where absolutely necessary, which is not the case here.
- b) Claims 7 and 8 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

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

- a) Reference is made to the following documents:

D1: P.N. BECKER ET AL.: "A New Method for 1,2-Diamination of Alkenes Using Cyclopentadienylnitrosylcobalt Dimer/NO/LiAlH₄" J. AM. CHEM. SOC., vol. 102, 1980, pages 5676-5677, XP002374266

D2: A. VISO ET AL.: "Highly Diastereoselective [3+2]Cycloadditions between Nonracemic p-Tolylsulfinimines and Iminoesters: An Efficient Entry to Enantiopure Imidazolidines and Vicinal Diaminoalcohols" CHEM. EUR. J., vol. 9, 2003, pages 2867-2876, XP002374267

D3: WO 03/055478 A (SMITHKLINE BEECHAM P.L.C.) 10 July 2003 (2003-07-10)

D4: US-A-3 145 209 (KRAPCHO JOHN) 18 August 1964 (1964-08-18)

- b) D1-D2 and D4 disclose the intermediates of formula (II) (see the process of claim 13). The compounds of formula (I) have not been disclosed in D1-D4.

**INTERNATIONAL PRELIMINARY
REPORT ON PATENTABILITY
(SEPARATE SHEET)**

International application No.

PCT/GB2005/004951

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The subject-matter of claims 1, 2 and 4-13 is novel vis-à-vis D1-D4.

- c) The document D3 is regarded as being the closest prior art to the subject-matter of claim 1, and discloses compounds useful as glycine transport inhibitors.

The problem underlying the present application is considered to be the provision of further compounds useful as glycine transport inhibitors.

In the light of the data given on pages 16-17 of the description, it appears that said problem has been solved by the compounds encompassed within the definition of claim 1.

The compounds according to the present application are not regarded as close structural analogues of the compounds disclosed in D3, for which activity as glycine transport inhibitors could have been obviously expected.

The subject-matter of claims 1-2 and 4-13 of the present application meets therefore the criteria of Article 33(1) PCT, because it involves an inventive step in the sense of Article 33(3) PCT.

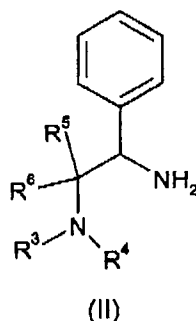
227

PB61205 PCT

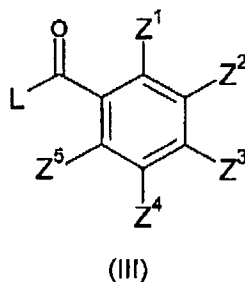
13. A method of preparing a compound as defined in any one of claims 1 to 3, comprising the step of:

reacting a compound of formula (II):

5



10 wherein R³, R⁴, R⁵ and R⁶ are as defined in formula (I) in any one of claims 1 to 3, with a compound of formula (III):



15 wherein Z¹, Z², Z³, Z⁴ and Z⁵ are as defined in formula (I) in any one of claims 1 to 3 and L represents a suitable leaving group;

and thereafter optionally:

- removing any protecting groups and/or
- 20 • converting a compound of formula (I) into another compound of formula (I) and/or
- forming a salt or solvate.



GlaxoSmithKline

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Corporate Intellectual Property

BY FACSIMILE AND AIRMAIL 00 31 70 340 3016

IPEA
European Patent Office
D-80298 Munchen
Germany

GlaxoSmithKline Services Unlimite
980 Great West Road
Brentford
Middlesex
TW8 9GS
Tel. +44 (0)20 8047 5000
www.gsk.com

1 August 2006

Our Ref. RQK/PB61205/WO

Direct tel +44 (0)20 8047 4429
Direct fax +44 (0)20 8047 6894
E-Mail Rie.q.kondo@gsk.com

Dear Sirs,

**Re: International Patent Application No. PCT/EP GB2005/004951
Glaxo Group Limited**

Further to the International Search Report and first written opinion dated 18 April 2006, the applicant hereby confirms that it considers the EPO to be the International Preliminary Examination Authority. Accordingly, enclosed herewith please find the PCT Demand for International Preliminary Examination (Form PCT/IPEA/401) together with a Fee sheet authorising deduction of the fee of EUR1724 from deposit account number 28050015. You are hereby authorised to deduct any deficiency from the same account.

The applicant would like to delete claim 14 from the present application. Please find enclosed a new page 132. Please delete page 133.

Please acknowledge receipt of this letter by returning the enclosed Form 1037.

Yours faithfully,

Rie Kondo
Authorised Representative

Enc. Form 1037
Demand and Fee Sheet

Registered in England & Wales
No. 1047315

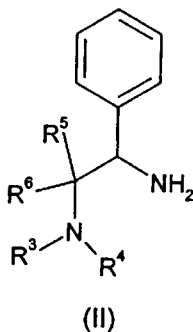
Registered office
980 Great West Road
Brentford, Middlesex TW8 9GS

349

13. A method of preparing a compound as defined in any one of claims 1 to 3, comprising the step of:

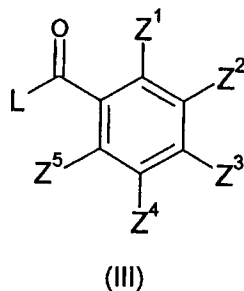
reacting a compound of formula (II):

5



wherein R^3 , R^4 , R^5 and R^6 are as defined in formula (I) in any one of claims 1 to 3,
with a compound of formula (III):

10



15 wherein Z^1 , Z^2 , Z^3 , Z^4 and Z^5 are as defined in formula (I) in any one of claims 1 to 3
and L represents a suitable leaving group;

and thereafter optionally:

- removing any protecting groups and/or
- 20 • converting a compound of formula (I) into another compound of formula (I) and/or
- forming a salt or solvate.

GR
Corporate IP
Received BRENTFORD
27 MAR 2006
ATTY: PAB/PB61205
ADMIN: PCT
ON: UPDATED ON:
ATTY: NOTIFICATION OF THE RECORDING
OF A CHANGE

PCT/GB2005/004951

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

To:

CONNELL, Anthony, Christopher
GlaxoSmithKline
Corporate Intellectual Property
(CN925.1)
980 Great West Road
Brentford
Middlesex TW8 9GS
United Kingdom

(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

Date of mailing (day/month/year) 09 March 2006 (09.03.2006)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference PAB/PB61205	
International application No. PCT/GB2005/004951	International filing date (day/month/year) 21 December 2005 (21.12.2005)

1. The following indications appeared on record concerning:

☒ the applicant ☒ the inventor ☐ the agent ☐ the common representative

Name and Address

MACRITCHIE, Jacqueline, Anne
Biofus Discovery Ltd
Chesterford Research Park
Saffron Walden
Essex CB10 1XL
United Kingdom

State of Nationality
GB

State of Residence
GB

Telephone No.

Facsimile No.

Teleprinter No.

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☐ the name ☒ the address ☐ the nationality ☐ the residence

Name and Address

MACRITCHIE, Jacqueline, Anne
Biofocus Discovery Ltd
Chesterfield Research Park
Saffron Walden
Essex CB10 1XL
United Kingdom

State of Nationality
GB

State of Residence
GB

Telephone No.

Facsimile No.

Teleprinter No.

3. Further observations, if necessary:
Correction of indications.

RECEIVED STEVENAGE

4. A copy of this notification has been sent to:

☒ the receiving Office ☐ the designated Offices concerned
☒ the International Searching Authority ☐ the elected Offices concerned
☐ the International Preliminary Examining Authority ☐ other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. (41-22) 338.89.65	Authorized officer James VANNIER Telephone No. (41-22) 338 8454
--	---

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference PAB/PB61205	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. PCT/GB2005/004951	International filing date (day/month/year) 21/12/2005	(Earliest) Priority Date (day/month/year) 23/12/2004
Applicant GLAXO GROUP LIMITED		

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

This International search report consists of a total of 5 sheets.

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

1. Basis of the report

a. With regard to the **language**, the international search was carried out on the basis of:

- ☒ the international application in the language in which it was filed
☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))

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

2. ☒ **Certain claims were found unsearchable** (See Box No. II)

3. ☐ **Unity of invention is lacking** (see Box No. III)

4. With regard to the **title**,

- ☐ the text is approved as submitted by the applicant
☒ the text has been established by this Authority to read as follows:

GLYCINE TRANSPORT INHIBITORS

5. With regard to the **abstract**,

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

6. With regard to the **drawings**,

- a. the figure of the **drawings** to be published with the abstract is Figure No. _____
☐ as suggested by the applicant
☐ as selected by this Authority, because the applicant failed to suggest a figure
☐ as selected by this Authority, because this figure better characterizes the invention
b. ☐ none of the figures is to be published with the abstract

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2005/004951

A. CLASSIFICATION OF SUBJECT MATTER

C07C233/78 A61K31/166 C07C211/36

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07C C07D A61K

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

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

EPO-Internal, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	P.N. BECKER ET AL.: "A New Method for 1,2-Diamination of Alkenes Using Cyclopentadienylnitrosylcobalt Dimer/NO/LiAlH ₄ " J. AM. CHEM. SOC., vol. 102, 1980, pages 5676-5677, XP002374266 Table I, third entry (2-methyl-1-phenylpropane-1,2-diamine) ----- -/--	14

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

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

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

Date of the actual completion of the international search

28 March 2006

Date of mailing of the international search report

18/04/2006

Name and mailing address of the ISA/

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

Authorized officer

Bueno Torres, M

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2005/004951

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	A. VISO ET AL.: "Highly Diastereoselective [3+2]Cycloadditions between Nonracemic p-Tolylsulfonimides and Iminoesters: An Efficient Entry to Enantiopure Imidazolidines and Vicinal Diaminoalcohols" CHEM. EUR. J., vol. 9, 2003, pages 2867-2876, XP002374267 Compound 18a -----	14
A	WO 03/055478 A (SMITHKLINE BEECHAM P.L.C.) 10 July 2003 (2003-07-10) cited in the application the whole document -----	1-14
X	US 3 145 209 A (KRAPCHO JOHN) 18 August 1964 (1964-08-18) Claims 1, 2, 6, examples 1, 2, example 5, example 6, example 16, ex 18, ex 24 -----	14

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB2005/004951

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Box II Observations where certain claims were found unsearchable (Continuation of Item 2 of first sheet)

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

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 7 and 8 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of Item 3 of first sheet)

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

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/GB2005/004951

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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WO 03055478	A	10-07-2003	AU 2002352483 A1	15-07-2003
			EP 1455777 A1	15-09-2004
			JP 2005519048 T	30-06-2005
			US 2005267152 A1	01-12-2005

US 3145209	A	18-08-1964	NONE
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PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

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To:

see form PCT/ISA/220

PCT

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

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

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/GB2005/004951

International filing date (day/month/year)
21.12.2005

Priority date (day/month/year)
23.12.2004

International Patent Classification (IPC) or both national classification and IPC
INV. C07C233/78 A61K31/166 C07C211/36

Applicant
GLAXO GROUP LIMITED

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

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

2. **FURTHER ACTION**

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

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

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

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

Name and mailing address of the ISA:



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

Authorized Officer

Bueno Torres, M

Telephone No. +49 89 2399-8290



**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No. 
PCT/GB2005/004951

Box No. I Basis of the opinion

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

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/GB2005/004951

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

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

- ☐ the entire international application,
- ☒ claims Nos. 3, 7-8

because:

- ☒ the said international application, or the said claims Nos. 7-8 relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

- ☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 3 are so unclear that no meaningful opinion could be formed (*specify*):

see separate sheet

- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☐ no international search report has been established for the whole application or for said claims Nos.
- ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:
 - the written form ☐ has not been furnished
 - ☐ does not comply with the standard
 - the computer readable form ☐ has not been furnished
 - ☐ does not comply with the standard
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.
- ☐ See separate sheet for further details

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/GB2005/004951

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Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1, 2, 4-13
	No: Claims	14
Inventive step (IS)	Yes: Claims	1,2, 4-13
	No: Claims	
Industrial applicability (IA)	Yes: Claims	1-6, 9-14
	No: Claims	

2. Citations and explanations

see separate sheet

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No. 360

PCT/GB2005/004951

Re Item III

- a) Claim 3 contains a reference to the description. According to Rule 6.2(a) PCT, claims should not contain such references except where absolutely necessary, which is not the case here.
- b) Claims 7 and 8 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

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

- a) Reference is made to the following documents:
 - D1: P.N. BECKER ET AL.: "A New Method for 1,2-Diamination of Alkenes Using Cyclopentadienylnitrosylcobalt Dimer/NO/LiAlH₄" J. AM. CHEM. SOC., vol. 102, 1980, pages 5676-5677, XP002374266
 - D2: A. VISO ET AL.: "Highly Diastereoselective [3+2]Cycloadditions between Nonracemic p-Tolylsulfinimines and Iminoesters: An Efficient Entry to Enantiopure Imidazolidines and Vicinal Diaminoalcohols" CHEM. EUR. J., vol. 9, 2003, pages 2867-2876, XP002374267
 - D3: WO 03/055478 A (SMITHKLINE BEECHAM P.L.C.) 10 July 2003 (2003-07-10)
 - D4: US-A-3 145 209 (KRAPCHO JOHN) 18 August 1964 (1964-08-18)
- b) The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 14 is not new in the sense of Article 33(2) PCT vis-à-vis D1,

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

361
International application No.

PCT/GB2005/004951

D2 and D4 (see the references indicated in the search report).

The subject-matter of claims 1, 2 and 4-13 is novel vis-à-vis D1-D4.

- c) The document D3 is regarded as being the closest prior art to the subject-matter of claim 1, and discloses compounds useful as glycine transport inhibitors.

The problem underlying the present application is considered to be the provision of further compounds useful as glycine transport inhibitors.

In the light of the data given on pages 16-17 of the description, it appears that said problem has been solved by the compounds encompassed within the definition of claim 1.

The compounds according to the present application are not regarded as close structural analogues of the compounds disclosed in D3, for which activity as glycine transport inhibitors could have been obviously expected.

The subject-matter of claims 1-2 and 4-13 of the present application meets therefore the criteria of Article 33(1) PCT, because it involves an inventive step in the sense of Article 33(3) PCT.

362



No. 07-062883- -00000-0000

Fecha: 2007-06-21 16:38:20 Dep. 2020 NUECREACIONES
Tra. 11 PATENTE/II Lve: 379 FASENACIONAL/II
Act 411 PRESENTACION Folios: 361

REQUISITOS MINIMOS PARA ADMISION A TRAMITE
PCT

PATENTE DE INVENCION

☒

MODELO DE UTILIDAD ☐

- ◆ Indicación de que se solicita la concesión de una patente ☒
- ◆ Datos de identificación del solicitante o de la persona que presenta la solicitud ☒
- ◆ Descripción de la invención ☒
- ◆ Dibujos de ser estos pertinentes ☒
- ◆ Comprobante de pago de las tasas establecidas ☒

COMPLETA ☒

INCOMPLETA ☐

DISEÑO INDUSTRIAL ☐

- ◆ Indicación de que se solicita el registro de Diseño Industrial ☐
- ◆ Datos de identificación del solicitante o de la persona que presenta la solicitud ☐
- ◆ Representación gráfica y fotográfica del Diseño Industrial o muestra del material que incorpora el diseño ☐
- ◆ Comprobante de pago de las tasas establecidas ☐

COMPLETA ☐

INCOMPLETA ☐

ESQUEMA DE TRAZADO ☐

- ◆ Indicación de que se solicita el registro de un Esquema de Trazado ☐
- ◆ Datos de identificación del solicitante o de la persona que presenta la solicitud ☐
- ◆ Representación gráfica del esquema trazado ☐
- ◆ Comprobante de pago de las tasas establecidas ☐

COMPLETA ☐

INCOMPLETA ☐

J J 13
Firma Responsable

Fecha 21 JUN 7

Carrera 13 No. 27-00 Piso 5, 7 y 10
Conmutador: 3 82 08 40
Fax: 350 52 20
E-mail: info@sic.gov.co
www.sic.gov.co
Bogotá, D.C., Colombia