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# PETITORIO

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SUPERINDUSTRIA Y COMERCIO
Radicacion : 03008184 00000000 Folios: 219
Fecha (AMD): 2003-02-04 17:13:59 cación
Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

Industria y Comercio
SUPERINTENDENCIA

## FORMULARIO ÚNICO DE SOLICITUD DE PATENTE
## PCT
## ENTRADA EN FASE NACIONAL

001

**① SOLICITUD DE :**

| | | | |
|---|---|---|---|
| [X] | Patente de Invención | [ ] | Patente de Modelo de Utilidad |
| [ ] | Capítulo I | [X] | Capítulo II |

**② SOLICITANTE (71)**

Nombre PFIZER INC

Dirección 235 East 42nd Street, New York, NewYork 10017, Estados Unidos de América.

Nacionalidad o Domicilio ESTADOUNIDENSE

Lugar de Constitución New York, Estados Unidos de América.

Teléfono Fax

E-Mail

IDENTIFICACION

C C [ ] NIT [ ]

C E [ ] Otro [ ]

Cual

Número

**③ REPRESENTANTE O APODERADO**

Nombre CARLOS R. OLARTE

Dirección Avda 82 No 10-62 Piso 6

Teléfono 634-1500 Fax 376-2211

E-Mail patents bogota@bakernet com

IDENTIFICACION

C C [X] NIT [ ]

C E [ ] Otro [ ]

Cual

Número 79 782 747 Btá TP 74.295

**④ INVENTOR (ES) (72)**

Nombre 1 MAVIS DIANE ADAM, 2 MARK LEONARD ELLIOTT, 3 HARRY RALPH HOWARD Jr , 4 MARK DAVID ANDREWS, 5 GEOFFREY EDWARD GYMER, 6 DAVID HEPWORTH, 7 DONALD STUART MIDDLETON, 8 ALAN STOBIE

Dirección 1, 2, 3 Eastern Point Road, Groton, Connecticut 06340, Estados Unidos de América.
4, 5, 6, 7, 8 Ramsgate Road, Sandwich, Kent, CT13 9NJ, Reino Unido

Nacionalidad o Domicilio 1, 2, 3, ESTADOUNIDENSE, 4, 5, 6, 7, 8, BRITANICA

ok

**⑤ PCT (85)**

Solicitud Internacional No PCT/IB01/01521 Fecha Agosto 22, 2001

Publicación Internacional No WO 02/18333 Fecha Marzo 7, 2002

**⑥ Título (54)** DERIVADOS DE FENOXIBENCILAMINA COMO SSRI

**⑦ Clasificación Internacional (51)** C07C323/20 // A61K31/18, 31/38

**⑧ Prioridad**

SI [X] NO [ ]

| (33) País de Origen | (32) Fecha | (31) Número de Solicitud |
|---|---|---|
| UK | Agosto 31, 2000 | 0021593 9 |
| UK | Marzo 21, 2001 | 0107116 6 |
| | | |

**⑨ Comprobante de pago No** 66538, 66539, 67397 **Fecha** 25-10-00, 23-10-01

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

## (10) ANEXOS

- [X] 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
- [X] Poderes, *si fuere el caso*
- [X] Documento de cesión del inventor al solicitante o a su causante 902
- [ ] Declaraciones
- [X] Copia de la solicitud internacional (Resumen, descripción, reivindicaciones, dibujos)
- [X] *Traducción de la solicitud internacional al castellano (Resumen, descripción, reivindicaciones, dibujos)*
- [X] Copia del examen preliminar 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
- [X] Otros Búsqueda Internacional

## (11) FIGURA CARATERISTICA

## (12) Solicito la concesión de la patente,

NOMBRE CARLOS R OLARTE

FIRMA

C C 79 782 747 de Bta T P 74295

*Instrucciones para la presentación de los anexos, ver reverso de esta página*

3

**Industria y Comercio**

SUPERINTENDENCIA

SUPERINDUSTRIA Y COMERCIO
Radicacion : 03008184 00000000 Folios: 219
Fecha (AMD): 2003-02-04 17:13:59
Tramite : 011 PCT-PATENT 379 FASE NAC1 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 66.538
FECHA : OCTUBRE 25 DE 2000

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

| DEPOSITANTE | TIPO PAGO | BANCO | SUCURSAL | CUENTA | No. PAGO | Vr. PAGO |
|---|---|---|---|---|---|---|
| INDUSTRIAS ALIMENTICIAS NCONSIGNACION | | BANCO POPULAR | BOGOTA | 050-00024-9 | 544522 | 176.000.00 |

***** C O N C E P T O *****

| CANT. | RENTISTICO | CONCEPTO | | TOTAL CONCEPTO |
|---|---|---|---|---|
| 1 | 50005-01-04 PRESENTACION DE OBSERVACIONES | 12 | MARCAS Y LEMAS COMERCIALES | 176.000.00 |
| | | | TOTAL : $ | 176.000.00 |

SON: CIENTO SETENTA Y SEIS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

Carrera 13 No. 27-00 Pisos 5 y 10
Conmutador 334 12 21
Fax: 281 31 25
e-mail: info@sic.gov.co
Santa Fe de Bogotá, D.C., Colombia

SUPERINDUSTRIA Y COMERCIO
Radicacion : 03008184 00000000 Folios: 219
Fecha (AMD): 2003-02-04 17:13:59
NIT : 800176089 Tramite : 011 PCT-PATENT 379 PAGE MACI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

RECIBO OFICIAL DE CAJA : 66.539
FECHA : OCTUBRE 25 DE 2000

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

| DEPOSITANTE | TIPO PAGO | BANCO | SUCURSAL | CUENTA | No. PAGO | Vr. PAGO |
|---|---|---|---|---|---|---|
| INDUSTRIAS ALIMENTICIAS NCONSIGNACION | | BANCO POPULAR | BOGOTA | 050-00024-9 | 544511 | 176.000.00 |
| INDUSTRIAS ALIMENTICIAS NCONSIGNACION | | BANCO POPULAR | BOGOTA | 050-00024-9 | 544524 | 352.000.00 |

##### C O N C E P T O #####

| CANT. | RENTISTICO | CONCEPTO | | TOTAL CONCEPTO |
|---|---|---|---|---|
| 1 | 50005-01-04 PRESENTACION DE OBSERVACIONES | 12 | MARCAS Y LEMAS COMERCIALES | 176.000.00 |
| | | | TOTAL : $ | 176.000.00 |

SON: CIENTO SETENTA Y SEIS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

Carrera 13 No. 27-00 Pisos 5 y 10
Conmutador 334 12 21
Fax: 281 31 25
e-mail: info@sic.gov.co
Santa Fe de Bogotá, D.C., Colombia

RC 5

**Industria y Comercio**

SUPERINTENDENCIA

NIT : 800176089-2

SUPERINDUSTRIA Y COMERCIO

RECIBO OFICIAL DE CAJA : 01 - 67,397 Radicacion : 03000184 00000000 Folios: 219

FECHA : OCTUBRE 23 DE 2001 Fecha (AMD): 2003-02-04 17:13:59

Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC

Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

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

| DEPOSITANTE | TIPO PAGO | BANCO | CUENTA | No. PAGO | FECHA PGO | Vr. PAGO |
|---|---|---|---|---|---|---|
| JORGE LUIS GOMEZ | CONSIGNACION | BANCO POPULAR | 050-00110-6 | 5568713 | 23/10/2001 | 18,004,400.00 |

***** C O N C E P T O *****

| CANT. | RENTISTICO | CONCEPTO | TOTAL CONCEPTO |
|---|---|---|---|
| 1 | 50003-01-01 SOLICITUDES | 83 INVOCACION DE UNA PRIORIDAD EN SI | 50.000.00 |
| | | TOTAL : $ | 50,000.00 |

SON: CINCUENTA MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

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

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

007

**PODER DE PFIZER INC.**

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**CONSULADO DE COLOMBIA EN LONDRES**

Fechado el 22 enero, 2001 certifica que Kenneth Greenwood, ejerce funciones de notario de Egham, Surrey Inglaterra, cuya firma fue reconocida por J.M.A. Mason, de Legalizaciones del Ministerio de Relaciones de Gran Bretaña; Que J. Trevor Lumb es el asesor de patentes de Pfizer Inc. sociedad establecida en Nueva York, Estados Unidos. Firma del cónsul: Jairo Berrio.

**CERTIFICACION NOTARIAL**

El 8 de enero del 2001 el Notario Público da fe:

1.compareció J. Trevor Lumb, domiciliado en Estados Unidos, quien suscribió el anterior documento. 2. Conozco al otorgante y tiene capacidad para el otorgamiento 3. ha suscrito el documento en su carácter de Asesor General Asesor de Patentes de Pfizer Inc, con sede en Nueva York, NY, 4. compañía legalmente constituida, con existencia legal actual y que el acto para el cual se otorgó el poder está dentro del objeto social. 5. El otorgante tiene la representación que ostenta y es legítima. 6. Baso las certificaciones 3, 4 y 5 en estos documentos.

Sello·

Certificado, verificado y autenticado en la localidad de Egham en Surrey el 8 enero, 2001, Kenneth Greenwood - Notario Público - Horne Engall & Freedam- sello notarial en alto relieve.

Al reverso:

Reino Unido de Gran Bretaña e Irlanda del Norte

No. D653465 - Fecha: 8 enero, 2001

Este documento lleva la firma/sello de K. Greenwood funciones de Notario Público, firmado por J.M.A. Mason.

Por el Secretario de Estado Principal de su Majestad para Asuntos exteriores y de la Mancomunidad. Sello redondo: Londres.

COMO NOTARIO DEL CIRCULO DE BOGOTA
FOTOCOPIA FIEL DEL ORIGINAL
04 FEB 2001
BOGOTA, D.C. - COLOMBIA
TERESA NAVARRO DE BAUTISTA
NOTARIA ENCARGADO

MARLEN NEIRA CASTRO
Traductor e Intérprete Oficial
Inglés Español - Inglés
Resolución No 2117 del 7 Oct 1987

7
083

## PODER DE REPRESENTACIÓN

Poder de representación otorgado por PFIZER INC.,compañía domiciliada en el número 235 Este Calle 42 Nueva York, Estado de Nueva York, Estados Unidos, a Carlos Reinaldo Olarte.

Dado y firmado en Nueva York, el 2 de enero de 2001 por:

Trevor Lumb

Asesor General Consejero Patentes.

---

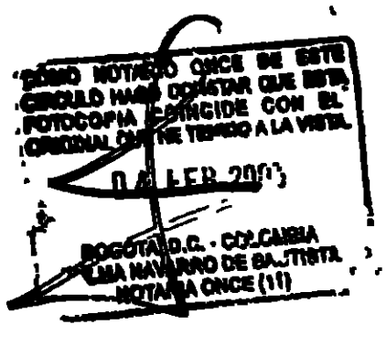
Sello en español:

Ministerio de Relaciones Exteriores No.407609_ certifica las funciones del J. Berrio a la fecha. Bogotá, febrero 2, 2001. Firma el Jefe de Legalizaciones.

--

Traducción certificada, con copia en archivo para confrontación, fechada el 6- 2-2001.

MARLEN NEIRA CASTRO
Traductor e Intérprete Oficial
Inglés - Español - Inglés
Resolución No 2117 del 7 Oct 1987



**CONSULADO GENERAL DE COLOMBIA**

3RD FLOOR 18-19 GREAT TITCHFIELD STREET LONDON W1W 8HZ
TELEPHONE 020 7637 9893 TELEFAX. 020 7637 5604
E-MAIL.CONSULCO@CONSULCO DEMON CO UK

8

001

El suscrito Cónsul General de Colombia en Londres, vistos los documentos presentados ante este despacho,

**CERTIFICA:**

Que el Señor **KENNETH GREENWOOD**, quien autenticó el documento precedente, ejercía en la fecha las funciones de Notario Público de Egham, Surrey, Inglaterra, y que su firma fue debidamente reconocida por **J. M. A. MASON**, Funcionario del Departamento de Legalizaciones del Ministerio de Relaciones de la Gran Bretaña, cuya firma se encuentra registrada en este Consulado General.

Que **PFIZER INC.** es una Sociedad debidamente constituída, organizada y existente en New York, N Y , Estados Unidos de América, y que cumple con su objeto social de acuerdo con las leyes de ese país

Que el Señor **J. TREVOR LUMB**, en su calidad de Asesor de Patentes Generales de la mencionada Sociedad, otorga el Poder precedente y su firma ha sido autenticada por el Notario **KENNETH GREENWOOD**

El Cónsul General no asume responsabilidad por el mencionado documento

Dado en Londres, Reino Unido de la Gran Bretaña, a los veintidos (22) días del mes de enero del año dos mil uno (2001).

Certificación No 01/0181
Derechos: US$106.00, CANCELADOS.

**JAIRO E. BERRIO VILLARREAL**
**Cónsul General**

COMO NOTARIO ONCE DE ESTE CIRCULO PUDO CONSTAR QUE ESTA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA.

04 FEB 2003

BOGOTA, D.C. - COLOMBIA
ELMA NAVARRO DE BAUTISTA
NOTARIA ONCE (11)

MINISTERIO DE RELACIONES EXTERIORES

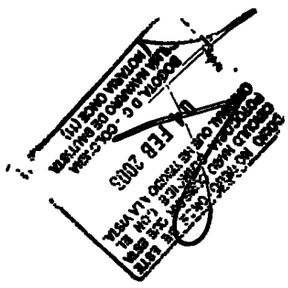
407609

CUYA FIRMA APARECE EN EL DOCUMENTO DESEMPEÑA LAS FUNCIONES INDICADAS

NO SE ASUME RESPONSABILIDAD DEL TEXTO

2001 FEB -2 P 3:11

JEFE DE LEGALIZACIONES SANTAFE DE BOGOTA D C



RAISBECK, LARA, RODRIGUEZ & RUEDA
Members of the Firm
BAKER & McKENZIE
ATTORNEYS AT LAW
APARTADO AEREO 3748
TELEFONO 288-1488
SANTAFE DE BOGOTA, D C
COLOMBIA

9

011

# NOTARIAL CERTIFICATION

On this 8th day of January 19. 2001, the undersigned Notary

**CERTIFIES**

1 That J. Trevor Lumb

of legal age and domiciled in U.S.A.

set his hand on the foregoing document.

2. That the grantor is to me personally known and that he/she has legal capacity to execute the instrument.

3. That the grantor has executed the foregoing document as

Assistant General Patent Counsel

of the juridical person

Pfizer Inc

4. That the juridical person

Pfizer Inc

having its home office in

New York, NY.

is duly organized, has present legal existence and that the purposes for which the power of attorney is granted are within the scope of its corporate purposes

5. That the grantor has in fact he referred to authority and that his/her representation is legal

6. That I have based certifications 3, 4 and 5 above on the following authentic documents for such purpose exhibited to me and which I mention specifically, giving their dates and their origin or antecedent

Certified Verified And Attested
In The Town Of Egham In Surrey
This 8th Day Of January 2001
KENNETH GREENWOOD
NOTARY PUBLIC
HORNE ENGALL AND FREEMAN
Notary Public

# CERTIFICACION NOTARIAL

A los días del mes de de 19, el suscrito Notario

**DA FE**

1 Que

mayor y domiciliado en

suscribio de su puño y letra el documento que antecede.

2. Que conozco al otorgante y que éste tiene capacidad legal para el otorgamiento.

3. Que el otorgante ha suscrito el referido documento en su carácter de

de la persona jurídica

4 Que la persona jurídica

con sede en

está legalmente constituida, que [illegible] legal actual y que el acto para el cual se ha otorgado el poder está comprendido entre los que constituyen su objeto social

5. Que el otorgante tiene efectivamente la representación que ostenta, y que esta es legítima

6. Que he basado las certificaciones 3, 4 y 5 anteriores en los siguientes documentos auténticos que al efecto se me exhibieron y que menciono especificamente con expresión de sus fechas y de su origen o procedencia

04 FEB 2003

El Notario Público

**UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND**

No **D653465**

Date **8 January, 2001**

This document bears
the signature / seal of **K Greenwood**

Acting in the capacity of **Notary Public**

Signed by **J. M. A. Mason**

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

RAISBECK, LARA, RODRIGUEZ & RUEDA
Members of the Firm
BAKER & McKENZIE
ATTORNEYS AT LAW
APARTADO AEREO 3748
TELEFONO 285-1466
SANTAFE DE BOGOTA, D C
COLOMBIA

014 10

# POWER OF ATTORNEY

The undersigned

**PFIZER INC.**

located in
235 East 42nd Street, New York
Estado de New York, Estados Unidos de América
declares that it hereby grants to

**CARLOS R. OLARTE**

a full and sufficient power of attorney to apply to the proper national officers and authorities for the issue of

**Letters Patent, mergers,changes of name, assignments, filing and prosecution of oppositions, changes of address**

to which end it empowers them to take all steps necessary before said authorities for the objects stated, to file petitions, prepare descriptions, make protests, declarations, appeals and objections, pay imposts, apply for certifications, receive documents and securities, abandon applications and collect refunds To the said mandatories sufficient power is granted hereby to receive notifications for and 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 patents, and to do everything that may be required, before administrative or judicial officers of any class giving them likewise power to substitute these presents and revoke such substitutions if necessary

Done and subscribed in New York, New York, United States of America.

On the 2nd day of January 2001

J. Trevor Lumb
Assistant General Patent Counsel

# PODER

La abajo firmada

**PFIZER INC.**

domiciliada en
235 East 42nd Street, New York
Estado de New York, Estados Unidos de América
declara por el presente otorgar a

**CARLOS R. OLARTE**

poder especial amplio y bastante para recabar de las oficinas y autoridades nacionales que correspondan, la obtención de

Solicitudes de Patentes de Invención, cambios de nombre, cesiones, presentación y tramitación de oposiciones, cambios de nombre

a cuyo efecto los faculta para dar ante dichas autoridades, todos los pasos necesarios al objeto indicado, elevar solicitudes, formular descripciones , protestas, declaraciones, apelaciones y reclamos, obiar impuestos, solicitar testimonios, recibir documentos y valores, desistir y percibir Se concede a los expresados mandatarios 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 las patentes se presentaren y hacer cuanto fuere necesario, ante las autoridades administrativas o judiciales de cualquier orden, dándoles asimismo facultad para sustituir el presente y en caso necesario revocar dichas sustituciones

Dado y firmado en

A los días del

19

COMO NOTARIO DEL CIRCULO HAGO CONSTAR QUE ESTA FOTOCOPIA CONCUERDA CON EL ORIGINAL QUE HE TENIDO A LA VISTA.
04 FEB 2002
BOGOTA, D.C. - COLOMBIA
LILIANA NAVARRO DE BAUTISTA
NOTARIA ONCE (11)

4203

11

913

**Traducción Oficial No 03-056**

Efectuada el día 1 de febrero de 2003, de un documento escrito en Inglés, al cual para su identificación se le estampa el sello de María del Pilar Iglesias, Traductora e Intérprete Oficial por Resolución No 819 del 15 de abril de 1971 expedida por el Ministerio de Justicia de la República de Colombia.

---

**CESIÓN**

**PCS10945ARCS CO-1**

Por contraprestación onerosa pagada a nosotros por **PFIZER LIMITED**, sociedad organizada y existente conforme a las leyes de Inglaterra, domiciliada en el Ramsgate Road, Sándwich, Kent, CT13 9NJ, Reino Unido, por el presente vendemos y cedemos a la mencionada **PFIZER LIMITED**, todo nuestro derecho, título e interés en nuestro invento para una nueva y útil Mejora en **DERIVADOS DE FENOXIBENZILAMINA COMO SSRIs** en cuanto respecta a la República de Colombia, tan ampliamente como se describe en las especificaciones y por el presente autorizamos y solicitamos al Comisario de Patentes de Colombia que expida dicha patente a **PFIZER LIMITED** de conformidad con esta Cesión.

En fe de lo cual firmamos de nuestro puño y letra así:

M. P. Iglesias

María del Pilar Iglesias
TRADUCTORA E
INTÉRPRETE OFICIAL

(Fdo) Mavis Diane ADAM, el 17 de Julio de 2001 en East Lyme, Connecticut, Estados Unidos de América.

(Fdo) Leonard Mark ELLIOT, el 9 de julio de 2001 en Grotton, Connecticut, Estados Unidos de América

(Fdo) Harry Ralph Howard Jr., el 9 de julio de 2001 en Grotton, Connecticut, Estados Unidos de América

Certificado, Verificado y Autenticado en la ciudad de Egham en Surrey a los 23 días del mes de agosto de 2001.

(Fdo) Kenneth Greenwood, Notario Público (Sello Oficial)

**APOSTILLA**

**(Convención de La Haya del 5 de octubre de 1961)**

1. País: Reino Unido de Gran Bretaña e Irlanda del Norte
   El presente documento público
2 Fue firmado por K. Greenwood
3. Que actuó en su calidad de Notario Público
4. Lleva el sello del mencionado Notario Público
   Se certificó
5. En Londres 6. El 2 de agosto de 2001
7 Por parte del Principal Secretario de Estado de Su Majestad para Asuntos Extranjeros y de la Mancomunidad.

8. Bajo el Número **G924207**

9 Sello de la Oficina de Asuntos Extranjeros y de la Mancomunidad

10. Firmado por A. Beckwith, Secretario de Estado

Es traducción fiel y completa efectuada por

María del Pilar Iglesias
C C.41.339.183 de Bogotá

María del Pilar Iglesias
C.C. [illegible] de Bogotá
Intérprete Oficial según Resolución No 815 de
15 de Abril de 1971 del Ministerio de Justicia

PC810945ARCS

CO-1

# ASSIGNMENT

For valuable consideration paid to me (us) by **PFIZER LIMITED** a corporation organized under the laws of England whose full post office address is **Ramsgate Road, Sandwich, Kent, CT13 9NJ, United Kingdom,** I (we) do hereby sell and assign to the said **PFIZER LIMITED,** all my (our) right, title and interest in and to my (our) invention for a new and useful Improvement in **PHENOXYBENZYLAMINE DERIVATIVES AS SSRIs** so far as the Republic of Colombia is concerned, as fully set forth and described in the specification, and I (we) do hereby authorize and request the Commissioner of Patents of Colombia to issue said patent to the said **PFIZER LIMITED** in accordance with this assignment

In witness whereof I (we) have hereunto set my (our) hand(s) this

Mavis Diane Adam 17 July 2001 East Lyme, Connecticut, USA
Place, date and signature - Mavis Diane ADAM

Sandwich, Kent, England July 2001 - Mark David ANDREWS

Mark Leonard Elliott 09 July 2001 Groton, Connecticut, USA
Place, date and signature - Mark Leonard ELLIOTT

Sandwich, Kent, England July 2001 - Geoffrey Edward GYMER

Sandwich, Kent, England July 2001 - David HEPWORTH

Harry Ralph Howard Jr 09 July 2001 Groton, Connecticut, USA
Place, date and signature - Harry Ralph HOWARD Jr

Sandwich, Kent, England July 2001 - Donald Stuart MIDDLETON

Sandwich, Kent, England July 2001 - Alan STOBIE

[illegible] was Authenticated
In The Town Of Egham In Surrey
This 2nd Day Of August 2001

KENNETH GREENWOOD
NOTARY PUBLIC
HORNE ENGALL AND FREEMAN

5573

15

**APOSTILLE**

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

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 **K Greenwood**
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

Certified/Attesté

5 at London/à Londres 6 the/le **02 August 2001**

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 **G924207**

9 Stamp / timbre

FOREIGN AND COMMONWEALTH OFFICE LONDON

10 Signature **A. Beckwith**

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

**Traducción Oficial No. 03-057**

017

Efectuada el día 1 de febrero de 2003, de un documento escrito en Inglés, al cual para su identificación se le estampa el sello de María del Pilar Iglesias, Traductora e Intérprete Oficial por Resolución No. 819 del 15 de abril de 1971 expedida por el Ministerio de Justicia de la República de Colombia.

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**CESIÓN**

**PCS1045ARCS CO-1X**

Por contraprestación onerosa pagada a nosotros por **PFIZER LIMITED**, sociedad organizada y existente conforme a las leyes de Inglaterra, domiciliada en el Ramsgate Road, Sándwich, Kent, CT13 9NJ, Reino Unido, por el presente vendemos y cedemos a la mencionada **PFIZER LIMITED**, todo nuestro derecho, título e interés en nuestro invento para una nueva y útil Mejora en **DERIVADOS DE FENOXIBENZILAMINA COMO SSRIs** en cuanto respecta a la República de Colombia, tan ampliamente como se describe en las especificaciones y por el presente autorizamos y solicitamos al Comisario de Patentes de Colombia que expida dicha patente a **PFIZER LIMITED** de conformidad con esta Cesión.

En fe de lo cual firmamos de nuestro puño y letra así.

(Fdo) Mark David ANDREWS, el 17 de Julio de 2001 en Sandwich, Kent, Inglaterra.

M P. Iglesias

[illegible]
TRADUCTORA E
INTERPRETE OFICIAL
[illegible]

(Fdo) Geoffrey Edward GYMER, el 17 de Julio de 2001 en Sandwich, Kent, Inglaterra

(Fdo) David HEPWORTH, el 17 de Julio de 2001 en Sandwich, Kent, Inglaterra

(Fdo) Allan STOBIE, el 17 de Julio de 2001 en Sandwich, Kent, Inglaterra

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CESIÓN

Por contraprestación onerosa recibida por mí de **PFIZER INC**, sociedad organizada y existente conforme a las leyes del Estado de Delaware, Estados unidos de América, domiciliada en el 235 East 42nd Street, Nueva York, Nueva York 10017, Estados Unidos de América, el suscrito por el presente vende y cede a la mencionada **PFIZER INC.**, todo mi derecho, título e interés en mi invento para una nueva y útil Mejora en los **DERIVADOS DE FENOXIBENZILAMINA COMO SSRIs** en cuanto respecta a la República de Colombia, tan ampliamente como se describe en las especificaciones y por el presente autorizo y solicito al Comisario de Patentes de Colombia que expida dicha patente a **PFIZER INC.** de conformidad con esta Cesión.

En fe de lo cual firmo de mi puño y letra, en Sándwich, Kent, Inglaterra, el 27 de julio de 2001.

[illegible]

Certificado, Verificado y Autenticado en la ciudad de Egham en Surrey a los 23 días del mes de Octubre de 2001.

(Fdo) Kenneth Greenwood, Notario Público (Sello Oficial)

**APOSTILLA**

**(Convención de La Haya del 5 de octubre de 1961)**

1. País: Reino Unido de Gran Bretaña e Irlanda del Norte
   El presente documento público
2. Fue firmado por K. Greenwood
3 Que actuó en su calidad de Notario Público
4. Lleva el sello del mencionado Notario Público
   Se certificó
5 En Londres 6 El 2 de agosto de 2001
7. Por parte del Principal Secretario de Estado de Su Majestad para Asuntos Extranjeros y de la Mancomunidad.
8 Bajo el Número **G924208**
9. Sello de la Oficina de Asuntos Extranjeros y de la Mancomunidad
10. Firmado por A. Beckwith, Secretario de Estado

Es traducción fiel y completa efectuada por:

María del Pilar Iglesias
C.C 41.339.183 de Bogotá

María del Pilar Iglesias
C.C. 41.339.183 de Bogotá

# ASSIGNMENT

For valuable consideration paid to me (us) by **PFIZER LIMITED** a corporation organized under the laws of England whose full post office address is **Ramsgate Road, Sandwich, Kent, CT13 9NJ, United Kingdom,** I (we) do hereby sell and assign to the said **PFIZER LIMITED**, all my (our) right, title and interest in and to my (our) invention for a new and useful Improvement in **PHENOXYBENZYLAMINE DERIVATIVES AS SSRIs** so far as the Republic of Colombia is concerned, as fully set forth and described in the specification, and I (we) do hereby authorize and request the Commissioner of Patents of Colombia to issue said patent to the said **PFIZER LIMITED** in accordance with this assignment

In witness whereof I (we) have hereunto set my (our) hand(s) this

Place, date and signature - Mavis Diane ADAM

Sandwich, Kent, England 17 July 2001 - Mark David ANDREWS

Place, date and signature - Mark Leonard ELLIOTT

Sandwich, Kent, England 17 July 2001 - Geoffrey Edward GYMER

Sandwich, Kent, England 17 July 2001 - David HEPWORTH

Place, date and signature - Harry Ralph HOWARD Jr

Sandwich, Kent, England 17 July 2001 - Donald Stuart MIDDLETON

Sandwich, Kent, England 17 July 2001 - Alan STOBIE

PCS10945ARCS 20

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ASSIGNMENT

For valuable consideration paid to me (us) by **PFIZER INC.**, a corporation organized under the laws of the State of Delaware, United States of America of 235 East 42nd Street, New York, New York 10017, United States of America, I (we) do hereby sell and assign to the said **PFIZER INC.**, all my (our) right, title and interest in and to my (our) invention for a new and useful Improvement in

**PHENOXYBENZYLAMINE DERIVATIVES AS SSRIs**

so far as the Republic of Colombia is concerned, as fully set forth and described in the specification, and I (we) do hereby authorize and request the Commissioner of Patents of Colombia to issue said patent to the said **PFIZER INC.** in accordance with this assignment.

In witness whereof I (we) have hereunto set my (our) hand(s) this

**PFIZER LIMITED**

Sandwich, Kent, England 27 July 2001 - **DAVID J. WOOD, DIRECTOR, EUROPEAN PATENTS DEPARTMENT**

Certified Verified and Authenticated
In The Town Of Egham In Surrey
This 2nd Day Of August 2001

KENNETH GREENWOOD
NOTARY PUBLIC
HORNE ENGALL AND FREEMAN

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# APOSTILLE

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

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 / a été signé par: K Greenwood

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

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

Certified/Attesté

5 at London/à Londres

6 the/le 02 August 2001

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: G924208

9 Stamp / timbre:

FOREIGN AND COMMONWEALTH OFFICE
UNION

10 Signature: A. Beckwith

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

PCS10945 15

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023

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
7 March 2002 (07.03.2002)

PCT

(10) International Publication Number
WO 02/18333 A1

(51) International Patent Classification[7] C07C 323/20, C07D 333/54, 327/06, 307/87, 333/72, C07C 311/37, C07D 215/18, 239/74, 277/62, A61K 31/18, 31/38, 31/39, 31/34 31/135, 31/47

(21) International Application Number: PCT/IB01/01521

(22) International Filing Date: 22 August 2001 (22.08.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data

| | | |
|---|---|---|
| 0021593.9 | 31 August 2000 (31.08.2000) | GB |
| 0107116.6 | 21 March 2001 (21.03.2001) | GB |

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

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

Published.
— *with international search report*

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

WO 02/18333 A1

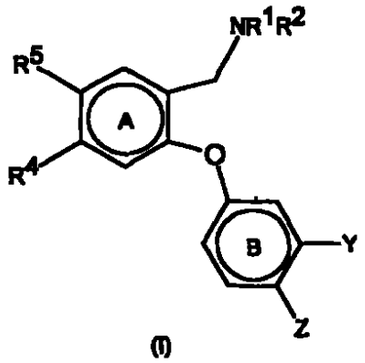
(54) Title: PHENOXYBENZYLAMINE DERIVATIVES AS SELECTIVE SEROTONIN RE-UPTAKE INHIBITORS

(57) Abstract: A compound of general formula (I) wherein $R^1$ and $R^2$ are H, $C_1$-$C_6$alkyl or $(CH_2)_d(C_3$-$C_6$cycloalkyl) wherein d = 0, 1, 2 or 3, or $R^1$ and $R^2$ together with the nitrogen to which they are attached from an azetidine ring, Z or Y is -$SR^3$ and the other Z or Y is halogen or -$R^3$, wherein $R^3$ is $C_1$-$C_4$ alkyl optionally substituted with fluorine, except that $R^3$ is not $CF_3$, or Z and Y are linked so that, together with the interconnecting atoms, Z and Y form a fused 5 to 7-membered carbocyclic or heterocyclic ring, and wherein when Z and Y form a heterocyclic ring in addition to carbon atoms, the linkage contains one or two heteroatoms independently selected from oxygen, sulfur and nitrogen, $R^4$ and $R^5$, which may be the same or different, are A-X, wherein A = -CH=CH- or -$(CH_2)_p$- where p is 0, 1 or 2, X is hydrogen, F, Cl, Br, I, $CONR^6R^7$, $SO_2NR^6R^7$, $SO_2NHC(=O)R^6$, OH, $C_1$-$_6$alkoxy, $NR^8SO_2R^9$, $NO_2$, $NR^6R^{11}$, CN, $CO_2R^{10}$, CHO, $SR^{10}$, $S(O)R^9$ or $SO_2R^{10}$; or a 5- or 6-membered heterocyclic ring containing 1, 2 or 3 heteroatoms selected from N, S and O, optionally substituted independently by one or more $R^{13}$ wherein $R^{13}$ is hydroxy, $C_1$-$C_4$alkoxy, F, $C_1$-$C_6$alkyl, haloalkyl, haloalkoxy, -$NH_2$, $NH(C_1$-$C_6$alkyl) or -$N(C_1$-$C_6$alkyl)$_2$ The compounds of general formula (I) inhibit monoamine reuptake and in particular exhibit activity as selective serotonin reuptake inhibitors.

# PHENOXYBENZYLAMINE DERIVATIVES AS SELECTIVE SEROTONIN RE-UPTAKE INHIBITORS

This invention relates to novel diphenyl ether compounds which inhibit monoamine re-uptake In particular compounds of the present invention exhibit activity as selective serotonin re-uptake inhibitors (SSRIs) and have utility therefore in a variety of therapeutic areas Notably the compounds of the present invention are useful in the treatment or prevention of a variety of disorders, including those in which the regulation of monoamine transporter function is implicated, such as depression, attention deficit hyperactivity disorder, obsessive-compulsive disorder, post-traumatic stress disorder, substance abuse disorders and sexual dysfunction including premature ejaculation, and to pharmaceutical formulations containing such compounds

According to a first aspect, the invention provides a compound of general formula (I), pharmaceutically acceptable salts, solvates or polymorphs thereof;




(I)

wherein,

$R^1$ and $R^2$, which may be the same or different, are H, $C_1$-$C_8$alkyl or $(CH_2)_d(C_3$-$C_8$cycloalkyl) wherein d = 0, 1, 2 or 3, or $R^1$and $R^2$ together with the nitrogen to which they are attached form an azetidine ring,

Z or Y is $-SR^3$ and the other Z or Y is halogen or $-R^3$; wherein $R^3$ is independently $C_1$-$C_4$ alkyl optionally substituted with fluorine, except that $R^3$ is not $CF_3$,

or Z and Y are linked so that, together with the interconnecting atoms, Z and Y form a fused 5 to 7-membered carbocyclic or heterocyclic ring which may be saturated, unsaturated or aromatic, and wherein when Z and Y form a heterocyclic ring, in addition to carbon atoms, the linkage contains one or two heteroatoms independently selected from oxygen, sulfur and nitrogen, with the proviso that when $R^5$ is fluorine and $R^2$ is methyl then the fused ring is not 1,3-dioxolane and Z and Y together do not form a fused phenyl ring,

$R^4$ and $R^5$, which may be the same or different, are

A-X, wherein A = -CH=CH- or $-(CH_2)_p-$ where p is 0, 1 or 2, X is hydrogen, F, Cl, Br, I, $CONR^8R^7$, $SO_2NR^8R^7$, $SO_2NHC(=O)R^8$, OH, $C_{1-4}$alkoxy, $NR^8SO_2R^9$, $NO_2$, $NR^8R^{11}$, CN, $CO_2R^{10}$, CHO, $SR^{10}$, $S(O)R^9$ or $SO_2R^{10}$, $R^6$, $R^7$, $R^8$ and $R^{10}$ which may be the same or different, are hydrogen or $C_{1-6}$alkyl optionally substituted independently by one or more $R^{12}$; $R^9$ is $C_{1-6}$ alkyl optionally substituted independently by one or more $R^{12}$, $R^{11}$ is hydrogen, $C_{1-6}$ alkyl optionally substituted independently by one or more $R^{12}$, $C(O)R^8$, $CO_2R^8$, $C(O)NHR^8$ or $SO_2NR^8R^7$, $R^{12}$ is F (preferably up to 3), OH, $CO_2H$, $C_{3-6}$cycloalkyl, $NH_2$, $CONH_2$, $C_{1-6}$alkoxy, $C_{1-6}$alkoxycarbonyl or a 5- or 6-membered heterocyclic ring containing 1, 2 or 3 heteroatoms selected from N, S and O optionally substituted independently by one or more $R^{13}$; or $R^8$ and $R^7$, together with the nitrogen to which they are attached, form a 4-, 5- or 6-membered heterocyclic ring optionally substituted independently by one or more $R^{13}$, or

a 5- or 6-membered heterocyclic ring containing 1, 2 or 3 heteroatoms selected from N, S and O, optionally substituted independently by one or more $R^{13}$, wherein $R^{13}$ is hydroxy, $C_1$-$C_4$alkoxy, F, $C_1$-$C_6$alkyl, haloalkyl, haloalkoxy, $-NH_2$, $-NH(C_1$-$C_6$alkyl) or $-N(C_1$-$C_6$alkyl)$_2$

Unless otherwise indicated, any alkyl group may be straight or branched and is of 1 to 6 carbon atoms, preferably 1 to 4 and particularly 1 to 3 carbon atoms

Unless otherwise indicated, any carbocyclyl group contains 3 to 8 ring-atoms, and may be saturated, unsaturated or aromatic. Preferred saturated carbocyclyl groups are cyclopropyl, cyclopentyl or cyclohexyl Preferred unsaturated carbocyclyl groups contain up to 3 double bonds A preferred aromatic carbocyclyl group is phenyl The term carbocylic should be similarly construed In addition, the term carbocyclyl includes any fused combination of carbocyclyl groups, for example naphthyl, phenanthryl, indanyl and indenyl

Unless otherwise indicated, any heterocyclyl group contains 5 to 7 ring-atoms up to 4 of which may be hetero-atoms such as nitrogen, oxygen and sulfur, and may be saturated, unsaturated or aromatic. Examples of heterocyclyl groups are furyl, thienyl, pyrrolyl, pyrrolinyl, pyrrolidinyl, imidazolyl, dioxolanyl, oxazolyl, thiazolyl, imidazolyl, imidazolinyl,

imidazolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, thiadiazolyl, pyranyl, pyridyl, piperidinyl, dioxanyl, morpholino, dithianyl, thiomorpholino, pyridazinyl, pyrimidinyl, pyrazinyl, piperazinyl, sulfolanyl, tetrazolyl, triazinyl, azepinyl, oxazepinyl, thiazepinyl, diazepinyl and thiazolinyl In addition, the term heterocyclyl includes fused heterocyclyl groups, for example benzimidazolyl, benzoxazolyl, imidazopyridinyl, benzoxazinyl, benzothiazinyl, oxazolopyridinyl, benzofuranyl, quinolinyl, quinazolinyl, quinoxalinyl, dihydroquinazolinyl, benzothiazolyl, phthalimido, benzofuranyl, benzodiazepinyl, indolyl and isoindolyl The term heterocyclic should be similarly construed

Halo means fluoro, chloro, bromo or iodo

Preferably $R^1$ and $R^2$, which may be the same or different, are hydrogen or $C_1$-$C_6$alkyl More preferably hydrogen or methyl

When Z or Y is $-SR^3$, $R^3$ is preferably methyl or ethyl

When Z and Y form a fused ring, the ring is preferably a heterocyclic ring More preferably, the linkage contains one or two sulfur atoms

Preferably $R^4$ and $R^5$ are not both hydrogen

Preferably $R^4$ and $R^5$, which may be the same or different, are

$-(CH_2)_p-X$, where p is 0, 1 or 2 (preferably 0 or 1), X is hydrogen, hydroxy, $CONR^6R^7$, $SO_2NR^6R^7$, $NR^8SO_2R^9$, $SR^{10}$, $SOR^9$ or $SO_2R^{10}$ wherein $R^6$, $R^7$, $R^8$, $R^9$ and $R^{10}$ are as defined in the first aspect, or

a 5- or 6-membered heterocyclic ring containing 1, 2 or 3 heteroatoms selected from N, S and O (preferably oxadiazolyl, triazolyl, imidazolyl, oxazolyl, pyrazolyl, pyridinyl or pyrimidinyl)

More preferably $R^4$ and $R^5$, which may be the same or different, are

$-(CH_2)_p-X$, where p is 0 or 1, X is hydrogen, hydroxy, $CONR^6R^7$, $SO_2NR^6R^7$ or $NR^8SO_2R^9$, wherein $R^6$ and $R^7$, which may be the same or different, are hydrogen or $C_1$-$C_3$alkyl optionally substituted by hydroxy, $-CONH_2$ or $C_1$-$C_3$alkoxy (preferably

methoxy), $R^8$ is hydrogen, hydroxyethyl or methyl, or $R^8$ is methyl, ethyl, isopropyl, trifluoromethyl or methoxyethyl, or

triazolyl, imidazolyl or pyrazolyl

More preferably still $R^4$ is hydrogen

Preferably $R^6$ and $R^7$, which may be the same or different, are hydrogen, $C_1$-$C_3$alkyl optionally substituted by hydroxy, -$CONH_2$ or $C_1$-$C_3$alkoxy (preferably methoxy) More preferably $R^6$ and $R^7$, which may be the same or different, are hydrogen or methyl, more preferably still hydrogen

When present, $R^{12}$ is preferably oxadiazolyl, triazolyl, imidazolyl, oxazolyl, pyrazolyl, pyridinyl or pyrimidinyl More preferably triazolyl, imidazolyl or pyrazolyl

In the case where $R^6$ and $R^7$, together with the nitrogen to which they are attached, form a heterocyclic ring, preferred rings are pyrrolidine or piperidine rings each of which may be substituted by OH or $CONH_2$ or a morpholine ring which may be substituted by $CONH_2$

Preferably $R^{11}$ is hydrogen or $C_{1-6}$ alkyl

Preferably $R^8$ is hydrogen, hydroxyethyl or methyl More preferably hydrogen

Preferably $R^9$ is methyl, ethyl, isopropyl, trifluoromethyl or methoxyethyl More preferably methyl or ethyl (preferably methyl)

Preferably $R^{10}$ is methyl or ethyl

Preferably p is 1 or 0, more preferably 0

Preferably

$R^1$ and $R^2$, which may be the same or different, are hydrogen or methyl,

when present, $R^3$ is methyl or ethyl, or Z and Y are linked so that, together with the interconnecting atoms, Z and Y form a fused 5 to 7-membered carbocyclic or heterocyclic ring which may be saturated, unsaturated or aromatic, and wherein

when Z and Y form a heterocyclic ring, in addition to carbon atoms, the linkage contains one or two heteroatoms independently selected from oxygen, sulfur and nitrogen, and

$R^4$ and $R^5$, which may be the same or different, are

$(CH_2)_p$-X, where p is 0 or 1, X is hydrogen, hydroxy, $CONR^6R^7$, $SO_2NR^6R^7$, $NR^6SO_2R^9$, $SR^{10}$, $SOR^9$ or $SO_2R^{10}$ and wherein $R^6$ and $R^7$, which may be the same or different, are hydrogen, $C_1$-$C_3$alkyl optionally substituted by hydroxy, $-CONH_2$ or $C_1$-$C_3$alkoxy (preferably methoxy), or $R^6$ and $R^7$, together with the nitrogen to which they are attached, may form a morpholine, pyrrolidine or piperidine ring each of which may be substituted by OH or $CONH_2$, $R^8$ is hydrogen, hydroxyethyl or methyl (preferably hydrogen), $R^9$ is methyl, ethyl, isopropyl, trifluoromethyl or methoxyethyl, and $R^{10}$ is methyl or ethyl, or

an oxadiazolyl, triazolyl, imidazolyl, oxazolyl, pyrazolyl, pyridinyl or pyrimidinyl group

More preferably

$R^1$ and $R^2$, which may be the same or different, are hydrogen or methyl,

when present, $R^3$ is methyl or ethyl, or Z and Y are linked so that, together with the interconnecting atoms, Z and Y form a fused 5 to 7-membered heterocyclic ring containing 1 or 2 sulfur atoms, and

$R^4$ and $R^5$, which may be the same or different, are

$-(CH_2)_p$-X, where p is 0 or 1, X is hydrogen, hydroxy, $CONR^6R^7$, $SO_2NR^6R^7$ or $NR^6SO_2R^9$, wherein $R^6$ and $R^7$, which may be the same or different, are hydrogen, $C_1$-$C_3$alkyl optionally substituted by hydroxy, $-CONH_2$ or $C_1$-$C_3$alkoxy (preferably methoxy), $R^8$ is hydrogen, hydroxyethyl or methyl, $R^9$ is methyl, ethyl, isopropyl, trifluoromethyl or methoxyethyl, or

triazolyl, imidazolyl or pyrazolyl

More preferably still

$R^1$ and $R^2$, which may be the same or different, are hydrogen or methyl,

when present $R^3$ is methyl or ethyl, or Z and Y are linked so that, together with the interconnecting atoms, Z and Y form a fused saturated 5 to 7-membered heterocyclic ring containing 1 or 2 sulfur atoms,

$R^4$ is hydrogen, and

$R^5$ is

$-(CH_2)_p-X$, where p is 0 or 1, X is hydrogen, hydroxy, $CONR^6R^7$, $SO_2NR^6R^7$ or $NR^6SO_2R^8$, wherein $R^6$ and $R^7$, which may be the same or different, are hydrogen, $C_1$-$C_3$alkyl optionally substituted by hydroxy, $-CONH_2$ or $C_1$-$C_3$alkoxy (preferably methoxy), $R^8$ is hydrogen, hydroxyethyl or methyl, $R^9$ is methyl, ethyl, isopropyl, trifluoromethyl or methoxyethyl, or

triazolyl, imidazolyl or pyrazolyl

More preferably still $R^4$ and $R^5$ are not both hydrogen

Preferred compounds are

4-(2,3-dihydro-1-benzothien-5-yloxy)-3-[(methylamino)methyl]-benzenesulfonamide (Example 2),

3-[(dimethylamino)methyl]-4-[3-methyl-4-(methylsulfanyl)phenoxy]-benzenesulfonamide (Example 12),

4-(2,3-dihydro-1-benzothien-5-yloxy)-3-[(dimethylamino)methyl]-benzenesulfonamide (Example 16);

4-[3-chloro-4-(methylsulfanyl)phenoxy]-3-[(dimethylamino)methyl]-benzenesulfonamide (Example 17),

3-[(dimethylamino)methyl]-4-[3-fluoro-4-(methylsulfanyl)phenoxy]-benzenesulfonamide (Example 18),

*N*,*N*-dimethyl-*N*-[2-(6-quinolinyloxy)benzyl]amine (Example 29),

3-[(methylamino)methyl]-4-(6-quinolinyloxy)benzenesulfonamide (Example 35),

4-(2,3-dihydro-1-benzothien-5-yloxy)-3-[(methylamino)methyl]benzamide (Example 60),

4-(2,3-dihydro-1-benzothien-5-yloxy)-*N*-methyl-3-[(methylamino)methyl]-benzamide (Example 62),

*N*-[3-[(methylamino)methyl]-4-[3-methyl-4-(methylsulfanyl)phenoxy]benzyl]methanesulfonamide (Example 75),

3-[(methylamino)methyl]-4-[3-methyl-4-(methylsulfanyl)phenoxy]benzamide (Example 79),

4-(2,3-dihydro-1,4-benzoxathiin-7-yloxy)-3-[(dimethylamino)methyl]benzamide (Example 88),

{3-[(dimethylamino)methyl]-4-[3-fluoro-4-(methylsulfanyl)phenoxy]phenyl}-methanol (Example 90),

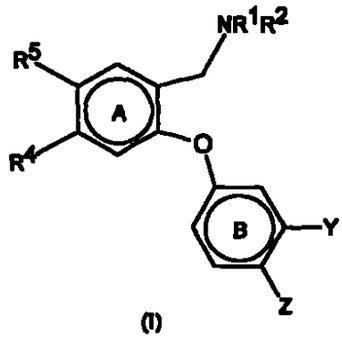
3-[(dimethylamino)methyl]-4-(6-quinolinyloxy)benzamide (Example 100),

3-[(methylamino)methyl]-4-(6-quinolinyloxy)benzamide (Example 102),

*N*-methyl-*N*-{3-[(methylamino)methyl]-4-[3-methyl-4-(methylsulfanyl)phenoxy]-phenyl}methanesulfonamide (Example 116) and

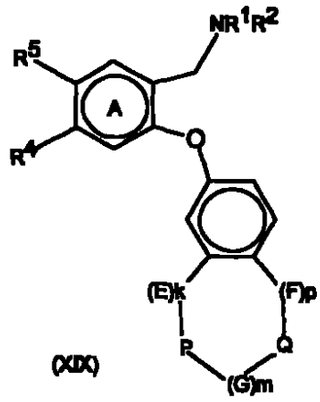
*N*-{4-(2,3-dihydro-1,4-benzoxathiin-7-yloxy)-3-[(dimethylamino)methyl]phenyl}-methanesulfonamide (Example 124)

According to a second aspect the invention provides compound of formula (I) or (XIX)




(I)

and pharmaceutically acceptable salts or solvates thereof wherein (in this aspect) $R^1$ and $R^2$ independently represent H, $C_1$-$C_8$ alkyl or $(CH_2)_d(C_3$-$C_6$cycloalkyl) wherein d = 0, 1, 2 or 3, or wherein $NR^1R^2$ when taken together represent a 4-membered ring wherein $R^1$ and $R^2$ together represent $C_3$ alkyl, Z and Y both independently represent $-SR^3$ wherein, when Z = $-SR^3$ then Y = halogen, $-OR^a$, $-R^a$ or $-SR^a$, or when Y = $-SR^3$ then Z = halogen, $-OR^a$, $R^a$ or $-SR^a$; and $R^3$ and $R^a$ independently represent $C_1$-$C_4$ alkyl (optionally substituted with fluorine atoms e g $-CF_3$), or Z and Y when taken together can represent a fused 5 to 7 membered ring as illustrated by general formula XIX, wherein said 5 to 7 membered ring may be saturated, unsaturated or aromatic, and wherein said 5 to 7 membered ring may optionally contain one or more heteroatoms P and Q, wherein P and Q = may be independently O, S or N, and wherein E, F, or G independently represent CH or $CH_2$ and wherein k and p may independently be = 0, 1, 2 or 3, and m = 1,2 or 3, and




(XIX)

$R^4$ and $R^5$ independently represent A-X wherein A = $-(CH_2)_n-$, wherein n represents 0, 1 or 2 and wherein X represents H, F, Cl, Br, I, $CONR^6R^7$ or $SO_2NR^6R^7$, OH, $NR^6SO_2R^9$, $NO_2$, $NR^6R^{11}$, CN, $CO_2R^{10}$, CHO, $S(O)_mR^{10}$ wherein m = 0, 1 or 2 and wherein $R^6$, $R^7$, $R^8$ and $R^{10}$ independently represent H or $C_{1-6}$ alkyl, wherein $R^9$ represents $C_{1-6}$ alkyl, $R^{11}$ represents H, $C_{1-6}$ alkyl, $C(O)R^6$, $CO_2R^9$, $C(O)NHR^6$ or $SO_2NR^6R^8$ and wherein said $C_{1-6}$ alkyl group is optionally substituted by one or more groups selected from OH, $CO_2H$, $C_{3-6}$ cycloalkyl, $NH_2$, $CONH_2$, $C_{1-6}$ alkoxy, $C_{1-6}$ alkoxycarbonyl and a 5- or 6-membered heterocyclic ring containing 1, 2 or 3 heteroatoms selected from N, S and O, or with the proviso that when P=Q= oxygen then both k and p are not zero, with the proviso that Z and Y together do not form a fused phenyl ring, $R^4$ or $R^5$ may be representative of a 5- or 6-membered heterocyclic ring containing 1, 2 or 3 heteroatoms selected from N, S and O, and in addition, $R^6$ and $R^7$ may, together with the N atom to which they are attached, represent a 5- or 6- membered heterocyclic ring which may be optionally substituted, and pharmaceutically acceptable salts or solvates thereof with the proviso that both $R^4$ and $R^5$ are not H

For the avoidance of doubt, unless otherwise indicated, the term substituted means substituted by one or more defined groups In the case where groups may be selected from a number of alternatives groups, the selected groups may be the same or different

For the avoidance of doubt, the term independently means that where more than one substituent is selected from a number of possible substituents, those substituents may be the same or different.

According to a third aspect, the invention provides a compound of general formula I and pharmaceutically acceptable salts thereof, wherein $R^1$, $R^2$ , $R^3$, Z and Y are as defined in the first aspect, and $R^4$ and $R^5$, which may be the same or different, are $-(CH_2)_p$-A', wherein p is 0, 1 or 2 and A' is a polar group In this aspect, polar groups may be defined as those having a negative π-value (see C Hansch and A Leo, 'Substituent Constants for Correlation Analysis in Chemistry and Biology', Wiley, New York, 1979) In this system, H has a π-value of 0 00, $-OCH_3$ has a π-value of –0 02, and $-SO_2NH_2$ has a π-value of –1 82, for example [see Table VI-i, 'Well-Characterized Aromatic Substituents', p 49, Ibid] More preferred polar groups have a more negative π-value thus, preferred groups have π-values of a greater negative value than –0 1, more preferably a greater negative value than –0 5, and most preferably a greater negative value than -1 0 Even when p is other

than zero in the above definition, the definition of A' is based on the above reference as if p was zero

Unless otherwise specified, the compounds of the first, second and third aspects are hereinafter defined as compounds of the invention

The compounds of the invention have the advantage that they are selective inhibitors of the re-uptake of serotonin (SRIs) (and so are likely to have reduced side effects), they have a rapid onset of action (making them suitable for administration shortly before an effect is required), they have desirable potency and associated properties Compounds that selectively inhibit the re-uptake of serotonin, but not noradrenaline or dopamine, are preferred

We have found that compounds of formula I which possess these properties have a relatively polar group at $R^4/R^5$

The pharmaceutically or veterinarily acceptable salts of the compounds of formula I which contain a basic centre are, for example, non-toxic acid addition salts formed with inorganic acids such as hydrochloric, hydrobromic, hydroiodic, sulfuric and phosphoric acid, with carboxylic acids or with organo-sulfonic acids Examples include the HCl, HBr, HI, sulfate or bisulfate, nitrate, phosphate or hydrogen phosphate, acetate, benzoate, succinate, saccharate, fumarate, maleate, lactate, citrate, tartrate, gluconate, camsylate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate and pamoate salts Compounds of the invention can also provide pharmaceutically or veterinarily acceptable metal salts, in particular non-toxic alkali and alkaline earth metal salts, with bases Examples include the sodium, potassium, aluminium, calcium, magnesium, zinc, diolamine, olamine, ethylenediamine, tromethamine, choline, megulamine and diethanolamine salts For reviews on suitable pharmaceutical salts see Berge *et al*, J Pharm, Sci , 66, 1-19, 1977, P L Gould, International Journal of Pharmaceutics, 33 (1986), 201-217, and Bighley *et al*, Encyclopedia of Pharmaceutical Technology, Marcel Dekker Inc, New York 1996, Volume 13, page 453-497

Hereinafter, the compounds, their pharmaceutically acceptable salts, their solvates and polymorphs, defined in any aspect of the invention (except intermediate compounds in chemical processes) are referred to as "compounds of the invention"

The pharmaceutically acceptable solvates of the compounds of the invention include the hydrates thereof

The compounds of the invention may possess one or more chiral centres and so exist in a number of stereoisomeric forms All stereoisomers and mixtures thereof are included in the scope of the present invention Racemic compounds may either be separated using preparative HPLC and a column with a chiral stationary phase or resolved to yield individual enantiomers utilising methods known to those skilled in the art In addition, chiral intermediate compounds may be resolved and used to prepare chiral compounds of the invention

In cases where the compounds of the invention exist as the E and Z isomers, the invention includes individual isomers as well as mixtures thereof

In cases where compounds of the invention exist as tautomeric isomers, the invention includes individual tautomers as well as mixtures thereof

In cases where the compounds of the invention exist as optical isomers, the invention includes individual isomers as well as mixtures thereof

In cases where the compounds of the invention exist as diastereoisomers, the invention includes individual diastereoisomers as well as mixtures thereof

Separation of diastereoisomers or E and Z isomers may be achieved by conventional techniques, e g by fractional crystallisation, chromatography or H P L C An individual enantiomer of a compound of the invention may be prepared from a corresponding optically pure intermediate or by resolution, such as by H P L C of the corresponding racemate using a suitable chiral support or by fractional crystallisation of the diastereoisomeric salts formed by reaction of the corresponding racemate with a suitable optically active acid or base, as appropriate

The compounds of the invention may exist in one or more tautomeric forms All tautomers and mixtures thereof are included in the scope of the present invention For example, a claim to 2-hydroxypyridinyl would also cover its tautomeric form, α-pyridonyl

It will be appreciated by those skilled in the art that certain protected derivatives of compounds of the invention, which may be made prior to a final deprotection stage, may not possess pharmacological activity as such, but may, in certain instances, be administered orally or parenterally and thereafter metabolised in the body to form compounds of the invention which are pharmacologically active Such derivatives may therefore be described as "prodrugs" Further, certain compounds of the invention may act as prodrugs of other compounds of the invention

All protected derivatives and prodrugs of compounds of the invention are included within the scope of the invention Examples of suitable pro-drugs for the compounds of the present invention are described in Drugs of Today, Volume 19, Number 9, 1983, pp 499 – 538 and in Topics in Chemistry, Chapter 31, pp 306 – 316 and in "Design of Prodrugs" by H Bundgaard, Elsevier, 1985, Chapter 1 (the disclosures in which documents are incorporated herein by reference)

It will further be appreciated by those skilled in the art, that certain moieties, known to those skilled in the art as "pro-moieties", for example as described by H Bundgaard in "Design of Prodrugs" (the disclosure in which document is incorporated herein by reference) may be placed on appropriate functionalities when such functionalities are present within the compounds of the invention

Preferred prodrugs for compounds of the invention include esters, carbonate esters, hemi-esters, phosphate esters, nitro esters, sulfate esters, sulfoxides, amides, carbamates, azo-compounds, phosphamides, glycosides, ethers, acetals and ketals

The invention also includes all suitable isotopic variations of the compounds of the invention An isotopic variation is defined as one in which at least one atom is replaced by an atom having the same atomic number but an atomic mass different from the atomic mass usually found in nature Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, sulphur, fluorine and chlorine such as $^{2}H$, $^{3}H$, $^{13}C$, $^{14}C$, $^{15}N$, $^{17}O$, $^{18}O$, $^{31}P$, $^{32}P$, $^{35}S$, $^{18}F$ and $^{36}Cl$, respectively Certain isotopic variations of the invention, for example, those in which a radioactive isotope such as $^{3}H$ or $^{14}C$ is incorporated, are useful in drug and/or substrate tissue distribution studies Tritiated, i e $^{3}H$, and carbon-14, i e $^{14}C$

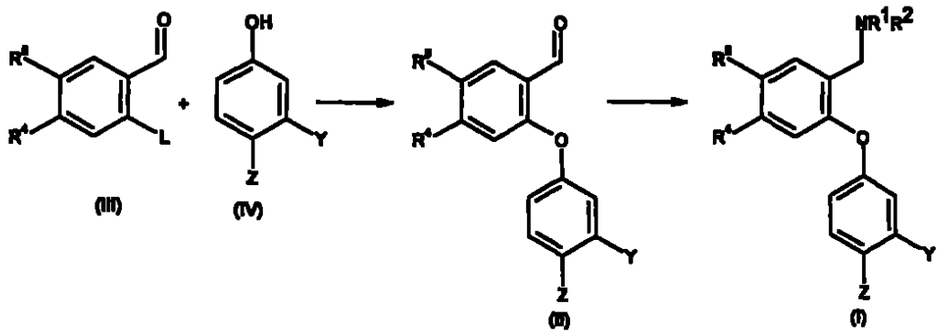
isotopes are particularly preferred for their ease of preparation and detectability Further, substitution with isotopes such as deuterium, i e $^{2}H$, may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased *in vivo* half-life or reduced dosage requirements and hence may be preferred in some circumstances Isotopic variations of the compounds of the invention can generally be prepared by conventional procedures such as by the methods or preparations described in the Examples and Preparations hereafter using appropriate isotopic variations of suitable reagents

Compounds of the invention may be prepared, in known manner in a variety of ways In the following reaction schemes and hereafter, unless otherwise stated, $R^1$ to $R^{13}$, Z and Y are as defined in the first aspect. These processes form further aspects of the invention

Throughout the specification, general formulae are designated by Roman numerals I, II, III, IV etc Subsets of these general formulae are defined as Ia, Ib, Ic etc, IVa, IVb, IVc etc.

Compounds of general formula (I) may be prepared from compounds of formula (II) by reaction with an amine of general formula $HNR^1R^2$, or with a suitable salt form thereof, together with a hydride reducing agent in a suitable solvent (see Scheme 1) When either $R^1$ or $R^2$ is hydrogen, suitable solvents include protic solvents such as ethanol, and sodium borohydride is an appropriate reducing agent as exemplified by Example 36 herein When neither $R^1$ or $R^2$ are hydrogen, tetrahydrofuran/ dichloromethane is a suitable solvent system and sodium triacetoxyborohydride is a suitable reducing agent. In such reactions the use of a salt form of $HNR^1R^2$, such as the hydrochloride is preferable, and an auxiliary base, to aid solubility of the $HNR^1R^2$ salt, such as triethylamine may optionally be added along with acetic acid, as exemplified by Example 25 herein

SCHEME 1

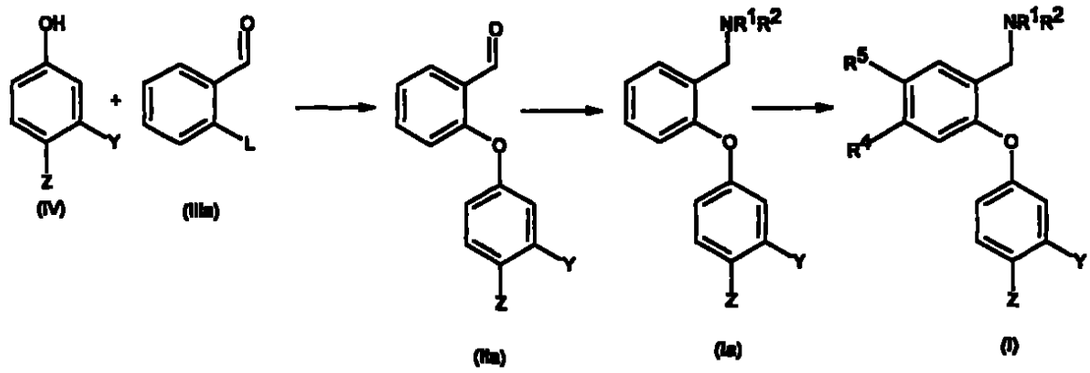



Compounds of formula (II) may be prepared in turn from the coupling of compounds of general formula (IV) with aldehyde compounds of general formula (III), wherein L is a suitable leaving group such as halogen (F, Cl, Br or I) or a sulfonate ester such as trifluoromethanesulfonate or methanesulfonate, preferably L is F or Cl Such coupling reaction may be accomplished by techniques known in the art, such as via reaction with potassium carbonate in a suitable solvent such as dimethylformamide under appropriate reaction conditions such as elevated temperature and in an inert atmosphere

Thus according to a further aspect, the invention provides a process for preparing compounds of general formula (I) from compounds of the general formula (II)

Alternatively, $R^4$ and/or $R^5$ may be introduced after ether coupling (see Scheme 2) Compounds of general formula (I) may be prepared from compounds of general formula (Ia), i e compounds of general formula (I) where $R^4$ and $R^5$ are hydrogen Compounds of general formula (Ia) may be prepared from (IIa) in an analogous fashion to the preparation of (I) from (II) (see Scheme 1), while compounds of general formula (IIa) may be prepared from (IV) and (IIIa) in an analogous fashion to the preparation of (II) (see Scheme 1)

SCHEME 2




Thus according to a further aspect, the invention provides a process for preparing compounds of general formula (I) from compounds of the general formula (Ia)

Methodologies for introducing $R^4$ and/or $R^5$ into compounds of formula (Ia) include

i) Where $R^4/R^5$ are halogen, by reaction of (Ia) with a suitable halogenating agent in an inert solvent which does not adversely affect the reaction Suitable halogenating agents include trifluoromethanesulfonic acid and *N*-Iodosuccinimide and suitable inert solvents include dichloromethane

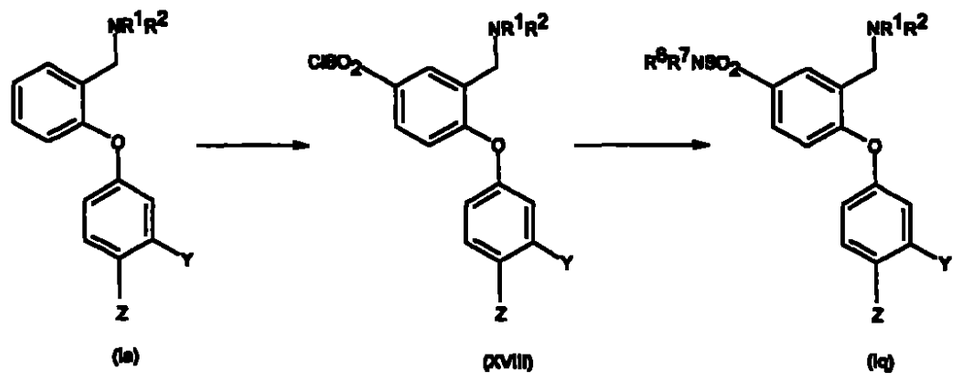
ii) Where $R^4/R^5$ are $-NO_2$, by reaction of (Ia) with a suitable nitrating agent, such as an alkali metal nitrate, in a solvent which does not adversely affect the reaction at, or below, room temperature Suitable nitrating agents include trifluoromethanesulfonic acid/ potassium nitrate and suitable solvents include trifluoroacetic acid

iii) Where $R^4/R^5$ is $-SO_2NR^6R^7$ by reaction of an intermediate sulfonyl chloride with the requisite amine of formula $HNR^6R^7$ in a suitable solvent. Suitable solvents include a mixture of water and dichloromethane and the reactions are generally performed at or below room temperature The intermediate sulfonyl chlorides may be prepared from compounds of formula (Ia) by reaction with chlorosulfonic acid under low temperature conditions in the presence of a solvent which does not adversely affect the reaction, either with or without subsequent treatment with a chlorinating agent such as phosphorus oxychloride, phosphorus pentachloride,

oxalyl chloride or thionyl chloride in a solvent which does not adversely affect the reaction Suitable solvents for the reaction with chlorosulfonic acid include trifluoroacetic acid and a typical reaction temperature is 0 °C Suitable solvents for the reaction with chlorinating agents include acetonitrile and suitable conditions include at reflux, as illustrated in Example 12 herein

For example, compounds of formula (Iq), where $R^5$ is $-SO_2NR^6R^7$, may be prepared via the intermediate sulfonyl chlorides (XVIII) from compounds of formula (Ia) by reaction of (Ia) with chlorosulfonic acid, either with or without subsequent treatment with a chlorinating agent such as phosphorus oxychloride, phosphorus pentachloride, oxalyl chloride or thionyl chloride, followed by reaction with $HNR^6R^7$ (see scheme 2a) Reaction conditions typically comprise low temperature The reaction can take place either neat, i e in the absence of solvent, or in the presence of an inert solvent which does not adversely affect the reaction The intermediate sulfonyl chloride (XVII) may be isolated, purified and then reacted with $HNR^6R^7$, alternatively it may be generated *in situ*, without isolation, and then reacted with $HNR^6R^7$

SCHEME 2a




(Ia) (XVIII) (Iq)

Thus according to a further aspect, the invention provides a process for preparing compounds of general formula (I) from compounds of the general formula (II) In a preferred embodiment, there is provided a process for preparing compounds of formula (Iq) by reacting compounds of formula (Ia) in a suitable solvent, with chlorosulfonic acid, either with or without subsequent treatment with a chlorinating agent such as phosphorus oxychloride, phosphorus pentachloride, oxalyl chloride or thionyl chloride, to give compounds of formula (XVIII) followed by reaction with $HNR^6R^7$ to give compounds

of formula (Iq) Preferably compounds of formula (XVIII) are generated *in situ* and reacted with $HNR^8R^7$ without isolation

Alternatively, compounds of general formula (I) having a particular $R^4/R^5$ substituent may be converted into other compounds of formula (I) using known techniques For example

i) When $R^4/R^5$ is halogen such as chloro, bromo or iodo, it may be converted to cyano via reaction with a cyanide salt in the presence of a Pd(0) or (II)catalyst in a high boiling solvent at elevated temperatures Suitable Pd catalysts include palladium tetrakis(triphenylphosphine), suitable cyanide salts include $Zn(CN)_2$ and suitable high boiling solvents which do not adversely affect the reaction include dimethylformamide as exemplified by Example 78 herein,

ii) When $R^4/R^5$ is halogen such as chloro, bromo or iodo, it may be converted to the corresponding ester $-CO_2R$ by treatment with carbon monoxide at high pressure with a Pd(0) or (II) catalyst, in an alcohol solvent (ROH wherein R is $C_1 - C_4$ alkyl), in the presence of a base at elevated temperatures For example the reaction may be carried out at pressures in the region of about 100 p s i, whilst suitable Pd catalysts include dichlorobis(triphenylphosphine) palladium (II), suitable bases include triethylamine and suitable alcohol solvents include methanol as exemplified by Preparation 50 herein,

iii) When $R^4/R^5$ is nitro, it may be reduced to the corresponding $-NH_2$ group via treatment with a reducing agent in a protic solvent at, or above, room temperature Suitable reducing agents include iron powder / calcium chloride, suitable protic solvents include aqueous ethanol and a typical reaction temperature is from about 70°C to about 100°C, preferably about 90°C, as exemplified by Example 103 herein;

iv) When $R^4/R^5$ is $-NH_2$, it may be converted to the corresponding $-NHSO_2R^8$ group by reaction with a sulfonylating agent in the presence of a base in an inert solvent which does not adversely affect the reaction at, or below, room temperature Suitable sulfonylating agents include methanesulfonyl chloride, suitable bases include triethylamine and suitable inert solvents include dichloromethane as exemplified by Example 128 herein,

v) When $R^4/R^5$ is a $-NHSO_2R^8$ group, it may be converted to the corresponding $-NR^8SO_2R^8$ group via treatment with an alkylating agent and a base in a suitable inert solvent Examples of suitable alkylating agents include methyl iodide, suitable bases include potassium carbonate and suitable inert solvents include acetonitrile, as exemplified by Preparation 88 herein,

vi) When $R^4/R^5$ is a nitrile –CN, it may be converted to the corresponding $-C(O)NH_2$ group by hydrolysis under basic, oxidative or acid conditions Basic hydrolysis is preferably conducted with a hydroxide salt such as potassium hydroxide in a protic solvent such as *t*-butanol at elevated temperatures, as exemplified in Example 79 herein

vii) When $R^4/R^5$ is an ester $-CO_2R$, it may be reduced to the corresponding alcohol group $-CH_2OH$ via treatment with a hydride reducing agent, such as lithium aluminium hydride, as exemplified by Preparation 69 herein,

viii) When $R^4/R^5$ is an ester $-CO_2R$, it may be converted to the corresponding acid $-CO_2H$ by treatment with a suitable hydroxide salt in the presence of water and a suitable co-solvent Suitable hydroxide salts include lithium hydroxide and suitable co-solvents include tetrahydrofuran, as exemplified by Preparation 55 herein,

ix) When $R^4/R^5$ is an acid $-CO_2H$, it may be converted to the corresponding amide $-CONR^6R^7$ by treatment with a coupling agent, a base and an amine $HNR^6R^7$ in a suitable inert solvent which does not adversely affect the reaction Suitable coupling agents include 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride in the presence of 1-hydroxybenzotriazole, suitable bases include triethylamine and suitable solvents include dichloromethane, as exemplified by Preparation 59 herein,

x) When $R^4/R^5$ is halogen such as chloro, bromo or iodo, it may be converted to an α,β-unsaturated amide, by treatment with acrylamide, a Pd(0) or (II) catalyst and a suitable base, in an inert solvent which does not adversely affect the reaction, at elevated temperatures Suitable Pd catalysts include palladium (II) acetate in

the presence of tri(o-tolyl)phosphine, suitable bases include triethylamine and suitable inert solvents include acetonitrile as exemplified by Example 50 herein,

xi) When $R^4/R^5$ is an α,β-unsaturated amide, it may be converted to $-CH_2CH_2CO_2NH_2$, by treatment with a suitable reducing agent at an appropriate temperature, in a suitable solvent which does not adversely affect the reaction Suitable reducing agents include samarium diiodide at room temperature and suitable solvents include tetrahydrofuran containing a small amount of water, as exemplified by Example 51 herein,

xii) When $R^4/R^5$ is $-CH_2OH$, it may be converted to $-CH_2NR^6SO_2R^6$ by means of a Mitsunobu reaction at an appropriate temperature, in a suitable solvent which does not adversely affect the reaction Suitable reagents include diethyl azodicarboxylate, triphenylphosphine and *tert*-butyl methylsulfonylcarbamate, 0°C is a suitable reaction temperature and tetrahydrofuran is a suitable solvent as exemplified by Preparation 72 herein,

Alternatively, compounds of general formula (I) having a particular $NR^1R^2$ group may be converted into other compounds of general formula (I) having a different $NR^1R^2$ group For example

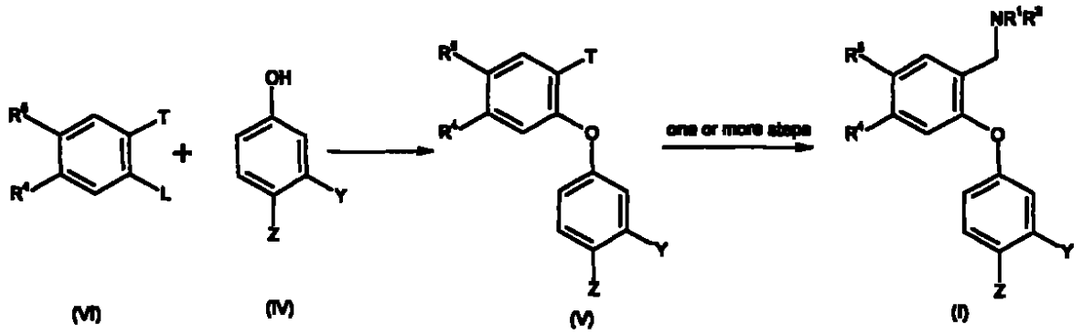
i) Compounds of formula (Ib) wherein either $R^1$ or $R^2$ is hydrogen, can be converted into a compound of formula (Ic) wherein neither $R^1$ nor $R^2$ are hydrogen, by reaction of the compound of formula (Ib) with an aldehyde and a hydride reducing agent Suitable aldehydes include formaldehyde, suitable reducing agents include sodium tri(acetoxy)borohydride and the reaction is preferably conducted in a solvent which does not interfere with the reaction, such as dichloromethane at or below room temperature, as exemplified by Example 12 herein

ii) Compounds of formula (Ib) wherein $R^1$ or $R^2$ is hydrogen, can be converted into a compound of formula (Ic) wherein $R^1$ or $R^2$ is methyl, by reaction of the compound of formula (Ib) with a formylating agent in a suitable solvent, followed by subsequent reduction of the intermediate *N*-formyl compound with a hydride reducing agent in an inert solvent, preferably at elevated temperature Suitable

formylating agents include pentafluorophenyl formate (formed from formic acid, pentafluorophenol and dicyclohexylcarbodiimide) and suitable solvents for the formylation include dichloromethane Suitable reducing agents include borane-tetrahydrofuran complex and suitable inert solvents for the reduction include tetrahydrofuran as exemplified by Example 110 herein

Alternatively, compounds of general formula (I) may be prepared from compounds of formula V (see Scheme 3) wherein L is as defined for Scheme 1 and T is a group which can be converted into $CH_2NR^1R^2$ Examples of suitable T substitutents include $-CO_2R^{10}$, -CN and $-C(O)NR^1R^2$

SCHEME 3




(VI) (IV) (V) (I)

Methodologies for converting compounds of formula (V) to (I), include

i) Where T is $-CO_2R^{10}$ and $R^{10}$ = methyl or ethyl, by reaction with an amine of general formula $NHR^1R^2$ to form an amide, followed by reduction to provide an amine

ii) Where T = -CN, by reduction to its corresponding amine of formula $-CH_2NH_2$

iii) Where T = $-C(O)NR^1R^2$, by reduction to provide an amine

Compounds of general formula (V) may be prepared in turn by the coupling of compounds of general formula (VI) and compounds of the general formula (IV) Reagents and conditions for such coupling reactions are as previously defined for the coupling of compounds of general formulae (IV) and (III) in Scheme 1

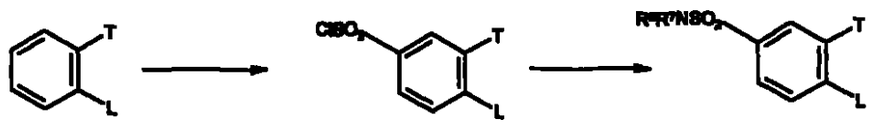
Compounds of general formula (VI) may be prepared in turn from compounds of general formula (VII) (see Scheme 4)

SCHEME 4


(VII) (VI)

Compounds of formula (VI) may be prepared by aromatic electrophilic substitution of compounds of formula (VII) to give compounds of formula (VI) directly Alternatively compounds of formula (VI) may be prepared in two or more steps, aromatic electrophilic substitution of compounds of formula (VII) to give intermediate compounds which then undergo further reaction to give compounds of formula (VI) The intermediate compounds may be isolated or generated *in situ* without isolation A preferred route is shown in Scheme 5

SCHEME 5




(VII) (VIII) (VIa)

Compounds of formula (VII) are reacted with sulfonyl chloride to give compounds of formula (VIII) followed by reaction with $NHR^6R^7$ to give compounds of formula (VIa)

According to further aspects, the invention provides compounds of formulae (II), (IIa) and (V) as defined above

Compounds of formulae (III), (IIIa), (IV), (VI) or (VII) are either known and available from commercial sources or are available from commercially available materials using known techniques (see Examples hereinafter)

It will be apparent to those skilled in the art that sensitive functional groups may need to be protected and deprotected during synthesis of a compound of formula I This may be achieved by conventional techniques, for example as described in 'Protective Groups in Organic Syntheels', 3rd edition, by T W Greene and P G M Wuts, John Wiley and Sons

Inc, 1999 Example 35 provides one example of a protecting group strategy employed in the synthesis of a compound of the present invention

The skilled chemist will appreciate that diaryl ethers may be prepared using a number of synthetic methodologies For a review of methodologies see J S Sawyer, *Tetrahedron*, 56 (2000) 5045-5065, incorporated herein by reference

The compounds of the invention are useful because they have pharmacological activity in mammals, including humans More particularly, they are useful in the treatment or prevention of a disorder in which the regulation of monoamine transporter function is implicated Disease states that may be mentioned include hypertension, depression (e g depression in cancer patients, depression in Parkinson's patients, postmyocardial infarction depression, subsyndromal symptomatic depression, depression in infertile women, paediatric depression, major depression, single episode depression, recurrent depression, child abuse induced depression, post partum depression and grumpy old man syndrome), generalized anxiety disorder, phobias (e g agoraphobia, social phobia and simple phobias), posttraumatic stress syndrome, avoidant personality disorder, premature ejaculation, eating disorders (e g anorexia nervosa and bulimia nervosa), obesity, chemical dependencies (e g addictions to alcohol, cocaine, heroin, phenobarbital, nicotine and benzodiazepines), cluster headache, migraine, pain, Alzheimer's disease, obsessive-compulsive disorder, panic disorder, memory disorders (e g dementia, amnestic disorders, and age-related cognitive decline (ARCD)), Parkinson's diseases (e g dementia in Parkinson's disease, neuroleptic-induced parkinsonism and tardive dyskinesias), endocrine disorders (e g hyperprolactinaemia), vasospasm (particularly in the cerebral vasculature), cerebellar ataxia, gastrointestinal tract disorders (involving changes in motility and secretion), negative symptoms of schizophrenia, premenstrual syndrome, fibromyalgia syndrome, stress incontinence, Tourette's syndrome, trichotillomania, kleptomania, male impotence, attention deficit hyperactivity disorder (ADHD), chronic paroxysmal hemicrania, headache (associated with vascular disorders), emotional lability, pathological crying, sleeping disorder (cataplexy) and shock

Disorders of particular interest include depression, attention deficit hyperactivity disorder, obsessive-compulsive disorder, post-traumatic stress disorder, substance abuse disorders and sexual dysfunction including (in particular) premature ejaculation

Premature ejaculation may be defined as persistent or recurrent ejaculation before, upon or shortly after penile penetration of a sexual partner It may also be defined as ejaculation occurring before the individual wishes [see 'The Merck Manual', 16th edition, p 1576, published by Merck Research Laboratories, 1992]

Thus, according to further aspects, the invention provides.

i) a compound of the invention for use as a pharmaceutical,

ii) the use of a compound of the invention in the manufacture of a medicament for the treatment or prevention of a disorder in which the regulation of monoamine transporter function is implicated, for example depression, attention deficit hyperactivity disorder, obsessive-compulsive disorder, post-traumatic stress disorder, substance abuse disorders or sexual dysfunction including premature ejaculation,

iii) the use of a compound of the invention in the manufacture of a medicament for the treatment or prevention of premature ejaculation,

iv) a method of treatment or prevention of depression, attention deficit hyperactivity disorder, obsessive-compulsive disorder, post-traumatic stress disorder, substance abuse disorders or sexual dysfunction including premature ejaculation, which comprises administering a therapeutically effective amount of a compound of the invention to a patient in need of such treatment or prevention,

v) a method of increasing ejaculatory latency which comprises the administration of an effective amount of a compound of the invention to a male desiring increased ejaculatory latency, and

vi) a compound of the invention for the treatment or prevention of a disorder in which the regulation of monoamine transporter function is implicated, for example depression, attention deficit hyperactivity disorder, obsessive-compulsive disorder, post-traumatic stress disorder, substance abuse disorders or sexual dysfunction including premature ejaculation

vii) a compound of the invention for treating premature ejaculation

It is to be appreciated that all references herein to treatment include curative, palliative and prophylactic treatment.

The compounds of the invention may be administered alone or as part of a combination therapy If a combination of active agents are administered, then they may be administered simultaneously, separately or sequentially In particular, the compounds of the invention may be combined with the following preferably for the treatment of PE

i) Alpha-blockers (e g phentolamine, doxazasim, tamsulosin, terazasin, prazasin and Example 19 of WO9830560 A possible rationale for alpha-blockers treating premature ejaculation is as follows Muscular activity of the ejaculatory smooth muscles (vas deferens, seminal vesicles and urethra) are controlled by the sympathetic nervous system through the release of noradrenalin Noradrenalin acts on the alpha 1 adrenoreceptors, stimulating muscle contractions, leading to seminal emission and subsequently ejaculation Blocking these receptors will therefore inhibit ejaculation

ii) Apomorphine - teachings on the use of apomorphine as a pharmaceutical may be found in US-A-5945117

iii) Dopamine D2 agonists (e g Premiprixal, Pharmacia Upjohn compound number PNU95666)

iv) Melanocortin receptor agonists (e g Melanotan II)

v) PGE1 receptor agonists (e g alprostadil)

vi) Mono amine transport inhibitors, particularly Noradrenaline Re-uptake Inhibitors (NRIs) (e g Reboxetine), other Serotonin Re-uptake Inhibitors (SRIs) (e g paroxetine) or Dopamine Re-uptake Inhibitors (DRIs)

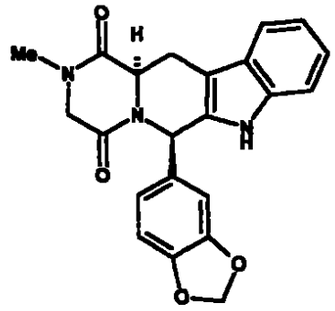
vii) 5-HT3 antagonists (e g. ondansetron and granisetron). A possible rationale for 5-HT3 antagonists treating premature ejaculation is as follows 5-HT3 receptors,

present in the lumen of the posterior portion of the urethra, are stmulated by 5-HT in the semen dunng seminal emission, leading to a sensitisation of the spinal relex pathway which leads to ejaculation Therefore, an antagonist would prevent this sensitisation and thus delay ejaculation

5

viii) PDE inhibitors such as PDE2 (e g erythro-9-(2-hydroxyl-3-nonyl)-adenine) and Example 100 of EP 0771799-incorporated herein by reference) and in particular a PDE5 inhibitor (e g sildenafil, 1-{[3-(3,4-dihydro-5-methyl-4-oxo-7-propylimidazo[5,1-f]-as-trazin-2-yl)-4-ethoxyphenyl]sulfonyl}-4-ethylpiperazine i e

10 vardenafil / Bayer BA 38-9456 or IC351 (see structure below, Icos Lilly)) A possible rationale for PDE inhibitors treating premature ejaculation is as follows c AMP and CGMP levels in the ejaculatory smooth muscles regulate muscle tone of these ejaculatory muscles and so delay ejaculation



IC351 (Icos Lilly)

15

ix) Potassium channel openers

x) P2X purinergic receptor antagonists

20 xi) Endothelin receptor antagonists

For human use the compounds of the invention can be administered alone but in human therapy will generally be administered in admixture with a suitable pharmaceutical excipient, diluent or carrier selected with regard to the intended route of administration

25 and standard pharmaceutical practice.

For example, the compounds of the invention, can be administered orally, buccally or sublingually in the form of tablets, capsules (including soft gel capsules), ovules, elixirs, solutions or suspensions, which may contain flavouring or colouring agents, for

immediate-, delayed-, modified-, sustained-, dual-, controlled-release or pulsatile delivery applications The compounds of the invention may also be administered via intracavernosal injection The compounds of the invention may also be administered via fast dispersing or fast dissolving dosage forms

Such tablets may contain excipients such as microcrystalline cellulose, lactose, sodium citrate, calcium carbonate, dibasic calcium phosphate, glycine, and starch (preferably corn, potato or tapioca starch), disintegrants such as sodium starch glycollate, croscarmellose sodium and certain complex silicates, and granulation binders such as polyvinylpyrrolidone, hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC), sucrose, gelatin and acacia Additionally, lubricating agents such as magnesium stearate, stearic acid, glyceryl behenate and talc may be included

Solid compositions of a similar type may also be employed as fillers in gelatin capsules Preferred excipients in this regard include lactose, starch, a cellulose, milk sugar or high molecular weight polyethylene glycols For aqueous suspensions and/or elixirs, the compounds of the invention, and their pharmaceutically acceptable salts, may be combined with various sweetening or flavouring agents, colouring matter or dyes, with emulsifying and/or suspending agents and with diluents such as water, ethanol, propylene glycol and glycerin, and combinations thereof

Modified release and pulsatile release dosage forms may contain excipients such as those detailed for immediate release dosage forms together with additional excipients that act as release rate modifiers, these being coated on and/or included in the body of the device Release rate modifiers include, but are not exclusively limited to, hydroxypropylmethyl cellulose, methyl cellulose, sodium carboxymethylcellulose, ethyl cellulose, cellulose acetate, polyethylene oxide, Xanthan gum, Carbomer, ammonio methacrylate copolymer, hydrogenated castor oil, carnauba wax, paraffin wax, cellulose acetate phthalate, hydroxypropylmethyl cellulose phthalate, methacrylic acid copolymer and mixtures thereof Modified release and pulsatile release dosage forms may contain one or a combination of release rate modifying excipients Release rate modifying excipients may be present both within the dosage form i e within the matrix, and/or on the dosage form, i e upon the surface or coating

Fast dispersing or dissolving dosage formulations (FDDFs) may contain the following ingredients aspartame, acesulfame potassium, citric acid, croscarmellose sodium, crospovidone, diascorbic acid, ethyl acrylate, ethyl cellulose, gelatin, hydroxypropylmethyl cellulose, magnesium stearate, mannitol, methyl methacrylate, mint flavouring, polyethylene glycol, fumed silica, silicon dioxide, sodium starch glycolate, sodium stearyl fumarate, sorbitol, xylitol. The terms dispersing or dissolving as used herein to describe FDDFs are dependent upon the solubility of the drug substance used i e where the drug substance is insoluble a fast dispersing dosage form can be prepared and where the drug substance is soluble a fast dissolving dosage form can be prepared

The compounds of the invention can also be administered parenterally, for example, intravenously, intra-arterially, intraperitoneally, intrathecally, intraventricularly, intraurethrally, intrasternally, intracranially, intramuscularly or subcutaneously, or they may be administered by infusion techniques For such parenteral administration they are best used in the form of a sterile aqueous solution which may contain other subs ances, for example, enough salts or glucose to make the solution isotonic with blood The aqueous solutions should be suitably buffered (preferably to a pH of from 3 to 9), if necessary The preparation of suitable parenteral formulations under sterile conditions is readily accomplished by standard pharmaceutical techniques well known to those skilled in the art

The following dosage levels and other dosage levels herein are for the average human subject having a weight range of about 65 to 70 kg The skilled person will readily be able to determine the dosage levels required for a subject whose weight falls outside this range, such as children and the elderly

For oral and parenteral administration to human patients, the daily dosage level of the compounds of the invention or salts or solvates thereof will usually be from 10 to 500 mg (in single or divided doses)

Thus, for example, tablets or capsules of the compounds of the invention may contain from 5 mg to 250 mg of active compound for administration singly or two or more at a time, as appropriate. The physician in any event will determine the actual dosage which will be most suitable for any individual patient and it will vary with the age, weight and

response of the particular patient The above dosages are exemplary of the average case There can, of course, be individual instances where higher or lower dosage ranges are merited and such are within the scope of this invention The skilled person will also appreciate that, in the treatment of certain conditions (including PE), compounds of the invention may be taken as a single dose on an "as required" basis (i e as needed or desired)

Example Tablet Formulation

In general a tablet formulation could typically contain between about 0 01mg and 500mg of a compound of the invention whilst tablet fill weights may range from 50mg to 1000mg An example formulation for a 10mg tablet is illustrated

| Ingredient | %w/w |
|---|---|
| Compound of the invention | 10 000* |
| Lactose | 64 125 |
| Starch | 21 375 |
| Croscarmellose Sodium | 3 000 |
| Magnesium Stearate | 1 500 |

* This quantity is typically adjusted in accordance with drug activity

The compounds of the invention can also be administered intranasally or by inhalation and are conveniently delivered in the form of a dry powder inhaler or an aerosol spray presentation from a pressurised container, pump, spray or nebulizer with the use of a suitable propellant, e g dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoro-ethane, a hydrofluoroalkane such as 1,1,1,2-tetrafluoroethane (HFA 134A [trade mark]) or 1,1,1,2,3,3,3-heptafluoropropane (HFA 227EA [trade mark]), carbon dioxide or other suitable gas In the case of a pressurised aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount The pressurised container, pump, spray or nebulizer may contain a solution or suspension of the active compound, e g using a mixture of ethanol and the propellant as the solvent, which may additionally contain a lubricant, e g. sorbitan trioleate Capsules and cartridges (made, for example, from gelatin) for use in an inhaler or insufflator may be formulated to contain a powder mix of a compound of the invention and a suitable powder base such as lactose or starch

Aerosol or dry powder formulations are preferably arranged so that each metered dose or "puff" contains from 1 to 50 mg of a compound of the invention for delivery to the patient. The overall daily dose with an aerosol will be in the range of from 1 to 50 mg which may be administered in a single dose or, more usually, in divided doses throughout the day

The compounds of the invention may also be formulated for delivery via an atomiser Formulations for atomiser devices may contain the following ingredients as solubilisers, emulsifiers or suspending agents water, ethanol, glycerol, propylene glycol, low molecular weight polyethylene glycols, sodium chloride, fluorocarbons, polyethylene glycol ethers, sorbitan trioleate, oleic acid

Alternatively, the compounds of the invention can be administered in the form of a suppository or pessary, or they may be applied topically in the form of a gel, hydrogel, lotion, solution, cream, ointment or dusting powder The compounds of the invention may also be dermally or transdermally administered, for example, by the use of a skin patch They may also be administered by the ocular, pulmonary or rectal routes

For ophthalmic use, the compounds can be formulated as micronized suspensions in isotonic, pH adjusted, sterile saline, or, preferably, as solutions in isotonic, pH adjusted, sterile saline, optionally in combination with a preservative such as a benzylalkonium chloride Alternatively, they may be formulated in an ointment such as petrolatum

For application topically to the skin, the compounds of the invention can be formulated as a suitable ointment containing the active compound suspended or dissolved in, for example, a mixture with one or more of the following mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene polyoxypropylene compound, emulsifying wax and water Alternatively, they can be formulated as a suitable lotion or cream, suspended or dissolved in, for example, a mixture of one or more of the following mineral oil, sorbitan monostearate, a polyethylene glycol, liquid paraffin, polysorbate 60, cetyl esters, wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water

The compounds of the invention may also be used in combination with a cyclodextrin Cyclodextrins are known to form inclusion and non-inclusion complexes with drug

molecules Formation of a drug-cyclodextrin complex may modify the solubility, dissolution rate, bioavailability and/or stability property of a drug molecule Drug-cyclodextrin complexes are generally useful for most dosage forms and administration routes As an alternative to direct complexation with the drug the cyclodextrin may be used as an auxiliary additive, e g as a carrier, diluent or solubiliser Alpha-, beta- and gamma-cyclodextrins are most commonly used and suitable examples are described in WO-A-91/11172, WO-A-94/02518 and WO-A-98/55148

For oral or parenteral administration to human patients the daily dosage levels of compounds of the invention will be from 0 01 to 30 mg/kg (in single or divided doses) and preferably will be in the range 0 01 to 5 mg/kg Thus tablets will contain 1mg to 0 4g of compound for administration singly or two or more at a time, as appropriate The physician will in any event determine the actual dosage which will be most suitable for any particular patient and it will vary with the age, weight and response of the particular patient The above dosages are, of course only exemplary of the average case and there may be instances where higher or lower doses are merited, and such are within the scope of the invention

Oral administration is preferred Preferably, administration takes place shortly before an effect is required

For veterinary use, a compound of the invention is administered as a suitably acceptable formulation in accordance with normal veterinary practice and the veterinary surgeon will determine the dosing regimen and route of administration which will be most appropriate for a particular animal

Thus according to a further aspect, the invention provides a pharmaceutical formulation containing a compound of the invention and a pharmaceutically acceptable adjuvant, diluent or carrier

The invention is illustrated by the following non-limiting examples in which the following abbreviations and definitions are used

| | |
|---|---|
| Arbocel® | filter agent |
| br | broad |

| | |
|---|---|
| Boc | *tert*-butoxycarbonyl |
| CDI | carbonyldiimidazole |
| δ | chemical shift |
| d | doublet |
| Δ | heat |
| DCCI | dicyclohexylcarbodiimide |
| DCM | dichloromethane |
| DMF | *N,N*-dimethylformamide |
| DMSO | dimethylsulfoxide |
| $ES^+$ | electrospray ionisation positive scan |
| $ES^-$ | electrospray ionisation negative scan |
| Ex | Example |
| h | hours |
| HOBt | 1-hydroxybenzotriazole |
| HPLC | high pressure liquid chromatography |
| m/z | mass spectrum peak |
| min | minutes |
| MS | mass spectrum |
| NMR | nuclear magnetic resonance |
| Prec | precursor |
| Prep | preparation |
| q | quartet |
| s | singlet |
| t | triplet |
| Tf | trifluoromethanesulfonyl |
| TFA | trifluoroacetic acid |
| THF | tetrahydrofuran |
| TLC | thin layer chromatography |
| $TS^+$ | thermospray ionisation positive scan |
| WSCDI | 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride |

$^1$H Nuclear magnetic resonance (NMR) spectra were in all cases consistent with the proposed structures Characteristic chemical shifts (δ) are given in parts-per-million downfield from tetramethylsilane using conventional abbreviations for designation of major peaks e g s, singlet; d, doublet, t, triplet; q, quartet; m, multiplet; br, broad

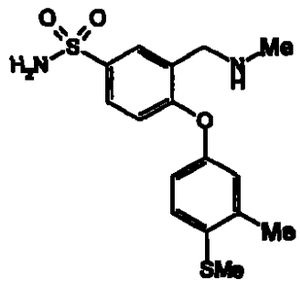
The following abbreviations have been used for common solvents $CDCl_3$, deuterochloroform, DMSO, dimethylsulfoxide The abbreviation psi means pounds per square inch and LRMS means low resolution mass spectrometry Where thin layer chromatography (TLC) has been used it refers to silica gel TLC using silica gel 60 $F_{254}$ plates, $R_f$ is the distance travelled by a compound divided by the distance travelled by the solvent front on a TLC plate Melting points were determined using a Perkin Elmer DSC7 at a heating rate of 20°C/minute)

Where indicated, compounds were characterised as their hydrochloride salts A typical procedure for formation of hydrochloride salts is given in Example 12. The procedure can be carried out with other solvents e g diethyl ether or DCM

Commercial starting materials were obtained from Aldrich Chemical Co, Lancaster Synthesis Ltd or Acros Organics

EXAMPLE 1

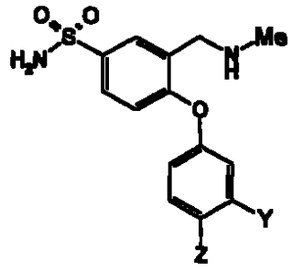
3-[(Methylamino)methyl]-4-[3-methyl-4-methylsulfanyl)phenoxy]-benzenesulfonamide



The amide of Preparation 8 (760 mg, 2 07 mmol) was slurried in THF (10 mL) and the resulting suspension was treated with borane tetrahydrofuran complex (1M solution in THF, 6 22 mL, 6 22 mmol) at room temperature The resulting solution was heated at reflux for 5 hours under an atmosphere of dry nitrogen The reaction was cooled to room temperature and treated cautiously with 6M HCl solution (6 mL) The resulting mixture was heated at reflux for 30 min After cooling to room temperature the mixture was diluted with water (10 mL) and basified by cautious addition of potassium carbonate solid The aqueous layer was extracted with EtOAc (20 mL) which gave a precipitate in the organic layer, and the aqueous layer was further extracted with DCM (2 x 20 mL) The EtOAc fraction was washed with 2M NaOH (20 mL) giving a clear two-phase separation and the basic layer was extracted with DCM (4 x 25 mL) All the organic fractions were combined and washed with brine (20 mL), dried ($MgSO_4$) and evaporated

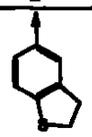
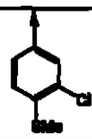
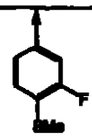
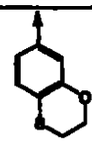
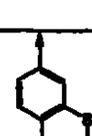
to a colourless oil. Purification by flash chromatography [$SiO_2$, 95 5 0 5 to 90 10 1 (EtOAc/ MeOH/ 880 $NH_3$)] afforded a white powder of the desired amine (646 mg, 89%) $\delta_H$ (300 MHz, $d_6$-DMSO) 2 26 (3H, d), 2 32 (3H, d), 2 45 (3H, d), 3.75 (2H, d), 6 90 (3H, m), 7.25 (3H, br), 7 67 (1H, t) 7.98 (1H, d), MS *m/z* ($TS^+$) 353 ($MH^+$)

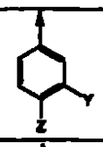
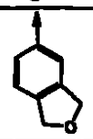
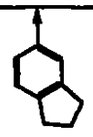
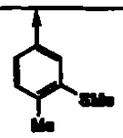
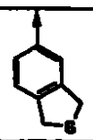
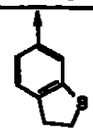
Compounds of formula Id, I e compounds of general formula I where $R^1$ is methyl, $R^2$ is hydrogen and $R^5$ is $-SO_2NH_2$ , shown in Table 1 were prepared in an analogous fashion to Example 1 from the precursors indicated.



(Id)

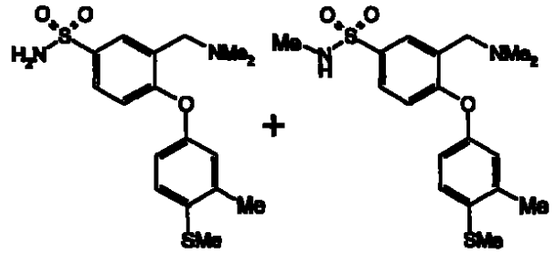
Table 1

| Example | Precursor | | data |
|---|---|---|---|
| 2 | Prep 9 |  | HCl salt: $\delta_H$ ($CD_3OD$, 400 MHz) 2 80 (3H, s), 3 42 (2H, m), 4 41 (2H, s), 6 86-7.00 (2H, m), 7 09 (1H, s), 7 23 (1H, d), 7 90 (1H, d), 8 05 (1H, s), MS *m/z* ($TS^+$) 351 ($MH^+$) |
| 3 | Prep 12 |  | HCl salt: $\delta_H$ ($CD_3OD$, 300 MHz) 2.54 (3H, s), 2 82 (3H, s), 4 43 (2H, s), 7 00 (1H, d), 7 20 (1H, d), 7.34 (1H, s), 7 42 (1H, d), 7 95 (1H, d), 8 11 (1H, s), MS *m/z* ($TS^+$) 373 ($MH^+$) |
| 4 | Prep 11 |  | HCl salt: $\delta_H$ ($CD_3OD$, 400 MHz) 2 45 (3H, s), 2 73 (3H, s), 5 44 (2H, s), 6 97 (3H, m), 7 42 (1H, m), 7 89 (1H, m), 8 03 (1H, s), MS *m/z* ($ES^+$) 357 ($MH^+$) |
| 5 | Prep 10 |  | HCl salt: $\delta_H$ ($CD_3OD$, 400 MHz) 2 79 (3H, s), 3 18 (2H, m), 4 38 (2H, s), 4 41 (2H, m), 6.68 (2H, m), 6 97 (1H, d), 7 13 (1H, d), 7 91 (1H, d), 8 03 (1H, s); MS *m/z* ($TS^+$) 367 ($MH^+$) |
| 6 | Prep 13 |  | HCl salt: $\delta_H$ ($CD_3OD$, 400 MHz) 2 78 (3H, s), 3 15 (2H, m), 4 38 (4H, m), 6 79 (1H, d), 6 85 (3H, m), 7 84 (1H, d), 8 00 (1H, s), MS *m/z* ($ES^+$) 367 ($MH^+$) |

| Example | Precursor |  | data |
|---|---|---|---|
| 7 | Prep 14 |  | HCl salt $\delta_H$ ($CD_3OD$, 400 MHz) 2 81 (3H, s), 4 43 (2H, s), 5 09 (4H, s), 6 93 (1H, d), 7 12 (2H, s+d), 7 40 (1H, d), 7 90 (1H, d), 8 08 (1H, s), MS *m/z* ($TS^+$) 335 ($MH^+$) |
| 8 | Prep 15 |  | HCl salt. $\delta_H$ ($CD_3OD$, 400 MHz) 2 16 (2H, m), 2 80 (3H, s), 2 92 (4H, t), 4 40 (2H, s), 6 86 (1H, d), 6 94 (1H, d), 7 03 (1H, s), 7 30 (1H, d), 7 88 (1H, d), 8 03 (1H, s), MS *m/z* ($TS^+$) 333 ($MH^+$) |
| 9 | Prep 16 |  | HCl salt $\delta_H$ ($CD_3OD$, 400 MHz) 2 32 (3H, s), 2 43 (3H, s), 2 81 (3H, s), 4 41 (2H, s), 6 84 (1H, d), 6 91 (1H, d), 7 06 (1H, s), 7 24 (1H, d), 7 89 (1H, d), 8 05 (1H, s), MS *m/z* ($ES^+$) 352 ($MH^+$) |
| 10 | Prep 17 |  | HCl salt. $\delta_H$ ($CD_3OD$, 400 MHz) 2 78 (3H, s), 4 21 (4H, s), 4 39 (2H, s), 6 89 (1H, d), 7 01 (1H, d), 7 08 (1H, s), 7 38 (1H, d), 7 85 (1H, d), 8 02 (1H, s), MS *m/z* ($TS^+$) 351 ($MH^+$) |
| 11 | Prep 18 |  | $\delta_H$ ($CD_3OD$, 400 MHz) 2 76 (3H, s), 3 30 (2H, m), 3 42 (2H, m), 4 33 (2H, s), 6 90 (1H, d), 6 94 (1H, d), 7 00 (1H, s), 7 29 (2H, d), 7 89 (1H, d), 8 04 (1H, s), MS *m/z* ($ES^+$) 351 ($MH^+$), ($ES^-$) 349 ($M-H^+$) |

EXAMPLES 12 and 13

3-[(Dimethylamino)methyl]-4-[3-methyl-4-(methylsulfanyl)phenoxy]-benzenesulfonamide (Example 12) and 3-[(dimethylamino)methyl]-*N*-methyl-4-[3-methyl-4-(methylsulfanyl)phenoxy]benzenesulfonamide (Example 13)



Formaldehyde (37% aq solution, 282 µL, 3 76 mmol) was added to a suspension of the secondary amine from Example 1 (409 mg, 1 16 mmol) in DCM (20 mL) at room temperature under nitrogen The resulting mixture was stirred for 15 minutes before the addition of sodium triacetoxyborohydride (984 mg, 4 64 mmol). The resulting reaction mixture was stirred for 5 hours before being basified with saturated $NaHCO_3$ solution (10 mL) and extracted with DCM (3×20 mL) The organic layers were washed with brine (10

mL), dried ($MgSO_4$) and evaporated to a yellow oil This was purified by HPLC (Phenomonex Luna $C_{18}$ 75 x 4 6 mm column, $CH_3CN$, $H_2O$, TFA) Fractions containing the major product were evaporated and the residue was treated with sat. $NaHCO_3$ solution (5 mL), and extracted with DCM (3×30 mL) The combined organic fractions were washed with brine (30 mL), dried ($MgSO_4$) and evaporated to give a white foam (155 mg, 36%) of Example 12, $\delta_H$ (300 MHz, $CDCl_3$) 2 30 (6H, s), 2 35 (3H, s), 2 48 (3H, s), 3 60 (2H, s), 6 83 (3H, m), 7 20 (1H, m), 7 28 (2H, s), 7 74 (1H, d), 8 08 (1H, s), MS *m/z* (TS+) 367 ($MH^+$)

A minor product was also obtained after HPLC purification The relevant fractions were evaporated and the residue was treated with sat $NaHCO_3$ solution (5 mL), and extracted with DCM (2×30 mL) The combined organic fractions were washed with brine (30 mL), dried ($MgSO_4$) and evaporated to a gum This was taken up in DCM (5 mL), treated with 1M ethereal HCl (2 mL) and evaporated to give a white powder (39 mg, 9%) of Example 13, HCl salt. $\delta_H$ ($CDCl_3$, 300 MHz) 2 30 (6H, s), 2 35 (3H, s), 2 48 (3H, s), 3 60 (2H, s), 6 83 (3H, m), 7 20 (1H, m), 7 28 (2H, s), 7 74 (1H, d), 8 08 (1H, s), MS *m/z* ($TS^+$) 381 ($MH^+$)

In a repeat reaction, using 1 equivalent of formaldehyde to the amine of Example 1, Example 12 was obtained in 78% yield after column chromatography [$SiO_2$, 95 5 0 5 to 90:10 1 (EtOAc/ MeOH/ 880 $NH_3$)] This was taken up in EtOAc and converted to the HCl salt by the addition of 1M ethereal HCl The resulting precipitate was filtered and dried *in vacuo* to give Example 12 HCl salt, m p 188°C

Alternatively, Example 12 can also be formed from the amine of Example 1 by the method of Example 110

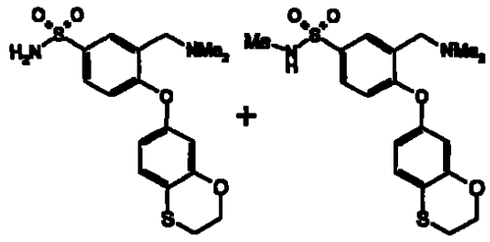
Example 12 was also prepared as follows.

A solution of the hydrochloride salt from Example 94 (20 g) in trifluoroacetic acid (100 mL) was slowly added to a solution of chlorosulfonic acid (72 g) keeping the temperature between 0 and 5 °C After 1 h the reaction mixture was quenched slowly into water (200 mL), at 0-20 °C The mixture was then extracted with dichloromethane (200 mL) and separated The aqueous layer was then extracted with dichloromethane (60 mL) and separated The combined organic layers were washed with water (200 mL) The layers

were separated and the dichloromethane removed *in vacuo* to give a solid Acetonitrile (240 mL) was added and to this slurry was added phosphorus oxychloride (28 8 mL) The solution was then heated at reflux overnight The reaction mixture was cooled to room temperature and quenched into a stirred mixture of ammonia (90 mL), dichloromethane (240 mL) and water (100 mL), keeping the temperature between 0 °C and 10 °C The mixture was adjusted with ammonia (if necessary) to greater than pH8 After 15 mins the reaction mixture was allowed to warm to room temperature and the layers separated The organic layer was concentrated *in vacuo* to give a thick brown oil This was dissolved in acetone (100 mL) and slurried with carbon (Norit SX plus, 50% w/w) filtered and treated with another charge of carbon (Norit SX plus, 50%w/w) This mixture was again filtered and the solution concentrated, replacing with water (200 mL) The slurry was granulated, filtered and vacuum dried overnight to give the title product as a creamy white solid (yield 40%)

EXAMPLES 14 and 15

4-(2,3-Dihydro-1,4-benzoxathiin-7-yloxy)-3-[(dimethylamino)methyl]-benzenesulfonamide and 4-(2,3-dihydro-1,4-benzoxathiin-7-yloxy)-3-[(dimethylamino)methyl]-*N*-methylbenzenesulfonamide



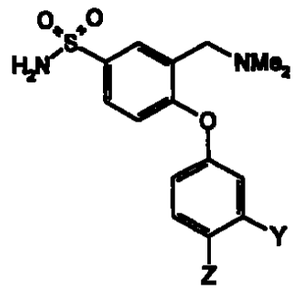
These compounds were formed in an analogous fashion to Examples 12 and 13 starting from the secondary amine of Example 5

EXAMPLE 14 HCl salt: $\delta_H$ ($CD_3OD$, 400 MHz) 2 97 (6H, s), 3 18 (2H, m), 4 42 (2H, m), 4 52 (2H, s), 6 68 (2H, d), 6 99 (1H, d), 7 14 (1H, d), 7 94 (1H, d), 8 07 (1H, s), MS *m/z* ($ES^+$) 381 ($MH^+$)

EXAMPLE 15, HCl salt: $\delta_H$ ($CD_3OD$, 400 MHz) 2 56 (3H, s), 2 80 (6H, s), 3 17 (2H, m), 4 35 (2H, s), 4 41 (2H, m), 6 68 (2H, m), 6 98 (1H, d), 7 13 (1H, d), 7 81 (1H, d), 8 00 (1H, s), MS *m/z* ($ES^+$) 395 ($MH^+$)

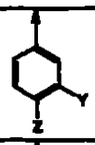
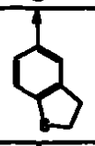
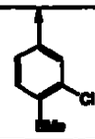
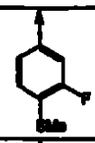
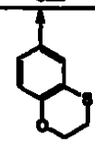
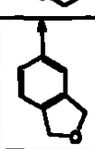
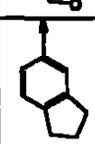
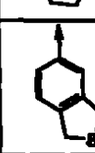
Compounds of formula Ie, i e compounds of general formula I where $R^1$ and $R^2$ are methyl and $R^5$ is $-SO_2NH_2$, shown in Table 2 were prepared according to Example 12

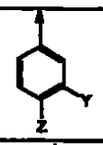
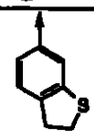
from the precursors indicated The *N*-methyl sulfonamides analogous to Example 13 were not isolated in these reactions and HPLC purification was not required



(Ie)

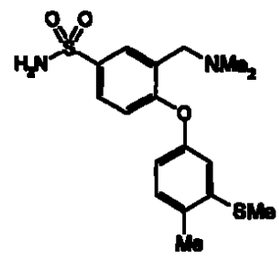
Table 2

| Example | Precursor |  | data |
|---|---|---|---|
| 16 | Example 2 |  | HCl salt. $\delta_H$ ($CD_3OD$, 400 MHz) 2.98 (6H, s), 3 41 (2H, m), 4 58 (2H, s), 6 95 (2H, m), 7 08 (1H, s), 7 25 (1H, d), 7 95 (1H, d), 8 05 (1H, s), MS *m/z* ($ES^+$) 365 ($MH^+$) |
| 17 | Example 3 |  | HCl salt $\delta_H$ ($CD_3OD$, 300 MHz) 2 54 (3H, s), 2 98 (6H, s), 4 53 (2H, s), 7 01 (1H, d), 7 20 (1H, dd), 7 33 (1H, s), 7 42 (1H, d), 7 99 (1H, d), 8 04 (1H, s), MS *m/z* ($TS^+$) 387 ($MH^+$) |
| 18 | Example 4 |  | HCl salt. $\delta_H$ ($CD_3OD$, 400 MHz) 2 43 (3H, s), 2 88 (6H, s), 4 42 (2H, s), 6 99 (3H, m), 7 42 (1H, t), 7 92 (1H, d), 8 06 (1H, s), MS *m/z* ($ES^+$) 371 ($MH^+$) |
| 19 | Example 6 |  | HCl salt $\delta_H$ ($CD_3OD$, 400 MHz) 2 89 (3H, s), 3 17 (2H, m), 4 39 (2H, m), 4 47 (2H, s), 6 78 (1H, d), 6 87 (3H, m), 7 89 (1H, d), 8 01 (1H, s), MS *m/z* ($TS^+$) 367 ($MH^+$) |
| 20 | Example 7 |  | TFA salt $\delta_H$ ($CDCl_3$, 400 MHz) 2 22 (6H, s), 3 60 (2H, t), 5 05 (4H, d), 6 75-6 90 (3H, m), 7 20 (1H, d), 7 60 (1H, m), 8 00 (1H, m), MS *m/z* 349 ($MH^+$) |
| 21 | Example 8 |  | HCl salt $\delta_H$ ($CD_3OD$, 400 MHz) 2 10 (2H, m), 2 85-3 00 (10H, m), 4 30 (1H, brs), 4 50 (2H, s), 6 80-6 95 (2H, m), 7 05 (1H, s), 7 25 (1H, d), 7 80 (1H, d), 8 10 (1H, s), MS *m/z* ($ES^+$) 347 ($MH^+$) |
| 22 | Example 10 |  | HCl salt $\delta_H$ ($CD_3OD$, 400 MHz) 2 93 (6H, s), 4 21 (4H, s), 4.50 (2H, s), 6 91 (1H, d), 7 02 (1H, d), 7 09 (1H, s), 7 37 (1H, d), 7 91 (1H, d), 8 05 (1H, s), MS *m/z* ($TS^+$) 365 ($MH^+$) |

| Example | Precursor |  | data |
|---|---|---|---|
| 23 | Example 11 |  | HCl salt $\delta_H$ (DMSO-$d_6$, 400 MHz) 2 76 (6H, s), 3 21 (2H, t), 3 38 (2H, t), 4 39 (2H, s), 6 80 (1H, d), 6 86 (1H, d), 7 10 (1H, s), 7 28 (3H, m), 7 80 (1H, d), 8 06 (1H, s), 10 23 (1H, br), MS *m/z* ($TS^+$) 365 ($MH^+$) |

EXAMPLE 24

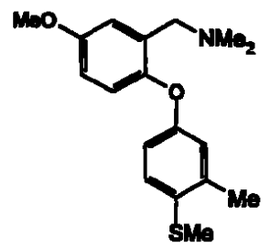
3-[(Dimethylamino)methyl]-4-[4-methyl-3-(methylsulfanyl)phenoxy]-benzenesulfonamide



The title compound was prepared from the secondary amine of Example 9 by the method of Example 110, $\delta_H$ ($CD_3OD$, 400 MHz) 2 27 (3H, s), 2 41 (3H, s), 2 61 (6H, s), 4 19 (2H, s), 6 76 (1H, d), 6 88-6 93 (2H, m), 7 20 (1H, d), 7 82 (1H, d), 8 03 (1H, d), MS *m/z* ($TS^+$) 367 ($MH^+$)

EXAMPLE 25

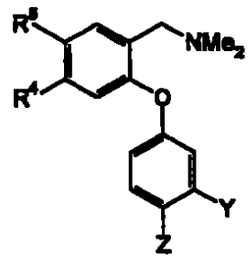
*N*-(5-Methoxy-2-[3-methyl-4-(methylsulfanyl)phenoxy]benzyl)-*N*,*N*-dimethylamine



Dimethylamine hydrochloride (424 mg, 5 2 mmol), $Et_3N$ (725 µL, 5 2 mmol), AcOH (298 µL, 5 2 mmol) and sodium triacetoxyborohydride (1 10 g, 5 2 mmol) were added to a solution of the aldehyde from Preparation 24 (1 00 g, 3 47 mmol) in THF (15 mL) and DCM (15 mL) and the mixture was stirred at room temperature for 16 h After removing the solvent *in vacuo* the residue was taken up in 2M HCl (20 mL) and washed with ether (2x15 mL) The aqueous layer was basified with NaOH pellets and extracted with DCM (4x20 mL) The combined DCM extracts were washed with brine, dried ($MgSO_4$) and evaporated The residue was taken up in a small amount of DCM and treated with 1M

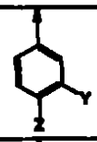
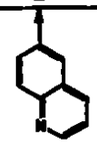
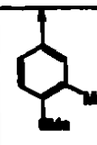
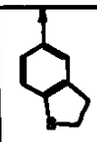
ethereal HCl to precipitate the HCl salt. This was filtered, washed with ether and dried to give a white solid (936 mg) contaminated with triethylamine hydrochloride This was dissolved in 1M NaOH (10 mL) and extracted with EtOAc (3x15 mL) The organic extracts were washed with brine (10 mL), dried ($MgSO_4$) and evaporated before being re-dissolved in EtOAc and evaporated again The residue was taken up in DCM and treated with 1M ethereal HCl to precipitate the HCl salt, which was filtered, washed with ether and dried to give a white solid (635 mg, 52%), $\delta_H$ ($CDCl_3$, 300 MHz) 2 35 (3H, s), 2 45 (3H, s), 2 79 (6H, s), 3 90 (3H, s), 4 21 (2H, s), 6 70 (1H, d), 6 73 (1H, s), 6 90 (2H, m), 7 18 (1H, d), 7 65 (1H, s), 12 83 (1H, brs), MS *m/z* ($TS^+$) 318 ($MH^+$)

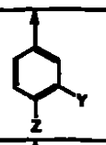
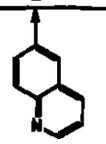
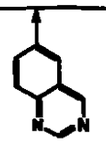
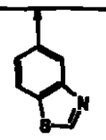
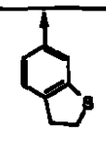
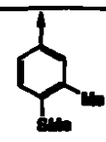
Compounds of formula If, i e compounds of general formula I where $R^1$ and $R^2$ are methyl, shown in Table 3 were prepared according to Example 25 from the precursors indicated




(If)

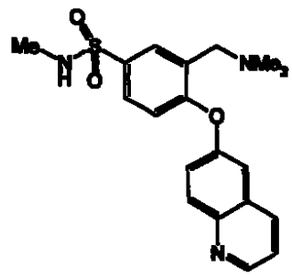
Table 3

| Example | Precursor | $R^4$ | $R^5$ |  | data |
|---|---|---|---|---|---|
| 26 | Prep 25 | H | F |  | HCl salt $\delta_H$ ($CDCl_3$, 300 MHz) 2 23 (6H, s), 3 41 (2H, s), 6.98 (2H, m), 7 34 (2H, m), 7.48 (1H, dd), 7 98 (1H, d), 8 08 (1H, d), 8 80 (1H, s), MS *m/z* ($TS^+$) 297 ($MH^+$) |
| 27 | Prep 39 | H | $-NO_2$ |  | $\delta_H$ ($CDCl_3$, 300 MHz) 2 32 (6H, s), 2 36 (3H, s), 2 47 (3H, s), 3 60 (2H, s), 6 80 (1H, d), 6 87 (2H, d), 7 19 (1H, d), 8 03 (1H, d), 8 40 (1H, d), MS *m/z* ($ES^+$) 333 ($MH^+$) |
| 28 | Prep 38 | H | $-NO_2$ |  | Taken on crude at ~75% purity; $\delta_H$ ($CDCl_3$, 400 MHz) 2 33 (6H, s), 3 24 (2H, m), 3 38 (2H, m), 3 66 (2H, s), 6 76 (2H, m), 6 86 (1H, m), 7 17 (1H, d), 8 00 (1H, dd), 8 37 (1H, d) |

| Example | Precursor | $R^4$ | $R^5$ |  | data |
|---|---|---|---|---|---|
| 29 | Prep 26 | H | H |  | $\delta_H$ ($CDCl_3$, 300 MHz) 2 28 (6H, s), 3 50 (2H, s), 7 03 (2H, m), 7 20-7 40 (3H, m), 7 52 (2H, m), 7 98 (1H, d), 8 09 (1H, d), 8 81 (1H, m), MS *m/z* ($TS^+$) 279 ($MH^+$) |
| 30 | Prep 27 | H | H |  | HCl salt $\delta_H$ ($d_6$-DMSO, 300 MHz) 2 77 (6H, d), 4 38 (2H, d), 7 08 (1H, d), 7 36 (1H, t), 7 52 (1H, t), 7 62 (1H, s), 7 80 (1H, d), 7 91 (1H, dd), 8 10 (1H, d), 9 25 (1H, s), 9 52 (1H, s); MS *m/z* ($TS^+$) 280 ($MH^+$) |
| 31 | Prep 29 | H | H |  | Maleate salt. $\delta_H$ ($d_6$-DMSO, 300 MHz) 2 77 (6H, s), 4 33 (2H, s), 5 98 (2H, s), 6 87 (1H, d), 7 21 (1H, dt), 7 30 (1H, dd), 7 41 (1H, dt), 7 58 (1H, dd), 7 88 (1H, d), 8 11 (1H, d), 9 32 (1H, s), MS *m/z* 285 ($MH^+$) |
| 32 | Prep 33 | H | Br |  | HCl salt $\delta_H$ (DMSO-$d_6$, 400 MHz) 2 77 (6H, d), 3 23 (3H, m), 3 39 (2H, m), 4 32 (2H, d), 6 75 (2H, m), 7 03 (1H, s), 7 26 (1H, d), 7 57 (1H, dd), 7 87 (1H, s), 10 06 (1H, br, s), MS *m/z* ($ES^+$) 366 ($MH^+$) |
| 33 | Prep 32 | Br | H |  | $\delta_H$ ($CDCl_3$, 400 MHz) 2.22 (6H, s), 2.30 (3H, s), 2 41 (3H, s), 3 41 (2H, s), 6 76 (2H, m), 6 94 (1H, s), 7 18 (1H, s), 7 21 (1H, obs), 7 30 (1H, d), MS *m/z* ($TS^+$) 368/368 ($MH^+$) |

**EXAMPLE 34**

**3-[(Dimethylamino)methyl]-*N*-methyl-4-(6-quinolinyloxy)benzenesulfonamide**

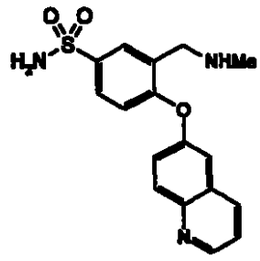


Chlorosulfonic acid (106 µL, 1 6 mmol) was added to a solution of Example 29 (50 mg, 0 16 mmol) in DCM (2 mL) and the mixture was stirred for 3 h at room temperature Water (2 mL) was added, the mixture was adjusted to pH 6 with sat aq $NaHCO_3$ and extracted with DCM (2×5 mL) The organic extracts were dried ($MgSO_4$) and filtered and

8M methylamine in EtOH (0 3 mL) was added After standing for 1 h the solvent was removed *in vacuo* and the residue was purified by column chromatography [$SiO_2$, 95 5 0 5 (DCM/ MeOH/ 880 $NH_3$)] The product was taken up in EtOAc and converted to the HCl salt by the addition of ethereal HCl This gave the desired product as a hygroscopic solid (3 mg, 5%), $\delta_H$ ($CD_3OD$, 300 MHz) 2 60 (3H, s), 2 99 (6H, s), 4 60 (2H, s), 7 21 (1H, d), 7 96 (1H, d), 8 04 (3H, m), 8 19 (1H, s), 8 38 (1H, d), 9 03 (1H, d), 9 18 (1H, d), MS *m/z* ($TS^+$) 371 ($MH^+$)

EXAMPLE 35

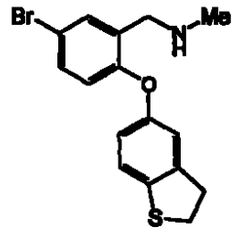
3-[(Methylamino)methyl]-4-(6-quinolinyloxy)benzenesulfonamide




Trifluoroacetic anhydride (0 96 mL, 6 8 mmol) was added to a solution of the amine of Example 48 (900 mg, 3 4 mmol) and triethylamine (1 9 mL, 13 6 mmol) in $CH_2Cl_2$ (15 mL) at 0°C and the mixture was stirred for 5 min The solvent was removed *in vacuo* and the residue was partitioned between $CH_2Cl_2$ and water The organic layer was washed with brine, dried ($MgSO_4$) and evaporated to give a yellow oil, which was used without further purification This crude oil was taken up in $CH_2Cl_2$ (20 mL), cooled to 0°C and $ClSO_3H$ (2 4 mL, 36 1 mmol) was added dropwise. The mixture was allowed to warm to room temperature and stirred for 4 h before being poured into ice water The mixture was extracted with $CH_2Cl_2$ (50 mL) and the organic layer was treated with a saturated solution of $NH_3$ in MeOH (10 mL) After stirring for 4 h 1M LiOH (20 mL) was added and stirring was continued overnight Tlc analysis indicated reaction was incomplete so further 1M LiOH (50 mL) was added and the mixture was stirred for 2 h The mixture was acidified to pH 8 with 2M HCl and extracted with $CH_2Cl_2$ (3×200 mL) The combined organic extracts were dried ($MgSO_4$) and evaporated and the residue was triturated with ether to give the title compound (500 mg, 43%) as a yellow solid, $\delta_H$ ($CDCl_3$, 400 MHz) 2 46 (3H, s), 3 87 (2H, s), 6 93 (1H, d), 7 25 (1H, s), 7 39 (1H, t), 7 42 (1H, d), 7 78 (1H, d), 8 00-8 08 (2H, m), 8 12 (1H, d), 8 86 (1H, s), MS *m/z* ($ES^+$) 344 ($MH^+$)

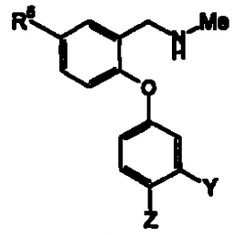
EXAMPLE 36

N-[5-Bromo-2-(2,3-dihydro-1-benzothien-5-yloxy)benzyl]-N-methylamine



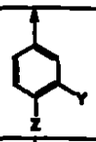
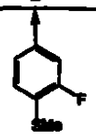
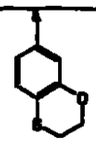
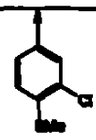
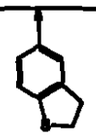
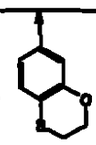
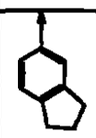
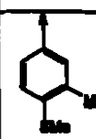
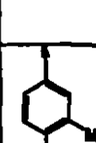
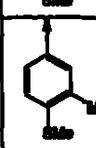

The aldehyde of Preparation 19 (1 10 g, 3 28 mmol) was dissolved in 8M methylamine in EtOH (4 1 mL, 32 8 mmol) and stirred for 5 h before the portionwise addition of $NaBH_4$ (372 mg, 9 83 mmol) over 30 min EtOH (100 mL) was added and the reaction was stirred for 16 h before being concentrated *in vacuo*. The residue was quenched with 6M HCl until pH 1 and the precipitated HCl salt was collected by filtration, washed with water (100 mL) and dried *in vacuo* to give a crystalline solid (1 04 g, 82%), $\delta_H$ ($CDCl_3$, 400 MHz) 2 62 (3H, s), 3 26 (2H, t), 3 41 (2H, t), 4 18 (2H, s), 6 66 (1H, d), 6 90 (1H, d), 7 03 (1H, s), 7 19 (1H, d), 7 39 (1H, d), 7 80 (1H, s), MS *m/z* ($ES^+$) 350, 352 ($MH^+$)

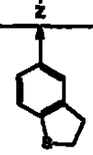
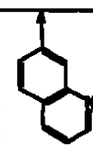
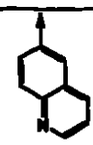
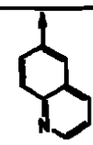
Compounds of formula Ig, i e compounds of general formula I where $R^1$ and $R^4$ are hydrogen and $R^2$ is methyl, shown in Table 4 were prepared according to Example 36 from the precursors indicated For those compounds which were isolated as the free base the reaction mixture was partitioned between 2M HCl and ether after removal of the reaction solvent *in vacuo* The aqueous layer was then basified and extracted with DCM, the DCM layer being dried ($MgSO_4$) and evaporated to give the desired secondary amine




(Ig)

Table 4

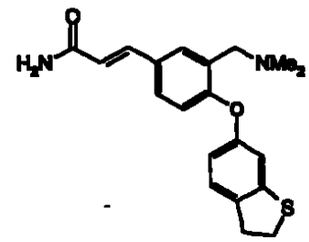
| Example | Precursor | $R^5$ |  | data |
|---|---|---|---|---|
| 37 | Prep 20 | Br |  | HCl salt $\delta_H$ ($d_6$-DMSO, 300 MHz) 2 48 (3H, s), 2.59 (3H, s), 4 18 (2H, s), 6 88 (1H, d), 7 01 (1H, d), 7 16 (1H, d), 7 45 (1H, t), 7 59 (1H, d), 7 91 (1H, s), MS *m/z* ($TS^+$) 356, 358 ($MH^+$) |
| 38 | Prep 21 | Br |  | $\delta_H$ ($CDCl_3$, 400 MHz) 2 43 (3H, s), 3 11 (2H, t), 3 78 (2H, s), 4 41 (2H, t), 6 44 (1H, s), 6 51 (1H, d), 6 77 (1H, d), 6 98 (1H, d), 7 31 (1H, d), 7 55 (1H, s), MS *m/z* ($ES^+$) 386, 388 ($MH^+$) |
| 39 | Prep 22 | Br |  | $\delta_H$ ($CDCl_3$, 400 MHz) 2 41 (3H, s), 2 45 (3H, s), 3 72 (2H, s), 6 77 (1H d), 6 85 (1H, d), 6 99 (1H, s), 7 18 (1H, d), 7 36 (1H, d), 7 59 (1H, s), MS *m/z* ($TS^+$) 372, 374 ($MH^+$) |
| 40 | Prep 38 | $-NO_2$ |  | $\delta_H$ ($CDCl_3$, 300 MHz) 2 55 (3H, s), 3 30 (2H, m), 3 43 (2H, m), 3 95 (2H, s), 6 80 (2H, m), 6 91 (1H, s), 7 22 (1H, d), 8 05 (1H, d), 8 40 (1H, s), MS *m/z* ($ES^+$) 317 ($MH^+$) |
| 41 | Prep 36 | $-NO_2$ |  | $\delta_H$ ($CDCl_3$, 400 MHz) 2 45 (3H, S), 3.10 (2H, m), 3 86 (2H, s), 4 40 (2H, m), 6 53 (2H, m), 6 80 (1H, d), 7 01 (1H, d), 8 00 (1H, d), 8 27 (1H, s), MS *m/z* ($TS^+$) 333 ($MH^+$) |
| 42 | Prep 40 | $-NO_2$ |  | $\delta_H$ ($CDCl_3$, 400 MHz) 2 14 (2H, m), 2 52 (3H, s), 2 93 (4H, t), 3 92 (2H, s), 6 78 (1H, d), 6 81 (1H, d), 6 91 (1H, s), 7 22 (1H, d), 8 02 (1H, dd), 8 29 (1H, s), MS *m/z* ($TS^+$) 299 ($MH^+$) |
| 43 | Prep 24 | -OMe |  | HCl salt $\delta_H$ ($CDCl_3$, 300 MHz) 2 35 (3H, s), 2 45 (3H, s), 2 60 (3H, s), 3 84 (3H, s), 4 17 (2H, s), 6 80 (1H, d), 6 82 (1H, s), 6 88 (2H, s), 7 15 (1H, d), 7 42 (1H, s), 9 85 (2H, brs), MS *m/z* ($TS^+$) 304 ($MH^+$) |
| 44 | Prep 23 | Br |  | $\delta_H$ ($CDCl_3$, 300 MHz) 2 35 (3H, s), 2 45 (6H, s), 3 77 (2H, s), 6 73 (2H, m), 6 80 (1H, s), 7 19 (1H, d), 7 32 (1H, d), 7 57 (1H, s), MS *m/z* ($TS^+$) 352, 354 ($MH^+$) |
| 45 | Prep 30 | H |  | HCl salt $\delta_H$ ($d_6$-DMSO, 400 MHz) 2 22 (3H, s), 2 42 (3H, s), 2 58 (3H, s), 4 18 (2H, s), 6 76 (1H, d), 6 96 (1H, d), 6 99 (1H, s), 7 18 (1H, t), 7 25 (1H, d), 7 38 (1H, t), 7 60 (1H, d), MS *m/z* ($ES^+$) 274 ($MH^+$) |

| Example | Precursor | $R^a$ | | data |
|---|---|---|---|---|
| 46 | Prep 31 | H |  | HCl salt $\delta_H$ ($CDCl_3$, 400 MHz) 2 55 (3H, brs), 3 21 (2H, t), 3 32 (2H, m), 4 17 (2H, s), 6 76 (1H, d), 6 84 (1H, d), 6 99 (1H, s), 7 04 (1H, m), 7 12 (1H, d), 7 28 (1H, obs), 7 61 (1H, d), MS *m/z* ($ES^+$) 272 ($MH^+$) |
| 47 | Prep 28 | H |  | Maleate salt $\delta_H$ (DMSO-$d_6$, 400 MHz) 2 60 (3H, s), 4 19 (2H, s), 5 99 (2H, s), 7 03 (1H, d), 7 29 (1H, m), 7 37 (1H, s), 7 45 (3H, m), 7 60 (1H, d), 8 06 (1H, d), 8 37 (1H, d), 8 74 (2H, br), 8 83 (1H, dd), MS *m/z* 264 ($MH^+$) |
| 48 | Prep 26 | H |  | $\delta_H$ ($CDCl_3$, 300 MHz) 2 64 (3H, s), 4 25 (2H, s), 6 89 (1H, d), 7 19 (1H, t), 7 30-7 41 (2H, m), 7 45 (1H, s), 7 49 (1H, d), 7 69 (1H, d), 8 08 (1H, d), 8 16 (1H, d), 8 87 (1H, d), MS *m/z* ($ES^+$) 529 ($2M+H^+$) |
| 49 | Prep 34 | -CN |  | HCl salt $\delta_H$ ($CD_3OD$, 400 MHz) 2 81 (3H, s), 3 30 (1H, br), 4 42 (2H, s), 7 17 (1H, br), 7 82 (1H, br), 8 06 (1H, br), 8 11 (3H, br), 8 39 (1H, br), 9 18 (1H, br), 9 21 (1H, br), MS *m/z* ($ES^+$) 290 ($MH^+$) |

[a] – 2M Methylamine in MeOH (2 equiv ) and $Ti(O^iPr)_4$ (2 equiv ) in EtOH (~0 1 M soln of aldehyde) were used in place of methylamine in EtOH After isolation of the free base it was converted to the maleate salt by standard methods

EXAMPLE 50

(2*E*)-3-[4-(2,3-Dihydro-1-benzothien-6-yloxy)-3-[(dimethylamino)methyl]phenyl]-2-propenamide

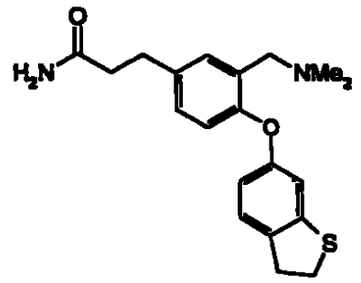


A mixture of the bromide of Example 32 (400 mg, 1 10 mmol), acrylamide (156 mg, 2 19 mmol), triethylamine (0 38 mL, 2 74 mmol), palladium II acetate (12 5 mg, 0 06 mmol) and tri-o-tolylphosphine (33.4 mg, 0 11 mmol) in acetonitrile (15 mL) was heated at reflux for 72 h After cooling to room temperature the solvent was removed *in vacuo* and

the residue was partitioned between EtOAc (50 mL) and 2M HCl (50 mL) The aqueous phase was basified with 2M NaOH and extracted with EtOAc (3×50 mL) The combined basic extracts were dried ($MgSO_4$) and evaporated The residue was purified by column chromatography [$SiO_2$, 96 4 0 5 (DCM/ MeOH/ 880 $NH_3$) increasing polarity to 90 10 1] to give the title compound (196 mg, 50%) as a beige foam, $\delta_H$ ($CDCl_3$, 400 MHz) 2 28 (6H, s), 3 24 (2H, t), 3 38 (2H, t), 3 51 (2H, s), 5 73 (2H, br), 6 42 (1H, d), 6 59 (1H, dd), 6 82 (2H, m), 7 10 (1H, d), 7 32 (1H, d), 7 60 (1H, d), 7 69 (1H, s), MS *m/z* ($ES^+$) 355 ($MH^+$)

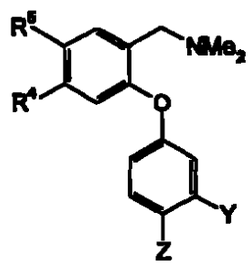
EXAMPLE 51

3-(4-(2,3-Dihydro-1-benzothien-6-yloxy)-3-[(dimethylamino)methyl]phenyl)propanamide



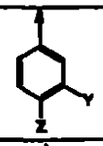
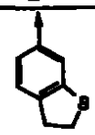
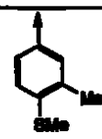
A solution of $SmI_2$ in THF (0 1 M, 21.9 mL, 2 19 mmol) was added to a solution of the alkene of Example 50 (194 mg, 0 55 mmol) in THF (5 mL) under nitrogen followed by water (1 mL). After stirring at room temperature for 10 min the reaction was quenched with 6M NaOH (10 mL) and stirred for 30 min The organic phase was separated and the aqueous phase was extracted with EtOAc (2×20 mL) The combined organic layers were dried ($MgSO_4$) and evaporated to an oil, which was purified by column chromatography [$SiO_2$, 93 7 1 (DCM/ MeOH/ 880 $NH_3$) increasing polarity to 90 10 1] to give the title compound (90 mg, 46%), $\delta_H$ ($CDCl_3$, 400 MHz) 2 25 (6H, s), 2 54 (2H, t), 2 97 (2H, t), 3 22 (2H, t), 3 36 (2H, t), 3 42 (2H, s), 5.20-5 46 (2H, br), 6 54 (1H, d), 6 73 (1H, s), 6 81 (1H, d), 7 05 (2H, m), 7.31 (1H, s), MS *m/z* ($TS^+$) 357 ($MH^+$).

Compounds of formula If, I e. compounds of general formula I where $R^1$ and $R^2$ are methyl, shown in Table 5 were prepared according to Preparation 50 from the precursors indicated.



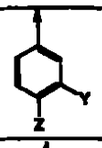
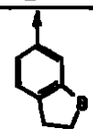
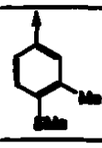
(If)

Table 5

| Example | Precursor | $R^4$ | $R^5$ |  | data |
|---|---|---|---|---|---|
| 52 | Example 32 | H | $-CO_2Me$ |  | $\delta_H$ ($CDCl_3$, 400 MHz) 2 29 (6H, s), 3 26 (3H, m), 3 39 (2H, m), 3 54 (2H, s), 3 89 (3H, s), 6 62 (1H, d), 6 84 (2H, m) 7 13 (1H, d), 7 86 (1H, d), 8 12 (1H, s), MS *m/z* ($TS^+$) 344 ($MH^+$) |
| 53 | Example 33 | $-CO_2Me$ | H |  | $\delta_H$ ($CDCl_3$, 400 MHz) 2.24 (6H, s), 2 33 (3H, s), 2 42 (3H, s), 3 48 (2H, s), 3 82 (3H, s), 6 73 (2H, m), 7 14 (1H, d), 7 50 (1H, s), 7 55 (1H, d), 7 78 (1H, d), MS *m/z* ($TS^+$) 346 ($MH^+$) |

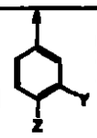
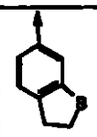
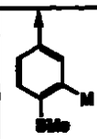
Compounds of formula If, i e compounds of general formula I where $R^1$ and $R^2$ are methyl, shown in Table 6 were prepared according to Preparation 55 from the precursors indicated

Table 6

| Example | Precursor | $R^4$ | $R^5$ |  | data |
|---|---|---|---|---|---|
| 54 | Example 52 | H | $-CO_2H$ |  | $\delta_H$ ($CD_3OD$, 400 MHz) 2 95 (6H, s), 3 29 (2H, m), 3 42 (2H, m), 4 52 (2H, s), 6 80 (1H, d), 6 89 (1H, d), 7 03 (1H, s), 7 29 (1H, d), 8 06 (1H, d), 8 23 (1H, s), MS *m/z* ($TS^+$) 330 ($MH^+$) |
| 55 (~80% purity) | Example 55 | $-CO_2H$ | H |  | $\delta_H$ ($CD_3OD$, 400 MHz) 2 27 (3H, s), 2 42 (3H, s), 2 88 (6H, s), 4 43 (2H, s), 6 95 (2H, m), 7 26 (1H, m), 7 42 (2H, m), 7 72 (1H, m) |

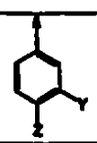
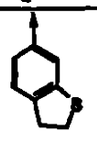
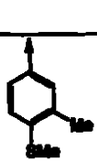
Compounds of formula If, i e compounds of general formula I where $R^1$ and $R^2$ are methyl, shown in Table 7 were prepared according to Preparation 59 from the precursors indicated

Table 7

| Example | Precursor | $R^4$ | $R^5$ |  | data |
|---|---|---|---|---|---|
| 56 | Example 54 | H | $-CONH_2$ |  | $\delta_H$ ($CDCl_3$, 400 MHz) 2 27 (6H, s), 3 25 (2H, m), 3 38 (2H, m), 3 54 (2H, s), 5 90-6 38 (2H, br), 6 59 (1H, d), 6 80 (1H, s), 6 86 (1H, d), 7 11 (1H, d), 7 71 (1H, d), 7 92 (1H, s), MS *m/z* ($TS^+$) 329 ($MH^+$) |
| 57 | Example 55 | $-CONH_2$ | H |  | HCl salt $\delta_H$ ($CD_3OD$, 400 MHz) 2 32 (3H, s), 2 43 (3H, s), 2 94 (6H, s), 4 47 (2H, s), 6 98 (2H, br), 7 27 (1H, br), 7 36 (1H, br), 7 62 (1H, br); MS *m/z* ($TS^+$) 331 ($MH^+$) |

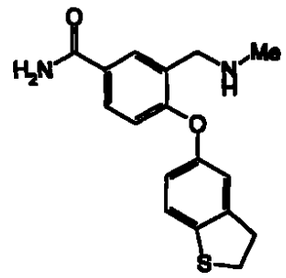
Compounds of formula If, i e compounds of general formula I where $R^1$ and $R^2$ are methyl, shown in Table 8 were prepared according to Preparation 69 from the precursors indicated

Table 8

| Example | Precursor | $R^4$ | $R^5$ |  | data |
|---|---|---|---|---|---|
| 58 | Example 52 | H | $-CH_2OH$ |  | HCl salt: $\delta_H$ (DMSO-$d_6$, 400 MHz) 2 76 (6H, s), 3 22 (2H, m), 3 40 (2H, m), 4 30 (2H, s), 4 49 (2H, s), 5 27 (1H, br, s), 6 88 (1H, d), 6 83 (1H, d), 6 97 (1H, s), 7 25 (1H, d), 7 37 (1H, d), 7 60 (1H, s), 10 07 (1H, br), MS *m/z* ($TS^+$) 316 ($MH^+$) |
| 59 | Example 53 | $-CH_2OH$ | H |  | HCl salt $\delta_H$ ($CD_3OD$, 400 MHz) 2 34 (3H, s), 2 46 (3H, s), 2 90 (6H, s), 4 40 (2H, s), 4 55 (2H, s), 6 89 (1H, s), 6 95 (2H, m), 7 18 (1H, d), 7 28 (1H, d), 7 50 (1H, d), MS *m/z* ($TS^+$) 318 ($MH^+$) |

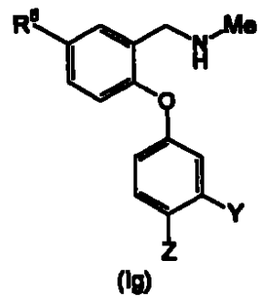
EXAMPLE 60

4-(2,3-Dihydro-1-benzothien-5-yloxy)-3-[(methylamino)methyl]benzamide



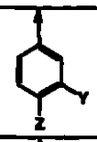
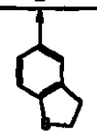
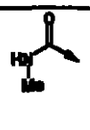
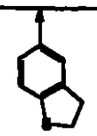
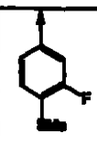
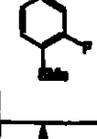
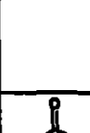
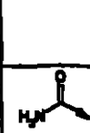
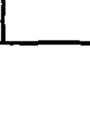
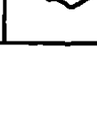
The protected amine of Preparation 59 (317 mg, 0 76 mmol) was dissolved in a saturated solution of HCl in DCM (25 mL) at 0°C and left for 1 h before being neutralised by the addition of 10% aq $K_2CO_3$ (25 mL) Water (50 mL) was added and the layers were separated The aqueous layer was extracted with DCM (25 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated The resulting oil was dissolved in EtOAc (10 mL) and treated with 1M ethereal HCl (1 mL) The white precipitate was collected by filtration and dried *in vacuo* to give the desired product (211 mg, 77%), $\delta_H$ ($CD_3OD$, 400 MHz) 2 77 (3H, s), 3 35 (2H, obs), 3 39 (2H, t), 4 34 (2H, s), 6 79 (1H, d), 6 90 (1H, dd), 7 02 (1H, s), 7 21 (1H, d), 7 83 (1H, d), 8 00 (1H, s), MS *m/z* ($TS^+$) 315 ($MH^+$)

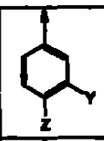
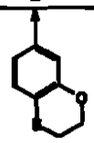
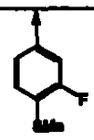
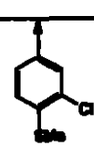
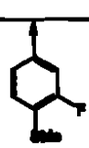
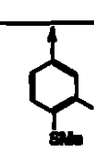
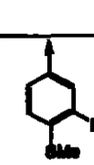
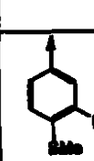
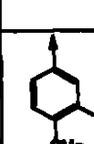
Compounds of formula Ig, i e compounds of general formula I where $R^1$ and $R^4$ are hydrogen and $R^2$ is methyl, shown in Table 9 were prepared according to Example 60 from the precursors indicated



(Ig)

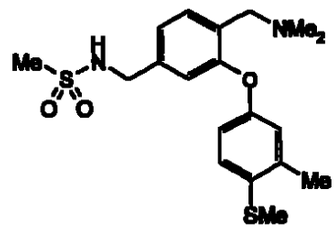
Table 9

| Ex | Prec | $R^5$ |  | data |
|---|---|---|---|---|
| 61 | Prep 61 |  |  | HCl salt $\delta_H$ ($CDCl_3$, 400 MHz) 2 77 (3H, d), 3 35 (2H, obs), 3 36 (3H, s), 3 39 (2H, t), 3 51 (4H, s), 4 35 (2H, s), 6 80 (1H, d), 6 90 (1H, dd), 7 01 (1H, s), 7 21 (1H, d), 7 79 (1H, d), 7 96 (1H, s), MS *m/z* ($TS^+$) 373 ($MH^+$) |
| 62 | Prep 60 |  |  | HCl salt $\delta_H$ ($CD_3OD$, 400 MHz) 2.77 (3H, s), 2 88 (3H, s), 3 35 (2H, obs), 3 39 (2H, t), 4 35 (2H, s), 6 79 (1H, d), 6 90 (1H, dd), 7.01 (1H, s), 7.20 (1H, d), 7 78 (1H, d), 7 96 (1H, s); MS *m/z* ($TS^+$) 329 ($MH^+$) |
| 63 | Prep 62 |  |  | HCl salt $\delta_H$ ($d_6$-DMSO, 300 MHz) 2 52 (3H, obs), 2.61 (3H, s), 4 21 (3H, s), 6 90 (1H, d), 7 07 (1H, d), 7 19 (1H, d), 7 40 (1H, brs), 7 48 (1H, t), 7 92 (1H, d), 7 96 (1H, s), 8 21 (1H, s), MS *m/z* ($TS^+$) 321 ($MNH_4^+$) |
| 64 | Prep 63 |  |  | HCl salt. $\delta_H$ ($d_6$-DMSO, 300 MHz) 2 52 (3H, obs), 2 60 (3H, s), 2 79 (3H, d), 4 21 (2H, s), 6 89 (1H, d), 7 07 (1H, d), 7 19 (1H, d), 7 48 (1H, t), 7 85 (1H, d), 8 19 (1H, s), 8.48 (1H, d), MS *m/z* ($TS^+$) 335 ($MH^+$) |
| 65 | Prep 64 |  |  | HCl salt. $\delta_H$ ($d_6$-DMSO, 300 MHz) 2 52 (3H, obs), 2 60 (3H, s), 3 27 (3H, s), 3 46 (4H, m), 4 22 (2H, s), 6 91 (1H, d), 7 08 (1H, d), 7.20 (1H, d), 7 50 (1H, t), 7 89 (1H, d), 8 10 (1H, s), 8 58 (1H, brs), MS *m/z* ($TS^+$) 379 ($MH^+$) |
| 66 | Prep 65 |  |  | HCl salt $\delta_H$ ($d_6$-DMSO, 300 MHz) 2.52 (3H, obs), 2 60 (3H, t), 4 11 (2H, s+$H_2O$), 6 82 (1H, d), 7 21 (1H, d), 7 40 (3H, s+d), 7 88 (1H, d), 7 96 (1H, brs), 8 21 (1H, s), MS *m/z* ($ES^+$) 337 ($MH^+$) |
| 67 | Prep 66 |  |  | HCl salt: $\delta_H$ ($d_6$-DMSO, 300 MHz) 2 52 (3H, obs), 2 60 (3H, t), 2 79 (3H, d), 4 22 (2H, t), 6.94 (1H, d), 7 22 (1H, d), 7 40 (2H, s+d), 7 83 (1H, d), 8 19 (1H, d), 8 46 (1H, d), MS *m/z* ($ES^+$) 351 ($MH^+$) |
| 68 | Prep 67 |  |  | $\delta_H$ ($CDCl_3$, 400 MHz) 2.41 (3H, s), 3 08 (2H, m), 3 80 (2H, s), 4 37 (2H, m), 5 94-6 36 (2H, brd), 6 46 (1H, s), 6 49 (1H, d), 6 81 (1H, d), 6 96 (1H, d), 7 65 (1H, d), 7 86 (1H, s), MS *m/z* ($TS^+$) 331 ($MH^+$) |

| Ex | Prec | $R^6$ |  | data |
|---|---|---|---|---|
| 69 | Prep 68 |  |  | HCl salt $\delta_H$ ($CDCl_3$, 400 MHz) 2 42 (3H, s), 3 08 (2H, m), 3 44-3 50 (4H, m), 3 80 (2H, s), 4 40 (2H, m), 6 45 (1H, s), 6 49 (1H, d), 6 62 (1H, brs), 6 83 (1H, d), 6 96 (1H, d), 7 62 (1H, d), 7 78 (1H, s), MS *m/z* ($TS^+$) 390 ($MH^+$) |
| 70 | Prep 70 |  |  | HCl salt. $\delta_H$ ($d_6$-DMSO, 300 MHz) 2 48 (3H, s), 2 58 (3H, s), 4 12 (2H, s), 4 50 (2H, d), 5 32 (1H, t), 6 92 (2H, m), 7 03 (1H, dd), 7 39 (1H, dd), 7 46 (1H, d), 7 60 (1H, s), MS *m/z* ($TS^+$) 308 ($MH^+$) |
| 71 | Prep 69 |  |  | HCl salt $\delta_H$ ($d_6$-DMSO, 300 MHz) 2,52 (3H, obs), 2 58 (3H, t), 4 10 (2H, s+$H_2O$), 4 48 (2H, s), 6 94 (1H, d), 7 11 (1H, d), 7 21 (1H, s), 7 25 (2H, m), 7 57 (1H, s), MS *m/z* ($ES^+$) 324 ($MH^+$) |
| 72 | Prep 49 | -C≡N |  | HCl salt. $\delta_H$ ($d_6$-DMSO, 300 MHz) 2 52 (3H, s), 2 60 (3H, s), 4 24 (2H, s), 6 94 (1H, d), 7 04 (1H, d), 7 28 (1H, d), 7 50 (1H, t), 7 86 (1H, d), 8 08 (1H, s), MS *m/z* ($TS^+$) 303 ($MH^+$) |
| 73 | Prep 73 |  |  | HCl salt $\delta_H$ ($CDCl_3$, 300 MHz) 2 48 (3H, s), 2 64 (3H, s), 2 99 (3H, s), 4 23 (2H, s), 4 30 (2H, d), 6 40 (1H, br), 6 81-6 89 (3H, m), 7 26-7 35 (2H, obs), 7 92 (1H, s), MS *m/z* ($ES^+$) 385 ($MH^+$), ($ES^-$) 383 ($M-H^+$) |
| 74 | Prep 71 |  |  | HCl salt. $\delta_H$ ($CD_3OD$, 400 MHz) 2 30 (3H, s), 2 44 (3H, s), 2 73 (3H, s), 4 25 (2H, s), 4 59 (2H, s), 6 81 (1H, d), 6 88-6 92 (2H, m), 7 24 (1H, d), 7 37 (1H, d), 7 46 (1H, s), MS *m/z* ($ES^+$) 304 ($MH^+$) |
| 75 | Prep 72 |  |  | HCl salt $\delta_H$ ($CD_3OD$, 300 MHz) 2 37 (3H, s), 2 48 (3H, s), 2.78 (3H, s), 2 96 (3H,s), 4.27 (2H, s), 4 31 (2H, s), 6 85 (1H, d), 6 92-7 00 (2H, m), & 31 (1H, d), 7 41 (1H, d), 7 57 (1H, s), MS *m/z* ($ES^+$) 381 ($MH^+$), ($ES^-$) 379 ($M-H^+$) |
| 76 | Prep 75 |  |  | HCl salt: $\delta_H$ ($CD_3OD$, 400 MHz) 2.29 (3H, s), 2 41 (3H, s), 2 43 (3H, s), 3 76 (2H, s), 4 30 (2H, s), 6 72-6 79 (3H, m), 7 12 (1H, br), 7 27 (2H, obs), MS *m/z* ($ES^+$) 435 ($MH^+$), ($ES^-$) 433 ($M-H^+$) |

EXAMPLE 77

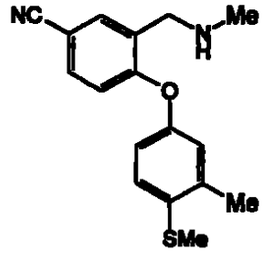
*N*-[4-[(Dimethylamino)methyl]-3-[3-methyl-4-(methylsulfanyl)phenoxy]benzyl]methanesulfonamide



Example 77 was prepared from the Boc protected sulfonamide of Preparation 74 by the method of Example 60 ,HCl salt. $\delta_H$ ($CD_3OD$, 400 MHz) 2 29 (3H, s), 2.42 (3H, s), 2 82 (3H, s), 2 89 (6H, s), 4 17 (2H, s), 4 39 (2H, s), 6.39 (3H, m), 7 19 (1H, d), 7 24 (1H, d), 7 48 (1H, d), MS *m/z* ($TS^+$) 395 ($MH^+$)

EXAMPLE 78

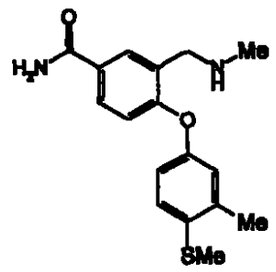
3-[(Methylamino)methyl]-4-[3-methyl-4-(methylsulfanyl)phenoxy]benzonitrile



$Zn(CN)_2$ (700 mg, 5 96 mmol) and $Pd(PPh_3)_4$ (1 97 g, 1 7 mmol) were added to a solution of the bromide of Example 44 (3 0 g, 8 52 mmol) in DMF (20 mL) and the mixture was heated at 100°C for 17 h The reaction was cooled to room temperature, diluted with water (100 mL) and extracted with ether (2×100 mL then 3×50 mL) The combined organic layers were washed with water (3×50 mL), dried ($MgSO_4$) and evaporated to a yellow oil Initial purification by column chromatography [$SiO_2$, 95 5 0 5 (DCM/ MeOH/ 880 $NH_3$)] was unsuccessful so the material was re-chromatographed [$SiO_2$, 50% pentane in 95 5 0 5 (DCM/ MeOH/ 880 $NH_3$) increasing polarity to 0% pentane] to give the product (1 275 g, 50%) as a pale yellow oil A sample was taken up in DCM (5 mL) and treated with 1M ethereal HCl to give the HCl salt as a white powder which was collected by filtration, $\delta_H$ ($CDCl_3$, 300 MHz) 2 35 (3H, s), 2 47 (6H, s), 3 88 (2H, s), 6 79 (1H, d), 6 87 (2H, m), 7 20 (1H, d), 7 46 (1H, d), 7 72 (1H, s), MS *m/z* ($TS^+$) 299 ($MH^+$)

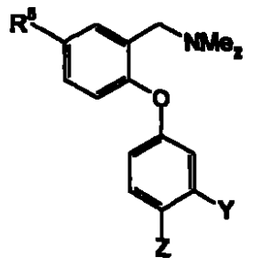
EXAMPLE 79

3-[(Methylamino)methyl]-4-[3-methyl-4-(methylsulfanyl)phenoxy]benzamide



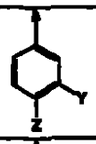
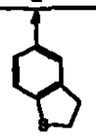
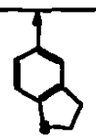
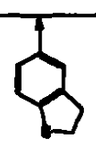
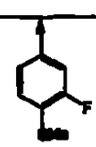
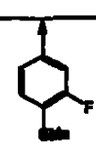
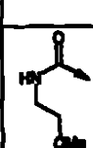
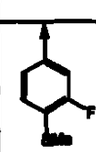
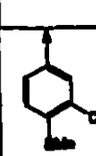
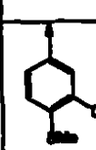
A mixture of the nitrile of Example 78 (404 mg, 1 35 mmol) and KOH (304 mg, 5 42 mmol) in *tert*-butanol (10 mL) was heated at reflux for 1 h under $N_2$. After cooling to room temperature the solvent was removed *in vacuo* and the residue was partitioned between water (10 mL) and DCM (10 mL) The aqueous layer was extracted with DCM (4 x 20 mL) and the combined organic layers were washed with brine, dried ($MgSO_4$) and evaporated The residue was purified by column chromatography [$SiO_2$, 93 7 1 (DCM/ MeOH/ 880 $NH_3$)] to give the desired product (376 mg, 88%) as a white foam, $\delta_H$ ($CDCl_3$, 300 MHz) 2.35 (3H, s), 2.47 (3H, s), 2.49 (3H, s), 3 88 (2H, s), 5.90-6.30 (2H, brs), 6 82 (3H, m), 7 19 (1H, d), 7 70 (1H, d), 7 90 (1H, s), MS *m/z* ($TS^+$) 317 ($MH^+$)

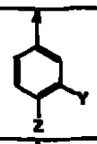
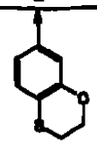
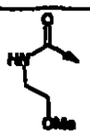
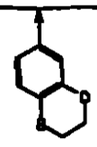
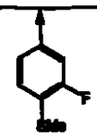
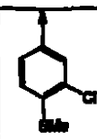
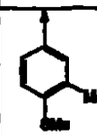
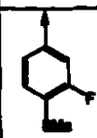
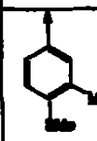
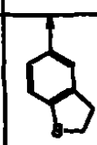
Compounds of formula Ih, I e compounds of general formula I where $R^1$ and $R^2$ are methyl and $R^4$ is hydrogen, shown in Table 10 where prepared according to Example 12 from the precursors indicated

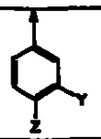
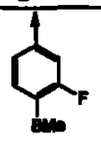
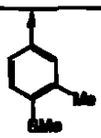
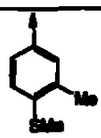
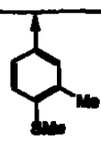
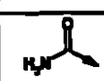
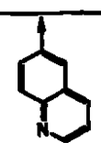


(Ih)

Table 10

| Example | Precursor | $R^5$ |  | data |
|---|---|---|---|---|
| 80 | Example 80 |  |  | $\delta_H$ ($CD_3OD$, 400 MHz) 2 91 (6H, s), 3 35 (2H, obs), 3 38 (2H, t), 4 45 (2H, s), 6 81 (1H, d), 6 90 (1H, d), 7 03 (1H, s), 7.21 (1H, d), 7 86 (1H, d), 8 03 (1H, s), MS *m/z* ($TS^+$) 329 ($MH^+$) |
| 81 | Example 62 |  |  | $\delta_H$ ($CD_3OD$, 400 MHz) 2 90-2 99 (9H, m), 3 35 (2H, obs), 3 43 (2H, t), 4 50 (2H, s), 6 88 (1H, d), 6 97 (1H, d), 7 07 (1H, s), 7 28 (1H, d), 7 85 (1H, d), 8 03 (1H, s), MS *m/z* ($TS^+$) 343 ($MH^+$) |
| 82 | Example 61 |  |  | $\delta_H$ ($CDCl_3$, 400 MHz) 2 90 (6H, brm), 3 35 (2H, obs), 3 37 (2H, brm), 3 51 (4H, brm), 4 43 (2H, brs), 6 80-6 94 (2H, brd), 7 01 (1H, brs), 7 20 (1H, brs), 7 82 (1H, brs), 7.98 (1H, brs), MS *m/z* ($TS^+$) 387 ($MH^+$) |
| 83 | Example 63 |  |  | $\delta_H$ ($CDCl_3$, 300 MHz) 2 29 (6H, s), 2.47 (3H, s), 3 51 (2H, s), 6 73 (2H, s), 6 97 (1H, d), 7 30 (1H, t), 7 79 (1H, d), 7 97 (1H, s), MS *m/z* ($TS^+$) 335 ($MNH_4^+$) |
| 84 | Example 64 |  |  | $\delta_H$ ($CDCl_3$, 300 MHz) 2 29 (6H, s), 2 46 (3H, s), 3 02 (3H, d), 3 54 (2H, s), 6 20 (1H, brs), 6 69 (2H, m), 6 97 (1H, d), 7 30 (1H, t), 7 75 (1H, d), 7 91 (1H, s); MS *m/z* ($TS^+$) 349 ($MH^+$) |
| 85 | Example 65 |  |  | HCl salt $\delta_H$ ($CDCl_3$, 300 MHz) 2 49 (3H, s), 2 94 (6H, s), 3 42 (3H, s), 3 65 (4H, m), 4 33 (2H, s), 6 79 (2H, d), 6 96 (1H, d), 7 35 (1H, t), 7 39 (1H, brs), 7 98 (1H, d), 8 68 (1H, s), MS *m/z* ($TS^+$) 393 ($MH^+$) |
| 86 | Example 66 |  |  | $\delta_H$ ($CDCl_3$, 400 MHz) 2.38 (6H, s), 2,47 (3H, s), 3 53 (2H, s), 6 88 (2H, d), 7 03 (1H, s), 7 19 (1H, d), 7 77 (1H, d), 7 95 (1H, s), MS *m/z* ($ES^+$) 351 ($MH^+$) |
| 87 | Example 67 |  |  | $\delta_H$ ($CDCl_3$, 400 MHz) 2 27 (6H, s), 2 46 (3H, s), 3 01 (3H, d), 3 50 (2H, s), 6 19 (1H, brs), 6 88 (2H, m), 7 00 (1H, s), 7 19 (1H, d), 7 72 (1H, d), 7 85 (1H, s), MS *m/z* ($ES^+$) 365 ($MH^+$) |

| Example | Precursor | $R^5$ |  | data |
|---|---|---|---|---|
| 88 | Example 68 |  |  | HCl salt: $\delta_H$ ($CDCl_3$, 400 MHz) 2 25 (6H, s), 3 07 (2H, s), 3 49 (2H, s), 4 37 (2H, m), 5 47-6 22 (2H, brd), 6 44 (1H, s), 6 49 (1H, d), 6 86 (1H, d), 6 95 (1H, d), 7 68 (1H, d), 7 87 (1H, s), MS *m/z* ($TS^+$) 346 ($MH^+$) |
| 89 | Example 69 |  |  | HCl salt $\delta_H$ ($CD_3OD$, 400 MHz) 2 91 (6H, s), 3 13 (2H, s), 3 27 (3H, s), 4 39 (2H, s), 4.46 (2H, s), 6 64 (2H, s+d), 6 87 (1H, d), 7 08 (1H, d), 7 95 (1H, d), 8 00 (1H, s), MS *m/z* ($TS^+$) 403 ($MH^+$) |
| 90 | Example 70 |  |  | HCl salt $\delta_H$ ($d_6$-DMSO, 300 MHz) 2 46 (3H, s), 2 74 (6H, s), 4 29 (2H, s), 4 51 (2H, s), 5 32 (1H, brs), 6 93 (2H, d), 7 08 (1H, d), 7 41 (2H, m), 7 63 (1H, s), MS *m/z* ($TS^+$) 322 ($MH^+$) |
| 91 | Example 71 |  |  | HCl salt. $\delta_H$ ($d_6$-DMSO, 400 MHz) 2 52 (3H, obs), 2 76 (6H, s), 4 09 (2H, s), 4 49 (2H, s), 5 32 (1H, brs), 6 87 (1H, d), 7 08 (1H, d), 7 26 (1H, s), 7.38 (2H, m), 7 60 (1H, s), MS *m/z* ($ES^+$) 338 ($MH^+$) |
| 92 | Example 78 | -C≡N |  | HCl salt $\delta_H$ ($CDCl_3$, 400 MHz) 2 35 (3H, s), 2 48 (3H, s), 2 87 (6H, d), 4 39 (2H, d), 6 85 (1H, d), 6 90 (1H, d), 6 93 (1H, dd), 7 21 (1H, d), 7 60 (1H, d), 8 17 (1H, s), MS *m/z* ($TS^+$) 313 ($MH^+$) |
| 93 | Example 72 | -C≡N |  | HCl salt $\delta_H$ ($d_6$-DMSO, 300 MHz) 2 49 (3H, obs), 2 79 (6H, s), 4 41 (2H, s), 6 97 (1H, d), 7 14 (1H, d), 7 32 (1H, d), 7 49 (1H, t), 7 87 (1H, d), 8 22 (1H, s), MS *m/z* ($TS^+$) 317 ($MH^+$) |
| 94 | Example 45 | H |  | HCl salt $\delta_H$ ($d_6$-DMSO, 400 MHz) 2 23 (3H, s), 2 42 (3H, s), 2 76 (6H, s), 4 34 (2H, s), 6 80 (1H, d), 7.97 (1H, dd), 7 00 (1H, s), 7 19 (1H, t), 7 24 (1H, d), 7 40 (1H, t), 7 67 (1H, d), MS *m/z* ($ES^+$) 288 ($MH^+$) |
| 95 | Example 46 | H |  | HCl salt $\delta_H$ ($CDCl_3$, 400 MHz) 2 74 (6H, s), 3 22 (2H, m), 3 38 (2H, m), 4 26 (2H, s), 6 71 (1H, d), 6 80 (2H, bm), 7 15 (2H, bm), 7 32 (1H, d), 7 79 (2H, d), MS *m/z* ($ES^+$) 286 ($MH^+$) |

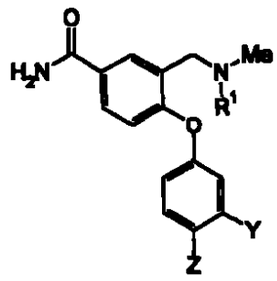
| Example | Precursor | $R^8$ |  | data |
|---|---|---|---|---|
| 96 | Example 73 |  |  | HCl salt. $\delta_H$ ($CD_3OD$, 300 MHz) 2 46 (3H, s), 3 93 (6H, s), 3 97 (3H, s), 4 24 (2H, s), 4 42 (2H, s), 6 91-7 00 (3H, m), 7 41-7 54 (2H, m), 7 61 (1H, s), MS *m/z* ($TS^+$) 399 ($MH^+$), ($ES^-$) 397 ($M-H^+$) |
| 97 | Example 75 |  |  | HCl salt $\delta_H$ ($CD_3OD$, 400 MHz) 2 31 (3H, s), 2 43 (3H, s), 2 86-2 94 (9H, m), 4.22 (2H, s), 4 39 (2H, s), 6 83 (1H, d) 6 89-6 94 (2H, m), 7.26 (1H, d), 7 40 (1H, d), 7 54 (1H, s), MS *m/z* ($ES^-$) 393 ($M-H^+$) |
| 98 | Example 74 |  |  | HCl salt $\delta_H$ ($CD_3OD$, 300 MHz) 2 36 (3H, s), 2 47 (3H, s), 2 98 (6H, s), 4 43 (2H, s), 4 63 (2H, s), 6 89 (1H, d), 6 91-7 00 (2H, m), 7 30 (1H, d), 7 43 (1H, d), 7 55 (1H, s), MS *m/z* ($ES^+$) 318 ($MH^+$) |
| 99 | Example 76 |  |  | HCl salt $\delta_H$ ($CD_3OD$, 300 MHz) 2 39 (3H, s), 2 47 (3H, s), 2 85 (6H, s), 4 32 (2H, s), 4 44 (2H, s), 6 80-6 86 (3H, m), 7 21 (1H, d), 7 35 (1H, d), 8 08 (1H, s), MS *m/z* ($ES^+$) 449 ($MH^+$), ($ES^-$) 447 ($M-H^+$) |
| 100 | Example 102 |  |  | $\delta_H$ ($CD_3OD$, 400 MHz) 2 26 (6H, s), 3 58 (2H, s), 6 97 (1H, d), 7 35 (1H, d), 7 46 (1H, dd), 7 54 (1H, d), 7 80 (1H, d), 8 03 (2H, m), 8 20 (1H, d), 8 74 (1H, d), MS *m/z* ($TS^+$) 322 ($MH^+$) |

Example 94 was also prepared as follows

A solution of the product from Preparation 30 (200 g, 0 78 mol) in DCM (1 4 L) was added to THF (1.4 L) To this mixture was added dimethylamine hydrochloride (69 5 g, 0 85 mol) and triethylamine (235 g, 2.33 mol) successively The temperature was adjusted to 20 °C and after 3 h sodium triacetoxyborohydride (246 g, 1 16 mol) was added (After 20 h, if the reaction has completed, continue with work up, otherwise see note below) Dichloromethane (2 L) was added and a solution of 8% sodium bicarbonate (0 9 L) was added over 0 5 h The layers were separated and the organic layer washed with water (1 L) The layers were again separated and the organic layer was concentrated Ethyl acetate (0 27 L) was added and the solvent removed replacing with

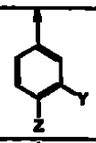
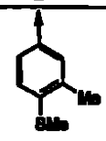
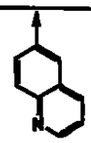
fresh ethyl acetate (800 ml) The solution was then cooled to below 5 °C and 7 02 M HCl/IPA (0 117 L, 0 82 mol) added whist the temperature was maintained below 10 °C After stirring for 1 h at below 5 °C, the slurry was filtered, washed with ethyl acetate (3 x 0 2 L) and dried in a vacuum oven at 50 °C overnight to give the desired product as a powdery solid (141 5 g, 56%) [Note if reaction hasn't completed after 20h Add another portion of dimethylamine hydrochloride (13g, 0 16mol) and triethylamine (43 4g, 0 43mol) successively After 2h at room temperature add sodium triacetoxyborohydride (46g, 0 22mol) Leave for a further 20h and then work up as above]

Compounds of formula Ii, I e compounds of general formula I where $R^2$ is methyl, $R^4$ is hydrogen and $R^5$ is $-C(=O)NH_2$, shown in Table 11 were prepared according to Example 79 form the precursors indicated



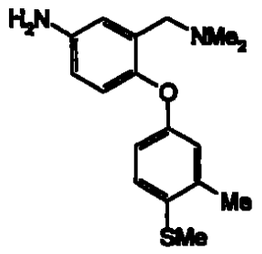
(II)

Table 11

| Example | Precursor | $R^1$ |  | data |
|---|---|---|---|---|
| 101 | Example 92 | Me |  | $\delta_H$ ($CDCl_3$, 300 MHz) 2 30 (6H, s), 2 35 (3H, s), 2 46 (3H, s), 3 58 (2H, s), 5 60-5 80 (1H, brs), 6 00-6.20 (1H, brs), 6 32 (3H, m), 7 19 (1H, m), 7 71 (1H, d), 7 90 (1H, s), MS *m/z* ($TS^+$) 331 ($MH^+$) |
| 102 | Example 49 | H |  | $\delta_H$ ($CDCl_3$, 400 MHz) 2 43 (3H, s), 3 84 (2H, s), 6 94 (1H, d), 7 20 (1H, d), 7 34-7 39 (1H, m), 7 43 (1H, dd), 7 70 (1H, d), 7 91 (1H, s), 7 99 (1H, d), 8 09 (1H, d), 8 82 (1H, d), MS *m/z* ($ES^+$) 309 ($MH^+$) |

EXAMPLE 103

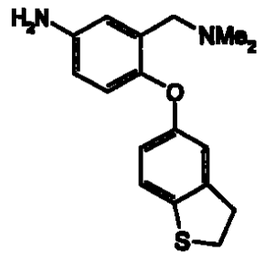
*N*-(5-Amino-2-[3-methyl-4-(methylsulfanyl)phenoxy]benzyl)-*N*,*N*-dimethylamine



A mixture of the nitro compound of Example 27 (2 0 g, 6 mmol), Fe powder (2 51 g, 44 9 mmol) and $CaCl_2$ (300 mg, 2 7 mmol) in EtOH (20 mL) and water (4 mL) was heated at reflux for 20 h After cooling to room temperature the solvent was removed *in vacuo* and the residue was partitioned between brine (100 mL) and ether (100 mL) The aqueous layer was extracted with ether (50 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated to give the product (1 47 g, 81%) as an orange oil, $\delta_H$ ($CDCl_3$, 300 MHz) 2.22 (6H, s), 2 32 (3H, s), 2 40 (3H, s), 3 33 (2H, s), 6 59 (1H, dd), 6 60-6 75 (2H, m), 6 78 (1H, dd), 6 94 (1H, s), 7 10-7 20 (3H, m), MS *m/z* ($ES^+$) 303 ($MH^+$).

EXAMPLE 104

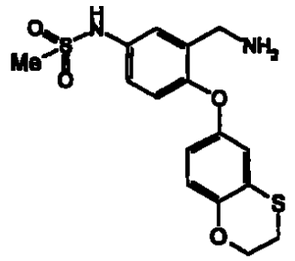
*N*-[5-Amino-2-(2,3-dihydro-1-benzothien-5-yloxy)benzyl]-*N*,*N*-dimethylamine



The title compound was prepared from the nitro compound of Example 28 by the method of Example 103, $\delta_H$ ($CDCl_3$, 400 MHz) 2.20 (6H, s), 3 16 (2H, t), 3 30 (4H, m), 3 54 (2H, br), 6 53 (1H, dd), 6 60 (1H, d), 6 71 (2H, m), 6.79 (1H, d), 7 01 (1H, d), MS *m/z* ($ES^+$) 301 ($MH^+$).

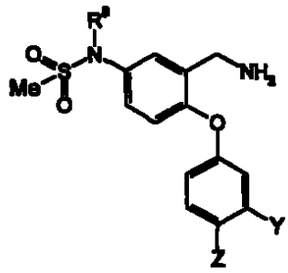
EXAMPLE 105

N-[3-(Aminomethyl)-4-(2,3-dihydro-1,4-benzoxathiin-6-yloxy)phenyl]-methanesulfonamide



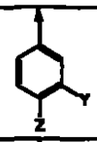
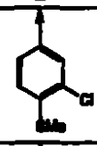
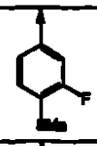
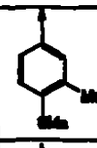
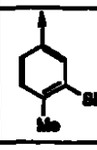
The nitrile of Preparation 95 (720 mg, 1 99 mmol) was dissolved in a 1M solution of $BH_3$ THF in THF (10 mL, 10 mmol) and the mixture was heated at reflux for 3 h After cooling to room temperature the reaction was quenched by the cautious addition of MeOH (10 mL) The solvent was evaporated, the residue was treated with 6M HCl (10 mL) and heated at reflux for 1 h After cooling, the mixture was basified with 2M NaOH and the pH was adjusted to 7 with sat aq $NH_4Cl$ The mixture was extracted with EtOAc (3x50 mL) and DCM (2x50 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated to give a beige foam (685 mg, 94%) which was used without further purification, $\delta_H$ ($CDCl_3$, 400 MHz) 3 00 (3H, s), 3 13 (2H, m), 3 87 (2H, s), 4 40 (2H, m), 6 62 (1H, d), 6 67 (1H, s), 6 79 (2H, d), 7 08 (1H, d), 7 25 (1H, d), MS *m/z* ($TS^+$) 367 ($MH^+$)

Compounds of formula Ij, i e compounds of general formula I where $R^1$, $R^2$ and $R^4$ are hydrogen and $R^5$ is -$NR^8$-$SO_2Me$, shown in Table 12 were prepared according to Example 105 from the precursors indicated



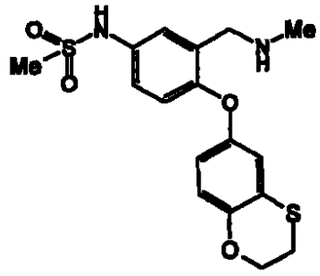
(II)

Table 12

| Example | Precursor |  | $R^8$ | data |
|---|---|---|---|---|
| 106 | Prep 96 |  | H | $\delta_H$ ($CDCl_3$, 300 MHz) 2 47 (3H, s), 3 02 (3H, s), 3 08 (3H, br), 3 85 (2H, s), 6 87 (2H, m), 6 99 (1H, d), 7 15 (1H, dd), 7 20 (1H, d), 7 30 (1H, d), MS *m/z* ($ES^-$) 371 ($M-H^+$) |
| 107 | Prep 97 |  | H | Used crude in a subsequent step $\delta_H$ ($CD_3OD$, 400 MHz) 2 37 (3H, s), 2 95 (3H, s), 3 75 (2H, s), 6 58 (1H, d), 6 71 (2H, m), 6 89 (1H, d), 7 15 (1H, dd), 7 28 (1H, obs) |
| 108 | Prep 100 |  | Me | Used crude in a subsequent step $\delta_H$ ($CDCl_3$, 300 MHz) 2 36 (3H, s), 2 46 3H, s), 2 90 (3H, s), 3 36 (3H, s), 3 93 (2H, s), 6 83 (3H, m), 7 20 (2H, m), 7 42 (1H, d) |
| 109 | Prep 99 |  | H | $\delta_H$ ($CD_3OD$, 400 MHz) 2 24 (3H, s), 2 40 (3H, s), 2 97 (3H, s), 3 80 (2H, s), 6 60 (1H, d), 6 81-6 87 (2H, m), 7 08-7 17 (2H, m), 7 29 (1H, d), MS *m/z* ($ES^+$) 353 ($MH^+$), ($ES^-$) 351 ($M-H^+$) |

EXAMPLE 110

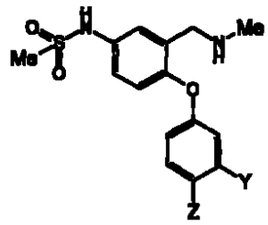
*N*-[4-(2,3-Dihydro-1,4-benzoxathiin-6-yloxy)-3-[(methylamino)methyl]phenyl]-methanesulfonamide



Dicyclohexylcarbodiimide (460 mg, 2 23 mmol) was added to a solution of pentafluorophenol (413 mg, 2.24 mmol) in ether (10 mL) followed by formic acid (95 µL, 2 5 mmol) The mixture was stirred for 2 h and then filtered, washing the residue with ether The filtrate was concentrated to ~5 mL and a solution of the primary amine of Example 105 (411 mg, 1 1 mmol) in DCM (10 mL) was added. The mixture was stirred for 16 h then concentrated to an oily residue This crude oil was taken up in a solution of $BH_3$.THF in THF (1M, 20 mL, 20 mmol) and heated at reflux for 1 5 h under $N_2$ After cooling to room temperature the reaction was quenched by the cautious addition of MeOH (10 mL) and then concentrated *in vacuo* The oily residue was treated with 6M

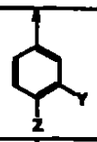
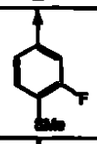
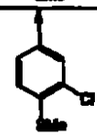
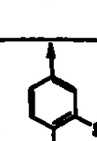
HCl and heated at reflux for 30 min After cooling to room temperature the mixture was basified with aq $K_2CO_3$ and extracted with DCM (3x) The combined organic extracts were dried ($MgSO_4$) and evaporated The residue was purified by column chromatography [$SiO_2$, 90 10 1 (DCM/ MeOH/ 880 $NH_3$)] to give a colourless oil which was taken up in EtOAc (20 mL) and treated with 1M ethereal HCl (2 mL) After stirring for 1 5 h the solid was collected by filtration to give the title product (282 mg, 60%), $\delta_H$ ($CD_3OD$, 400 MHz) 2 78 (3H, s), 2 98 (3H, s), 3 18 (2H, m), 4 29 (2H, s), 4 39 (2H, m),, 6 74 (1H, d), 6 80-6 90 (3H, m), 7 22 (1H, d), 7 44 (1H, s), MS *m/z* ($TS^+$) 381 ($MH^+$)

Compounds of formula Ik, i e compounds of general formula I where $R^1$ and $R^4$ are hydrogen, $R^2$ is methyl and $R^5$ is -$NHSO_2Me$, shown in Table 13 were prepared according to Example 110 from the precursors indicated

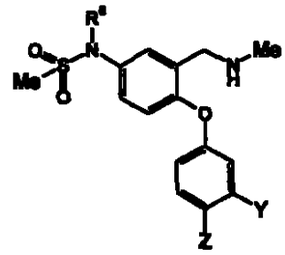


(Ik)

Table 13

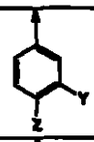
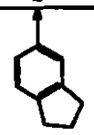
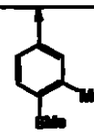
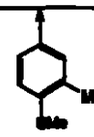
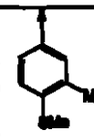
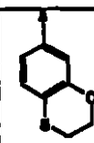
| Example | Precursor |  | data |
|---|---|---|---|
| 111 | Example 107 |  | $\delta_H$ ($CDCl_3$, 400 MHz) 2 40 (6H, s), 2 99 (3H, s), 3 70 (2H, s), 6 64 (2H, t), 6 88 (1H, d), 7 15 (1H, d), 7 25 (2H, s), MS *m/z* ($TS^+$) 371 ($MH^+$) |
| 112 | Example 108 |  | HCl salt. $\delta_H$ ($CD_3OD$, 400 MHz) 2 55 (3H, s), 3 82 (3H, s), 3 04 (3H, s), 4 32 (2H, s), 6 97 (1H, d), 7 11 (1H, d), 7 23 (1H, s), 7 30 (1H, d), 7 39 (1H, d), 7 56 (1H, s), MS *m/z* ($TS^+$) 387 ($MH^+$) |
| 113 | Example 109 |  | HCl salt $\delta_H$ ($CD_3OD$, 400 MHz) 2.24 (3H, s), 2 39 (3H, s), 2 76 (3H, s), 2 93 (3H, s), 4 25 (2H, s), 6 69 (1H, d), 6 82 (1H, d), 6 93 (1H, s), 7 17 (1H, d), 7 21 (1H, d), 7 43 (1H, s), MS *m/z* ($ES^+$) 367 ($MH^+$), ($ES^-$) 365 ($M-H^+$) |

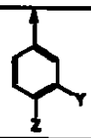
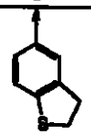
Compounds of formula Im, i e compounds of general formula I where $R^1$ and $R^4$ are hydrogen, $R^2$ is methyl and $R^5$ is $-NR^8SO_2Me$, shown in Table 14 were prepared according to Example 110 from the precursors indicated



(Im)

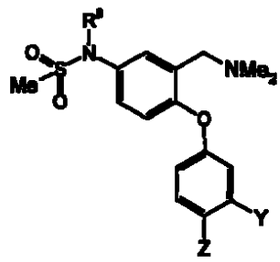
Table 14

| Example | Precursor | $R^8$ |  | data |
|---|---|---|---|---|
| 114 | Prep 85 | H |  | HCl salt: $\delta_H$ ($CDCl_3$, 400 MHz) 2.09 (2H, m), 2 73 (3H, s), 2 88 (4H, t), 3 00 (3H, s), 4 21 (2H, s), 6 80 (2H, m), 6 88 (1H, s), 7 19 (1H, d), 7 34 (1H, d), 7 75 (1H, s), MS *m/z* ($TS^+$) 347 ($MH^+$) |
| 115 | Prep 84 | H |  | HCl salt $\delta_H$ ($d_6$-DMSO, 400 MHz) 2 20 (3H, s), 2 40 (3H, s), 2 55 (3H, s), 2 97 (3H, s), 4 08 (2H, s), 6 80 (1H, d), 6 87 (1H, d), 6 91 (1H, s), 7 14 (1H, d), 7 20 (1H, d), 7 39 (1H, s), MS *m/z* ($TS^+$) 367 ($MH^+$) |
| 116[a] | Prep 88 | Me |  | $\delta_H$ ($CDCl_3$, 300 MHz) 2 17 (3H, s), 2,37 (3H, s), 2.48 (3H, s), 2 62 (3H, s), 2 97 (3H, s), 3 34 (3H, s), 4 23 (2H, s), 6 79 (1H, d), 6 94 (2H, s), 7 35 (2H, m), 7 81 (1H, s), MS *m/z* ($TS^+$) 381 ($MH^+$) |
| 117 | Prep 89 |  |  | HCl salt. $\delta_H$ ($CDCl_3$, 400 MHz) 2 29 (3H, s), 2 39 (3H, s), 2 42 (3H, s), 2 94 (3H, s), 3 60 (2H, t), 3 74 (2H, t), 3 79 (2H, s), 6 78 (3H, m), 7 14 (2H, m), 7 41 (1H, s), MS *m/z* ($TS^+$) 410 ($MH^+$) |
| 118 | Prep 87 | H |  | $\delta_H$ ($CDCl_3$, 400 MHz) 2 42 (3H, s), 2 58-2 79 (2H, br), 2 94 (3H, s), 3 08 (2H, m), 3 71 (2H, s), 4 38 (2H, m), 6.39 (1H, s), 6 47 (1H, d), 6.82 (1H, d), 6 94 (1H, d), 7 07 (1H, d), 7 18 (1H, s), MS *m/z* ($TS^+$) 381 ($MH^+$) |

| Example | Precursor | $R^8$ |  | data |
|---|---|---|---|---|
| 119 | Prep 86 | H |  | $\delta_H$ ($CD_3OD$, 400 MHz) 2 80 (3H, s), 3 00 (3H, s), 3 27 (2H, m), 3 40 (2H, m), 4 28 (2H, m), 6 85 (2H, m), 7 00 (1H, s), 7 20 (1H, d), 7 24 (1H, dd), 7 47 (1H, d), MS *m/z* ($TS^+$) 365 ($MH^+$) |

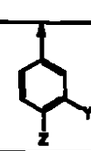
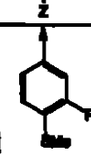
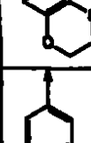
[a] – Also made from Example 108 by the method of Example 110

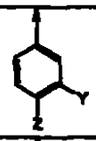
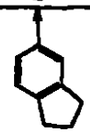
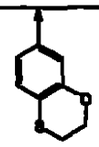
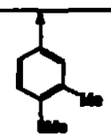
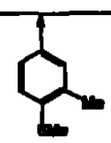
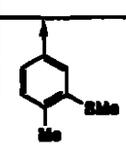
Compounds of formula In, i e compounds of general formula I where $R^1$ and $R^2$ are methyl, $R^4$ is hydrogen, and $R^5$ is $-NR^8SO_2Me$, shown in Table 15 were prepared according to Example 12 from the precursors indicated



(In)

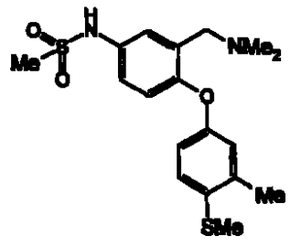
Table 15

| Example | Precursor | $R^8$ |  | Data |
|---|---|---|---|---|
| 120 | Example 111 | H |  | HCl salt $\delta_H$ ($CD_3OD$, 400 MHz) 2 42 (3H, s), 2 89 (6H, s), 2 98 (3H, s), 4 37 (2H, s), 6 88 (2H, m), 6 97 (1H, d), 7 28 (1H, d), 7 39 (1H, t), 7 48 (1H, s), MS *m/z* ($TS^+$) 385 ($MH^+$) |
| 121 (from primary amine) | Example 105 | H |  | $\delta_H$ ($CDCl_3$, 400 MHz) 3 00 (3H, s), 3 13 (2H, m), 3 87 (2H, s), 4 40 (2H, m), 6 62 (1H, d), 6 67 (1H, s), 6 79 (2H, d), 7 08 (1H, d), 7 25 (1H, d); MS *m/z* ($TS^+$) 367 ($MH^+$) |
| 122 (from primary amine) | Example 106 | H |  | HCl salt $\delta_H$ ($CD_3OD$, 400 MHz) 2 49 (3H, s), 2 93 (6H, s), 3 00 (3H, s), 4 41 (2H, s), 6 95 (1H, d), 7.07 (1H, d), 7 21 (1H, s), 7 33 (2H, m), 7 54 (1H, s), MS *m/z* ($TS^+$) 395 ($MH^+$) |

| Example | Precursor | $R^8$ |  | Data |
|---|---|---|---|---|
| 123 | Example 114 | H |  | HCl salt. $\delta_H$ ($CDCl_3$, 400 MHz) 2 12 (2H, m), 2 81 (6H, s), 2 91 (4H, t), 3 13 (3H, s), 4 25 (2H, s), 6 73 (1H, d), 6 83 (2H, m), 7 10 (1H, d), 7 39 (1H, d), 7 90 (1H, s), MS *m/z* ($TS^+$) 360 ($MH^+$) |
| 124 | Example 118 | H |  | $\delta_H$ ($CDCl_3$, 400 MHz) 2 22 (6H, s), 2 98 (3H, s), 3 07 (2H, m), 3 41 (2H, s), 4.38 (2H, m), 6 36 (1H, s), 6 45 (1H, d), 6 86 (1H, d), 6 92 (1H, d), 7 12 (1H, d), 7 27 (1H, s), MS *m/z* ($TS^+$) 395 ($MH^+$) |
| 125 | Example 117 |  |  | HCl salt. $\delta_H$ ($CDCl_3$, 300 MHz) 2 38 (3H, s), 2 48 (3H, s), 2 86 (6H, brs), 3 15 (3H, s), 3 73 (2H, brs), 3 87 (2H, brs), 4.35 (2H, brs), 6 82 (3H, brs), 7 20 (2H, m), 7 41 (1H, d), MS *m/z* ($TS^+$) 425 ($MH^+$) |
| 126 (from primary amine) | Example 108 | Me |  | HCl salt $\delta_H$ ($CD_3OD$, 400 MHz) 2 29 (3H, s), 2 43 (3H, s), 2 89 (3H, s), 2 91 (6H, s), 3 26 (3H, s), 4 42 (2H, s), 6 84 (1H, d), 6 97 (2H, m), 7 27 (1H, d), 7 47 (1H, dd), 7 60 (1H, d), MS *m/z* ($TS^+$) 395 ($MH^+$) |
| 127 (from primary amine) | Example 109 | H |  | HCl salt $\delta_H$ ($CD_3OD$, 400 MHz) 2 27 (3H, s), 2 42 (3H, s), 2 94 (6H, s), 2 99 (3H, s), 4 42 (2H, s), 6 77 (1H, d), 6 89 (1H, d), 6 99 (1H, s), 7 19 (1H, d), 7 28 (1H, dd), 7 50 (1H, s), MS *m/z* ($TS^+$) 381 ($MH^+$), ($ES^+$) 381 ($MH^+$), ($ES^-$) 379 ($M-H^+$) |

EXAMPLE 128

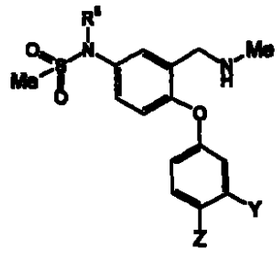
*N*-[3-[(Dimethylamino)methyl]-4-[3-methyl-4-(methylsulfanyl)phenoxy]-phenyl]methanesulfonamide



Methanesulfonyl chloride (371 µL, 4 79 mmol) was added to a solution of the aniline of Example 103 (725 mg, 2 4 mmol) and $Et_3N$ (1 mL, 7 17 mmol) in DCM (10 mL) at 0°C After stirring at 0°C for 1 h the reaction was allowed to warm to room temperature before the solvent was removed *in vacuo*. 2M NaOH (10 mL) was added to the residue and the mixture was stirred overnight The resulting clear solution was neutralised by the addition

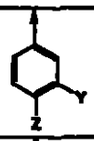
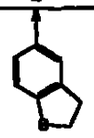
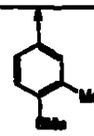
of sat aq $NH_4Cl$ and extracted with DCM (2x30 mL) The combined organic layers were dried ($MgSO_4$) and evaporated to give an oil This was taken up in EtOAc (10 mL), the HCl salt was precipitated by the addition of 1M ethereal HCl and the product (669 mg, 67%) was collected by filtration, $\delta_H$ ($d_6$-DMSO, 400 MHz) 2 23 (3H, s), 2 42 (3H, s), 2 75 (6H, s), 3 04 (3H, s), 4 38 (2H, s), 6 84 (1H, d), 6 93 (1H, d), 6 98 (1H, s), 7 17-7 25 (2H, m), 7 50 (1H, s), MS *m/z* ($ES^+$) 381 ($MH^+$)

Compounds of formula Ip, i e compounds of general formula I where $R^1$ and $R^2$ are methyl, $R^4$ is hydrogen, and $R^5$ is $-NHSO_2R^9$, shown in Table 16 were prepared according to Example 128 from the precursors indicated



(Ip)

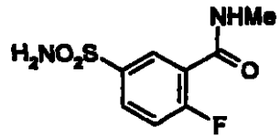
Table 16

| Example | Precursor | $R^9$ |  | data |
|---|---|---|---|---|
| 129 | Example 104 | Me |  | HCl salt $\delta_H$ ($CD_3OD$, 400 MHz) 2 92 (6H, s), 2 99 (3H, s), 3 26 (2H, t), 3 40 (2H, t), 4.41 (2H, s), 6 88 (2H, d), 7 00 (1H, s), 7 10 (1H, d), 7 27 (1H, d), 7 50 (1H, s), MS *m/z* ($TS^+$) 381 ($MH^+$) |
| 130 | Example 103 | Et |  | HCl salt $\delta_H$ ($d_6$-DMSO, 400 MHz) 1 21 (3H, t), 2 23 (3H, s), 2.42 (3H, s), 2 74 (6H, s), 3 16 (2H, q), 4 26 (2H, s), 6 92 (1H, d), 6 92 (1H, d), 6.98 (1H, s), 7 18-7 25 (2H, m), 7 51 (1H, s), MS *m/z* ($ES^+$) 395 ($MH^+$) |

PREPARATIONS

PREPARATION 1

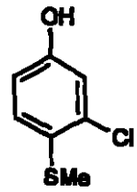
5-(Aminosulfonyl)-2-fluoro-*N*-methylbenzamide




To a solution of 5-(aminosulfonyl)-2-fluorobenzoic acid [prepared according to *Chem Pharm. Bull* 1995, 43, 582-7] (22.98 g, 105 mmol) in THF (500 mL) at room temperature under nitrogen was added carbonyldiimidazole (17 g, 105 mmol) After stirring for 2 25 h a solution of methylamine in THF (2M, 70 mL, 140 mmol) was added dropwise and the reaction was allowed to stir for 18 h The crude reaction mixture was concentrated to a low volume and EtOAc (150 mL) was added to the resulting thick oil This mixture was stirred and a granular precipitate formed which was collected by filtration This crude product, contaminated with imidazole, was suspended in DCM (300 mL) and heated at reflux for 5 h After cooling to room temperature the mixture was filtered to give the desired product (19 8 g, 81%) containing <2% w/w imidazole, $^1$H NMR $\delta_H$ (300 MHz, $d_4$-MeOH) 2 97 (3H, s), 7 40 (1H, t), 8 05 (1H, m), 8 29 (1H, d), MS *m/z* ($TS^+$) 250 ($MNH_4^+$)

PREPARATION 2

3-Chloro-4-(methylsulfanyl)phenol




(i) Preparation of 2-chloro-1-(methylsulfanyl)-4-nitrobenzene

To a solution of 4-fluoro-3-chloronitrobenzene (27 g, 156 mmol) in DMF (150 mL) at room temperature was added 5-*tert*-butyl-4-hydroxy-2-methylphenyl sulfide (100 mg) followed by sodium thiomethoxide (NaSMe) (10 g, 143 mmol) and the reaction was stirred for 6h The DMF was removed *in vacuo* and the residue was partitioned between ether (1 L) and water (1 L) The ether layer was washed with water (1 L) and brine (1 L), dried ($MgSO_4$) and the solvent was removed under reduced pressure The residue was purified by column chromatography ($SiO_2$, DCM pentane 1 5 increasing polarity to 3 7)

to give the title compound (15 22 g, 49%) as a yellow solid, $\delta_H$ (400 MHz, $CDCl_3$) 2 53 (3H, s), 7 20 (1H, d), 8 09 (1H, dd), 8 20 (1H, d)

(ii) Preparation of 3-chloro-4-(methylsulfanyl)aniline

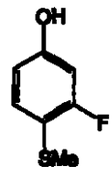
To a mixture of the above compound (14 08 g, 69 mmol) in acetic acid (300 mL) and water (60 mL) was added Fe powder (23 g, 412 mmol) and the reaction mixture was swirled until all the starting material had dissolved The mixture was left to stand for 1 5 h and the acetic acid was then removed under reduced pressure The residue was taken up in sat $NaHCO_3$ (aq) (500 mL) and EtOAc (500 mL) and filtered through Arbocel The layers were separated, the aqueous phase was extracted with EtOAc (300 mL) and the combined organics were washed with brine, dried ($MgSO_4$) and the solvent was removed *in vacuo* to give the title compound (11 52 g, 96%) as a beige solid, $\delta_H$ (400 MHz, $CDCl_3$) 2 38 (3H, s), 3 66 (2H, br), 6 53 (1H, dd), 6 70 (1H, d), 7 12 (1H, d), MS *m/z* ($ES^+$) 174 ($MH^+$)

(iii) Preparation of 3-chloro-4-(methylsulfanyl)phenol

The above aniline (11 5 g, 66 2 mmol) was dissolved in the minimum THF (~15 mL) and water (500 mL) was added with vigorous stirring, followed by conc $H_2SO_4$ (25 mL) The mixture was cooled in an ice-water bath and a solution of $NaNO_2$ (5 0 g, 72 5 mmol) in iced water (10 mL), was added via pipette under the surface of the reaction mixture The reaction was stirred at 0°C for 1 5 h and the resulting yellow/brown solution was decanted from the remaining solid into a dropping funnel containing ice (~200 g) This solution was added at a steady rate over 7 mm to a vigorously stirred mixture of $Cu(NO_3)_2$ (230 g, 0.99 mol) and $Cu_2O$ (8 52 g, 67 4 mmol) in water (1 L) at room temperature After the addition was complete the mixture was stirred for a further 15 min before being extracted with ether (500 mL) The residual red/brown solid in the reaction flask was taken up in MeOH (100 mL) and diluted with ether (300 mL) before being poured into the aqueous layer from above The ether layer was separated and the combined organic layers were extracted with 1M NaOH (3 x 100 mL) The aqueous extracts were acidified with conc. HCl and then extracted with ether (2 x 150 mL) The ether layers were then washed with brine, dried ($MgSO_4$) and the solvent was removed *in vacuo* to give the phenol (5 465 g, 47%) as a brown crystalline solid, $\delta_H$ (400 MHz, $CDCl_3$) 2 44 (3H, s), 5 08 (1H, br), 6 77 (1H, d), 6 93 (1H, d), 7 18 (1H, d), MS *m/z* ($ES^-$) 173 ($M-H^+$)

PREPARATION 3

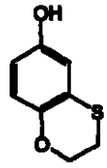
3-Fluoro-4-(methylsulfanyl)phenol




This compound was prepared using a similar method to that described above for Preparation 2 starting from commercially available 3,4-difluoronitrobenzene, $\delta_H$ ($CDCl_3$, 300 MHz) 2 40 (3H, s), 5 03 (1H, br), 6 60 (2H, m), 7 27 (1H, m obscured), MS *m/z* ($ES^-$) 157 ($M-H^+$)

PREPARATION 4

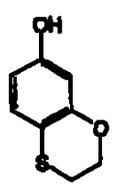
2,3-Dihydro-1,4-benzoxathiin-6-ol




1,2-Dibromoethane (2 3 mL, 26 7 mmol) and $K_2CO_3$ (6 21 g, 59 4 mmol) were slurried in acetone (250 mL) and a solution of 2-sulfanyl-1,4-benzenediol (prepared according to *J Org Chem* 1990, 55, 2736) (4.22 g, 29 7 mmol) in acetone (50 mL) was added over 4 h to the stirred mixture Once the addition was complete stirring was continued for a further 10 h before the solvent was removed *in vacuo* The residue was partitioned between water (50 mL) and EtOAc (50 mL), the aqueous layer was extracted with EtOAc (50 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated Purification of the residue by column chromatography [$SiO_2$; 9:1 (pentane/EtOAc)] gave the title compound (2 48 g, 55%) as a pale orange oil, $\delta_H$ ($CDCl_3$, 400 MHz) 3 08 (2H, m), 4.31 (2H, m), 4 44 (1H, s), 6 42 (1H, d), 6 49 (1H, s), 6 66 (1H, d), MS *m/z* ($ES^-$) 167 ($M-H^+$)

PREPARATION 5

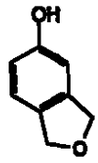
2,3-Dihydro-1,4-benzoxathiin-7-ol



The title compound was prepared in a similar manner to the compound of Preparation 4 starting from 4-sulfanyl-1,3-benzenediol (prepared according to *J Org Chem* 1979, *26*, 4971-4973), $\delta_H$ ($CDCl_3$, 400 MHz) 3 05 (2H, t), 4 37 (2H, t), 6 32 (1H, s), 6 35 (1H, d), 6 84 (1H, d), MS *m/z* ($TS^+$) 169 ($MH^+$)

PREPARATION 6

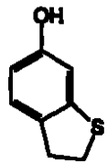
1,3-Dihydro-2-benzofuran-5-ol




1,3-Dihydro-2-benzofuran-5-amine (prepared according to US4000286) (2 7 g, 20 mmol) was dissolved in a mixture of water (300 mL) and conc. $H_2SO_4$ (21 mL), cooled to 0°C and $NaNO_2$ (1 43 g, 20 7 mmol) in water (10 mL) was added over 15 mm After stirring at 0°C for 1 h the mixture was allowed to stir at 10°C for 30 min and urea was added until a negative test with starch/KI paper was observed The solution was then poured over 2 min into a mixture of water (180 mL) and conc $H_2SO_4$ (12 6 mL) at 90°C and stirred at this temperature for 1 5 h The hot mixture was filtered then allowed to cool to room temperature The aqueous mixture was extracted with EtOAc (2 × 100 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated to give the title phenol (974 mg, 36%) as a cream solid, $\delta_H$ ($CDCl_3$, 400 MHz) 5 03 (4H, s), 6 71 (2H, m), 7 08 (1H, d)

PREPARATION 7

2,3-Dihydro-1-benzothiophen-6-ol




(i) Preparation of 2,3-dihydro-1-benzothiophen-6-ol 1,1-dioxide

A suspension of 2,3-dihydro-1-benzothiophen-6-amine 1,1-dioxide [prepared according to *J Am. Chem Soc.* 1955, 77, 5939] (15 73 g, 85 8 mmol) in water (500 mL) and conc. $H_2SO_4$ (35 mL) was warmed until solution was achieved The mixture was cooled to 0°C and a solution of $NaNO_2$ (6.22 g, 90 mmol) in water (15 mL) was then added over 5 min The reaction was stirred at 0°C for 1 h then urea was added, to remove excess nitrite,

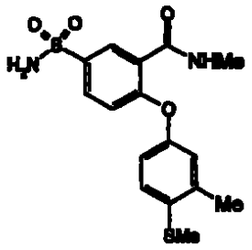
until a negative test with starch/KI paper was obtained The mixture was allowed to warm to room temperature then added with stirring to a mixture of conc. $H_2SO_4$ (55 mL) and water (750 mL) at 90°C The reaction was re-heated to 90°C and stirred at this temperature for 30 min The hot reaction mixture was filtered through Arbocel® then stirred at room temperature overnight. The aqueous mixture was extracted with ether (2 5 L) and then EtOAc (5 × 500 mL) and the combined organic layers were dried (MgSO4) and evaporated to give the desired phenol (12 7 g, 80%) which was used without further purification, $\delta_H$ ($CDCl_3$, 400 MHz) 3 30 (2H, m), 3 50 (2H, m), 7 05 (1H, m), 7 14 (1H, s), 7 23 (1H, m), MS *m/z* ($ES^-$) 183 ($M-H^+$)

(ii) Preparation of 2,3-dihydro-1-benzothiophen-6-ol

A solution of the sulfone from stage (i) (4 84 g, 26 3 mmol) in toluene (100 mL) and THF (70 mL) was added to a solution of DIBAL in toluene (1M, 100 mL, 100 mmol) and the mixture was then heated at reflux for 16 h After cooling to room temperature EtOH (75 mL) was added cautiously followed by water (100 mL) with stirring 6M HCl was added to the resulting thick suspension and the organic layer was separated The aqueous layer was extracted with EtOAc (3 × 150 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated to a beige solid Purification by column chromatography [$SiO_2$, DCM/ MeOH/ 880 $NH_3$ (97 3 0.25) increasing polarity to (95 5.0 5)] afforded the desired title phenol as a beige solid (1 85 g, 53%), $\delta_H$ ($CD_3OD$, 400 MHz) 3 13 (2H, t), 3 30 (2H, m), 6 41 (1H, d), 6 60 (1H, s), 6 98 (1H, d), MS *m/z* ($ES^-$) 151 ($M-H^+$)

PREPARATION 8

5-(Aminosulfonyl)-2-[3-methyl-4-(methylsulfanyl)phenoxy]-*N*-methylbenzamide

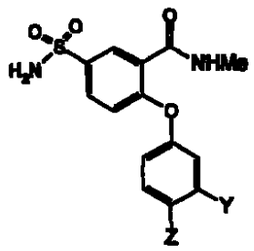



The fluoroamide of Preparation 1 (732 mg, 3 15 mmol) was treated with 4-(methylthio)-*m*-cresol (commercially available) (535 mg, 3 47 mmol) and potassium carbonate (457 mg, 3 31 mmol) in DMF (10 mL) The mixture was heated at 100 °C for 5 hours The solvent was removed by evaporation under reduced pressure and the residue was treated with 2M HCl (10 mL) The resulting suspension was extracted several times with dichloromethane. The combined dichloromethane layers contained a suspension and

were evaporated to a solid residue The residue was triturated with ether (5 mL) and the remaining solid was washed with ether (3x10 mL) to give an off-white solid (765 mg, 66%) $\delta_H$ (300 MHz, $d_6$-DMSO) 2.28 (3H, s), 2 48 (3H, s), 2 70 (3H, d), 6.90 (1H, d), 7 02 (1H, d), 7 03 (1H, s), 7 30 (1H, d), 7 35 (2H, s), 7 79 (1H, d), 8 10 (1H, d), 8 30 (1H, m), MS *m/z* (TS$^+$) 367 ($MH^+$), 385 ($MNH_4^+$)

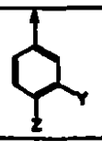
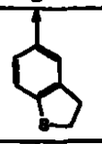
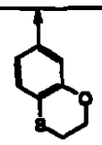
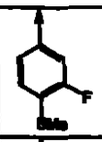
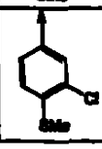
PREPARATIONS 9-18

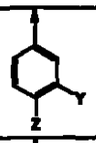
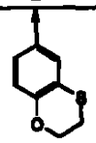
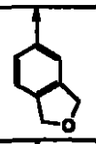
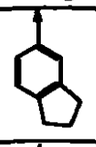
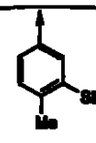
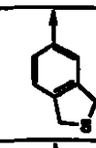
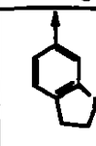
Compounds of formula Va, i e compounds of general formula V where T is -C(=O)NHMe, $R^4$ is hydrogen and $R^5$ is $-SO_2NH_2$, shown in Table 17 were prepared according to Preparation 8 using the sulfonamide of Preparation 1 and the phenol indicated




(Va)

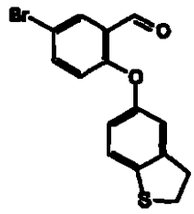
Table 17

| Preparation | Precursor phenol |  | data |
|---|---|---|---|
| 9 | *Synth Commun* 1991, 21, 959-964 |  | $\delta_H$ ($d_6$-DMSO,400 MHz) 2 80 (3H, d), 3 20 (2H, t), 3,40 (2H, t), 6 90 (1H, m), 7 05 (1H, s), 7 25 (1H, d), 7 35 (1H, s), 7 80 (1H, m), 8 10 (1H, s), 8 30 (1H, brs), MS *m/z* (TS$^+$) 365 ($MH^+$) |
| 10 | Prep 5 |  | $\delta_H$ ($CD_3OD$, 400 MHz) 2 92 (3H, s), 3 17 (2H, m), 4 41 (2H, m), 6 60-6 70 (2H, m), 6 97 (1H, d), 7 18 (1H, d), 7 90 (1H, d), 8 31 (1H, s), MS *m/z* (TS$^+$) 381 ($MH^+$) |
| 11 | Prep 3 |  | $\delta_H$ ($CD_3OD$, 400 MHz) 2 43 (3H, s), 2 97 (1H, s), 6 89 (2H, m), 7.00 (1H, d), 7.39 (1H, br), 7.88 (1H, brd), 8 23 (1H, s), MS *m/z* (ES$^+$) 371 ($MH^+$) |
| 12 | Prep 2 |  | $\delta_H$ ($CD_3OD$, 400 MHz) 2 85 (3H, s), 2 99 (3H, s), 6 99 (1H, d), 7 09 (1H, d), 7 22 (1H, s), 7.37 (1H, d), 7 92 (1H, d), 8 28 (1H, s), MS *m/z* (ES$^+$) 387 ($MH^+$) |

| Preparation | Precursor phenol |  | data |
|---|---|---|---|
| 13 | Prep 4 |  | $\delta_H$ ($CD_3OD$, 400 MHz) 2.87 (3H, brs), 3.13 (2H, brs), 4 37 (2H, brs), 6 73 (1H, brs), 6 82 (3H, m), 7 82 (1H, s), 8 28 (1H, brs), MS *m/z* ($ES^+$) 381 ($MH^+$) |
| 14 | Prep 6 |  | $\delta_H$ ($d_6$-DMSO, 400 MHz) 2 79 (3H, s), 4 98 (4H, brs), 6 92 (1H, d), 7 04 (1H, d), 7 09 (1H, s), 7 37 (3H, m), 7.79 (1H, m), 8 10 (1H, s), 8 30 (1H, s); MS *m/z* ($TS^+$) 349 ($MH^+$) |
| 15 | Commercial |  | $\delta_H$ ($CD_3OD$, 400 MHz) 2 08 (2H, m), 2 90 (7H, m), 6 84 (2H, m), 6 97 (1H, s), 7.23 (1H, d), 7 81 (1H, d), 8 31 (1H, s), MS *m/z* ($TS^+$) 347 ($MH^+$) |
| 16 | *Tetrahedron* 1982, 38, 2721 & *Synthesis* 1982, 475 |  | Product used without purification |
| 17 | Prep 101 |  | $\delta_H$ ($CD_3OD$, 400 MHz) 2 88 (3H, s), 4 20 (4H, s), 6 89 (1H, d), 6 97 (1H, d), 7 01 (1H, s), 7 30 (1H, d), 7 84 (1H, d), 8 28 (1H, s), MS *m/z* ($TS^+$) 382 ($MNH_4^+$) |
| 18 | Prep 7 |  | $\delta_H$ (DMSO-$d_6$, 400 MHz) 2.78 (3H, d), 3 23 (2H, m), 3 40 (2H, m), 6 75 (1H, dd), 6 90 (1H, d), 7 02 (1H, s), 7 27 (1H, d), 7 34 (1H, d), 7 80 (1H, d), 8 10 (1H, s), 8 26 (1H, br, d), MS *m/z* ($ES^-$) 363 ($M-H^+$) |

PREPARATION 19

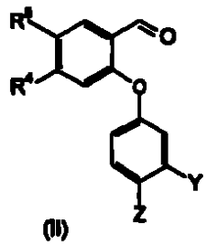
5-Bromo-2-(2,3-dihydro-1-benzothien-5-yloxy)benzaldehyde



A mixture of 5-bromo-2-fluorobenzaldehyde (1 08 g, 5 32 mmol), 5-hydroxy-2,3-dihydrobenzothiophene (prepared as described in *Synth. Commun.* 1991, 21, 959-964) (808 mg, 5 31 mmol) and $K_2CO_3$ (1 47 g, 10 6 mmol) in DMF (5 mL) was heated at 90°C for 16 h After cooling to room temperature the mixture was partitioned between water (50 mL) and ether (50 mL), the aqueous layer being extracted with ether (50 mL). The combined organic extracts were washed with water (50 mL), dried ($MgSO_4$) and evaporated The residue was purified by column chromatography [$SiO_2$, 9·1

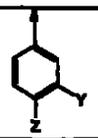
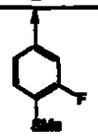
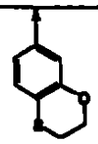
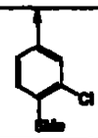
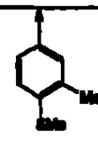
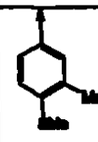
(pentane/EtOAc)], then triturated with ether, to give the product (1 1 g, 62%) as a pale yellow solid, $\delta_H$ ($CDCl_3$, 400 MHz) 3 28 (2H, t), 3 41 (2H, t), 6 78 (1H, d), 6 84 (1H, d), 6 92 (1H, s), 7 20 (1H, d), 7 58 (1H, d), 8 00 (1H, s), 10 43 (1H, s)

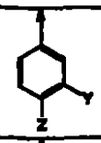
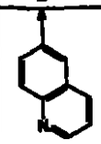
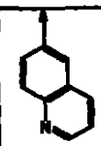
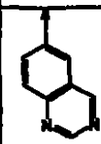
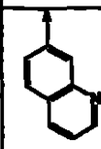
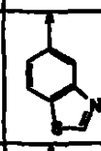
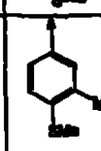
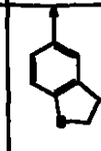
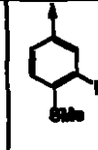
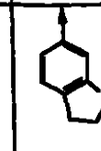
Compounds of general formula II shown in Table 18 were prepared according to Preparation 19 by reacting the phenol indicated with the required 2-fluorobenzaldehyde In most cases the crude reaction product after aqueous work-up was used directly in subsequent steps without further purification

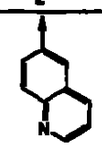


(II)

Table 18

| Preparation | Precursor Phenol | $R^4$ | $R^5$ |  | data |
|---|---|---|---|---|---|
| 20 | Prep 3 | H | Br |  | $\delta_H$ ($CDCl_3$, 300 MHz) 2 48 (3H, s), 6 81 (3H, m), 7 37 (1H, t), 7 64 (1H, d), 8 06 (1H, s), 10 39 (1H, s), MS *m/z* ($TS^+$) 358, 360 ($MNH_4^+$) |
| 21 | Prep 5 | H | Br |  | $\delta_H$ ($CDCl_3$, 400 MHz) 3 13 (2H, m), 4 42 (2H, m), 6 55 (1H, s), 6 59 (1H, d), 6 81 (1H, d), 7 04 (1H, d), 7 59 (1H, d), 8 01 (1H, s), 10 40 (1H, s) |
| 22 | Prep 2 | H | Br |  | $\delta_H$ ($CDCl_3$, 400 MHz) 2 43 (3H, s), 6 78 (1H, d), 6 94 (1H, d), 7 08 (1H, s), 7 19 (1H, d), 7 59 (1H, d), 8 00 (1H, s) |
| 23 | commercial | H | Br |  | $\delta_H$ ($CDCl_3$, 300 MHz) 2 35 (3H, s), 2 49 (3H, s), 6 78 (1H, d), 6 90 (2H, s), 7 22 (1H, d), 7 59 (1H, d), 8 05 (1H, s), 10 45 (1H, s), MS *m/z* ($TS^+$) 356, 354 ($MNH_4^+$) |
| 24 | commercial | H | MeO |  | $\delta_H$ ($CDCl_3$, 300 MHz) 2 35 (3H, s), 2 45 (3H, s), 3 87 (3H, s), 6 82 (1H, d), 6 83 (1H, s), 6 92 (1H, d), 7 13 (1H, dd), 7 19 (1H, d), 7 40 (1H, d), 10 40 (1H, s), MS *m/z* ($TS^+$) 389 ($MH^+$) |

| Preparation | Precursor Phenol | $R^4$ | $R^5$ |  | data |
|---|---|---|---|---|---|
| 25 | commercial | H | F |  | $\delta_H$ ($CDCl_3$, 300 MHz) 7 02 (1H, dd), 7 21 (1H, s), 7 30 (1H, m), 7 40 (1H, m), 7 54 (1H, d), 7 66 (1H, dd), 8 01 (1H, d), 8 18 (1H, d), 8 88 (1H, d), 10 43 (1H, s), MS *m/z* ($ES^+$) 268 ($MH^+$) |
| 26 | commercial | H | H |  | $\delta_H$ ($CDCl_3$, 400 MHz) 6 97 (1H, d), 7 21-7 27 (2H, m), 7 38 (1H, dd), 7 49-7 58 (2H, m), 7 92-8 01 (2H, m), 8 11 (1H, d), 8 83 (1H, d), 10 50 (1H, s), MS *m/z* ($ES^+$) 272 ($MNa^+$), ($ES^-$) 248 ($M-H^+$) |
| 27 | *J Chem Soc.* 1952, 4985-4993 | H | H |  | $\delta_H$ ($CDCl_3$, 300 MHz) 7 08 (1H, d), 7 36 (2H, m), 7 65 (1H, m), 7 79 (1H, dd), 8.01 (1H, d), 8 13 (1H, d), 9 29 (1H, d), 10 45 (1H, s), MS *m/z* ($TS^+$) 251 ($MH^+$) |
| 28 | commercial | H | H |  | $\delta_H$ ($CDCl_3$, 400 MHz) 7 09 (1H, d), 7 28 (1H, m), 7 35 (1H, m), 7 40 (1H, m), 7 50 (1H, br), 7 59 (1H, m), 7 86 (1H, dd), 7 99 (1H, dt), 8 15 (1H, d), 8.86 (1H, m), 10 46 (1H, s), MS *m/z* 250 ($MH^+$) |
| 29 | *Chem Pharm Bull*, 1978, 26, 1443 | H | H |  | $\delta_H$ ($CDCl_3$, 400 MHz) 6 91 (1H, d), 7 25 (2H, m), 7 55 (2H, m), 7 96 (1H, m), 8 12 (1H, d), 8 95 (1H, s), 10 5 (1H, s); MS *m/z* 256 ($MH^+$) |
| 30 | commercial | H | H |  | $\delta_H$ ($CDCl_3$, 300 MHz) 2 35 (3H, s), 3 44 (3H, s), 6 87 (3H, m), 7 17 (2H, m), 7 50 (1H, t), 7 92 (1H, dd), 10 52 (1H, s), MS *m/z* ($TS^+$) 259 ($MH^+$) |
| 31 | *Synth Commun* 1991, 21, 959-964 | H | H |  | $\delta_H$ ($CDCl_3$, 400 MHz) 3 26 (2H, t), 3 39 (2H, m), 6 85 (2H, t), 6 92 (1H, s), 7 18 (2H, m), 7 48 (1H, t), 7 92 (1H, d), 10 51 (1H, s), MS *m/z* ($TS^+$) 257 ($MH^+$) |
| 32 | commercial | Br | H |  | $\delta_H$ ($CDCl_3$, 400 MHz) 2 36 (3H, s), 2 44 (3H, s), 6 88 (2H, m), 6.96 (1H, s), 7 18-7 25 (2H, obs), 7.77 (1H, d), 10 43 (1H, s) |
| 33 | Prep 7 | H | Br |  | $\delta_H$ ($CDCl_3$, 400 MHz) 3 27 (2H, m), 3 42 (2H, m), 6 67 (1H, d), 6 80 (1H, d), 6 90 (1H, s), 71 6 (1H, d), 7 58 (1H, d), 8 01 (1H, s), 10 41 (1H, s), MS *m/z* ($TS^+$) 354 ($MNH_4^+$) |

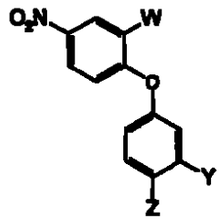
| Preparation | Precursor Phenol | $R^4$ | $R^5$ |  | data |
|---|---|---|---|---|---|
| 34[a] | commercial | H | CN |  | $\delta_H$ (DMSO-$d_6$, 300 MHz) 6 26 (1H, d), 6 43 (1H, d), 7 49 (1H, d), 7 65-7 71 (2H, m), 7 88 (1H, d), 8 07 (1H, d), 8 17 (1H, s), 8 73 (1H, d), 8 89 (1H, s), MS *m/z* (ES-) 273 (M-H), ($ES^+$) 275 ($MH^+$) |

[a] - 4-Fluoro-3-formylbenzonitrile was synthesised according to *Synth Commun* 1997, 27(7), 1199 and *J Org Chem* 1961, 26, 2522

The product from Preparation 30 was also prepared as follows

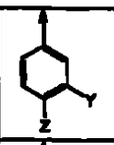
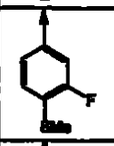
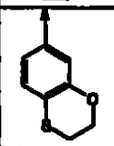
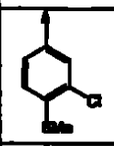
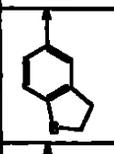
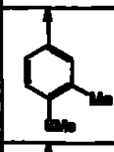
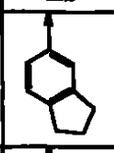
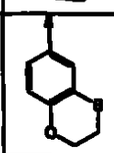
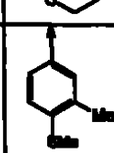
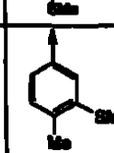
Potassium carbonate (334 1 g, 2 42 mol) and 4-(methylthio)-m-cresol (273 4 g, 1 77 mol) were added successively to DMF (2 L) 2-Fluorobenzaldehyde (200 g, 1 61 mol) was then added to the slurry and the mixture heated in the range 100-110 °C After 48 h the reaction mixture was allowed to cool to room temperature and water (1 2 L) added The solution was cooled to below 10 °C and the pH adjusted to 5 with concentrated HCl (0 37 L), keeping the temperature below 10 °C Water (0 15 L) and dichloromethane (0 9 L) were added and the mixture stirred The layers were separated and the organic layer was washed with water (4 x 0 75 L) The solvent was distilled to azeotropically remove the water Fresh dichloromethane was added as required The dry dichloromethane solution was then concentrated *in vacuo* to give the crude product as an oil (422 g, 100%)

Compounds of formula IX shown in Table 19 were prepared according to Preparation 19, using either 2-chloro-5-nitrobenzaldehyde or 2-chloro-5-nitrobenzonitrile with the phenol indicated For these reactions a shorter reaction time (ca 2-3 h) was usually sufficient to achieve good conversion In most cases the crude reaction product after aqueous work-up was used directly in subsequent steps without further purification



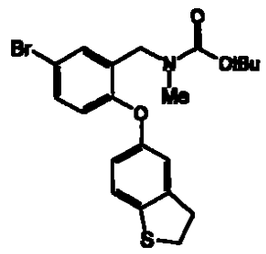
(IX)

Table 19

| Preparation | Precursor | W |  | data |
|---|---|---|---|---|
| 35 | Prep 3 | -C≡N |  | $\delta_H$ ($CDCl_3$, 400 MHz) 2 48 (3H, s), 6 85-6 95 (3H, m), 7 28 (1H, t), 8 30 (1H, d), 8 52 (1H, s) |
| 36 | Prep 5 |  |  | $\delta_H$ ($CDCl_3$, 400 MHz) 3 14 (2H, d), 4 43 (2H, d), 6 62 (2H, m), 6 92 (1H, d), 7 08 (1H, d), 8 27 (1H, d), 8 72 (1H, s), 10 51 (1H, s), MS *m/z* ($TS^+$) 318 ($MH^+$) |
| 37 | Prep 2 | -C≡N |  | $\delta_H$ ($CDCl_3$, 300 MHz) 2 55 (3H, s), 6 94 (1H, d), 7 09 (1H, dd), 7.22 (1H, d), 7 27 (1H, d), 8 36 (1H, dd), 8 60 (1H, d), MS *m/z* ($TS^+$) 338 ($MNH_4^+$) |
| 38 | *Synth. Commun* 1991, 21, 959-964 |  |  | $\delta_H$ ($CDCl_3$, 400 MHz) 3 29 (2H, m), 3 42 (2H, m), 6 88 (2H, m), 6 96 (1H, s), 7 23 (1H, d), 8 26 (1H, d), 8.75 (1H, s), 10 54 (1H, s) |
| 39 | commercial |  |  | $\delta_H$ ($CDCl_3$, 400 MHz) 2 38 (3H, s), 2 50 (3H, s), 6 92 (1H, d), 6 99 (2H, m), 7.24 (1H, d), 8 28 (1H, dd), 8 78 (1H, d), 10 57 (1H, s) |
| 40 | commercial |  |  | $\delta_H$ ($CDCl_3$, 400 MHz) 2 18 (2H, m), 2 95 (4H, t), 6 90 (2H, m), 7 29 (1H, d), 8 27 (1H, d), 8 79 (1H, s), 10 59 (1H, s), MS *m/z* ($TS^+$) 301 ($MNH_4^+$) |
| 41 | Prep 4 | -C≡N |  | $\delta_H$ ($CDCl_3$, 400 MHz) 3 18 (2H, t), 4 44 (2H, t), 6 76 (1H, d), 6 86 (1H, s), 6 92 (2H, d), 8.32 (1H, d), 8.57 (1H, s), MS *m/z* ($TS^+$) 332 ($MNH_4^+$) |
| 42 | commercial | -C≡N |  | $\delta_H$ ($CDCl_3$, 400 MHz) 2 32 (3H, s), 2 47 (3H, s), 6 87 (1H, d), 6 94 (2H, m), 7 21 (1H, d), 8 26 (1H, dd), 8 51 (1H, d), MS *m/z* ($TS^+$) 318 ($MNH_4^+$) |
| 43 | *Tetrahedron* 1982, 38, 2721 & *Synthesis* 1982, 475 | -C≡N |  | $\delta_H$ ($CDCl_3$, 400 MHz) 2 31 (3H, s), 2 41 (3H, s), 6 76 (1H, dd), 6 85 (2H, m), 7 19 (1H, d), 8 24 (1H, dd), 8 53 (1H, d), MS *m/z* ($TS^+$) 318 ($MNH_4^+$) |

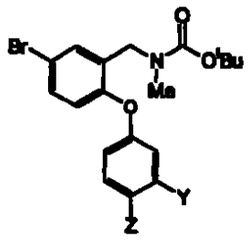
PREPARATION 44

*tert*-Butyl 5-bromo-2-(2,3-dihydro-1-benzothien-5-yloxy)benzyl(methyl)carbamate



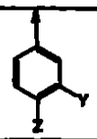
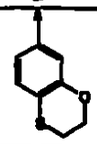
The hydrochloride salt of Example 36 (1 04 g, 2 7 mmol) was slurried in DCM (12 mL) and $Et_3N$ (750 µL, 5 38 mmol) was added, followed by di-*tert*-butyl dicarbonate (766 mg, 3 51 mmol) After stirring at room temperature for 20 min the reaction was quenched by the addition of 0 2M HCl (20 mL) The well shaken mixture was separated and the aqueous layer was extracted with DCM (10 mL) The combined organic layers were dried ($MgSO_4$) and evaporated to give the product (assumed quantitative yield) as a colourless oil which was used without further purification, $\delta_H$ ($CDCl_3$, 400 MHz) 1 56 (9H, s), 2 82-2 98 (3H, brd), 3 23 (2H, t), 3 40 (2H, t), 4 44 (2H, brd), 6 71 (2H, d), 6 79 (1H, s), 7 12 (1H, d), 7 29 (1H, d), 7 39 (1H, s)

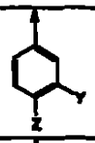
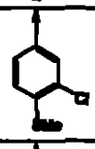
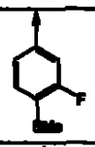
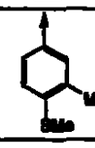
Compounds of formula X shown in Table 20 were prepared according to Preparation 44 starting from the precursors indicated



(X)

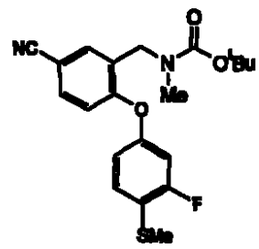
Table 20

| Preparation | Precursor |  | data |
|---|---|---|---|
| 45 | Example 38 |  | $\delta_H$ ($CDCl_3$, 400 MHz) 1 41 (9H, brs), 2 81 (3H, m), 3 07 (2H, m), 4 36 (4H, m), 6 38 (1H, s), 6.43 (1H, d), 6 71 (1H, d), 6 92 (1H, d), 7 26 (1H, d), 7 34 (1H, s), MS *m/z* ($ES^+$) 468 ($MH^+$) |

| Preparation | Precursor |  | data |
|---|---|---|---|
| 46 | Example 39 |  | $\delta_H$ ($CDCl_3$, 400 MHz) 1 48 (9H, s), 2 41 (3H, s), 2,82 (3H, brd), 4 39 (2H, brd), 6 73 (1H, d), 6 80 (1H, d), 6 93 (1H, s), 7 04 (1H, d), 7 32 (1H, d), 7 39 (1H, s), MS *m/z* ($TS^+$) 474 ($MH^+$) |
| 47 | Example 37 |  | $\delta_H$ ($CDCl_3$, 300 MHz) 1 46 (9H, brs), 2 46 (3H, s), 2 89 (3H, brs), 4 41 (2H, brs), 6 68 (2H, m), 6 82 (1H, d), 7 27 (1H, obs), 7 40 (1H, d), 7 43 (1H, s), MS *m/z* ($TS^+$) 458 ($MH^+$) |
| 48 | Example 44 |  | $\delta_H$ ($CDCl_3$, 300 MHz) 1 45 (9H, br) 2 38 (3H, s), 2 44 (3H, s), 2 90 (3H, br), 4 47 (2H, br), 6 70-6 81 (3H, m) 7 20 (1H, d), 7.24-7 58 (2H, m) |

PREPARATION 49

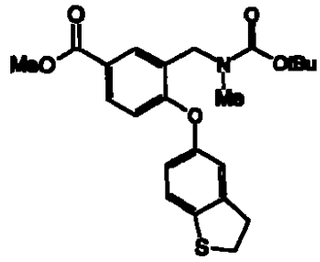
*tert*-Butyl 5-cyano-2-[3-fluoro-4-(methylsulfanyl)phenoxy]benzyl-(methyl)carbamate



The title compound was prepared from the bromide of Preparation 47 by the method of Example 78 ;$\delta_H$ ($CDCl_3$, 300 MHz) 1 48 (9H, brs), 2 50 (3H, s), 2 93 (3H, brs), 4 55 (2H, brs), 6 79 (2H, m), 6 88 (1H, d), 7 35 (1H, t), 7 53 (1H, d), 7 59 (1H, s), MS *m/z* ($TS^+$) 403 ($MH^+$)

PREPARATION 50

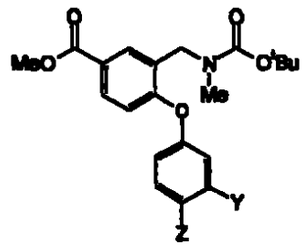
Methyl 3-[[(*tert*-butoxycarbonyl)(methyl)amino]methyl]-4-(2,3-dihydro-1-benzothien-5-yloxy)benzoate



A mixture of the bromide of Preparation 44 (1 22 g, 2 7 mmol), $Et_3N$ (1 13 mL, 8 11 mmol) and dichlorobis(triphenylphosphine)palladium (II) (190 mg, 0.27 mmol) in MeOH

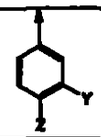
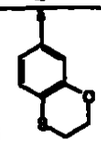
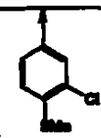
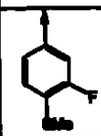
(14 mL) was heated at 80°C under 100 psi pressure of CO for 18 h Analysis by tlc indicated the reaction was not complete so a further portion of catalyst (190 mg, 0 27 mmol) was added and the mixture was heated at 100°C under 100 psi pressure of CO for 24 h The mixture was diluted with EtOAc (20 mL) and filtered through a pad of silica gel, eluting with excess EtOAc The solvent was removed *in vacuo* and the residue was partitioned between EtOAc (50 mL) and a 2 1 mixture of water-880 $NH_3$ (50 mL) The aqueous layer was extracted with EtOAc (25 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated Purification by column chromatography [$SiO_2$, 4 1 (pentane/EtOAc)] gave the product (970 mg, 84%) as an oil, $\delta_H$ ($CDCl_3$, 400 MHz) 1 42 (9H, s), 2 90 (3H, brs), 3 22 (2H, t), 3 38 (2H, t), 3 84 (3H, s), 4 50 (2H, brd), 6 74 (2H, d), 6 82 (1H, s), 7 13 (1H, d), 7 82 (1H, d), 7 93 (1H, brd), MS *m/z* ($ES^+$) 430 ($MH^+$)

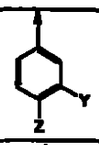
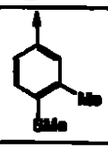
Compounds of formula XI shown in Table 21 were prepared according to Preparation 50 starting from the precursors indicated




(XI)

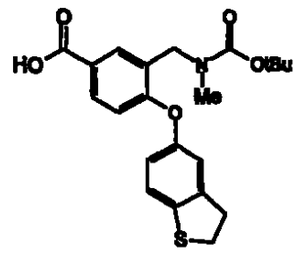
Table 21

| Preparation | Precursor |  | data |
|---|---|---|---|
| 51 | Prep 45 |  | $\delta_H$ ($CDCl_3$, 400 MHz) 1 42 (9H, s), 2 86 (2H, m), 3 07 (2H, m), 3 85 (3H, s), 4 37 (2H, m), 4 48 (2H, m), 6 48 (2H, m), 6 79 (1H, d), 6 97 (1H, d), 7 83 (1H, d), 7 95 (1H, s), MS *m/z* ($ES^+$) 446 ($MH^+$) |
| 52 | Prep 46 |  | $\delta_H$ ($CDCl_3$, 400 MHz) 1 43 (9H, brs), 2 47 (3H, s), 2.88 (3H, brd), 3 90 (3H, s), 4 51 (2H, brd), 6 81 (1H, d), 6 91 (1H, d), 7 06 (1H, s), 7 20 (1H, d), 7.89 (1H, d), 7 98 (1H, brd), MS *m/z* ($TS^+$) 469 ($MNH_4^+$) |
| 53 | Prep 47 |  | $\delta_H$ ($CDCl_3$, 300 MHz) 1 47 (9H, brs), 2 46 (3H, s), 2 91 (3H, brs), 3 94 (3H, s), 4 52 (2H, brs), 6 78 (2H, m), 6 91 (1H, d), 7 35 (1H, m), 7 92 (1H, d), 8 02 (1H, brs), MS *m/z* ($TS^+$) 453 ($MNH_4^+$) |

| Preparation | Precursor |  | data |
|---|---|---|---|
| 54 | Prep 48 |  | $\delta_H$ ($CDCl_3$, 300 MHz) 1.44 (9H, s), 2 37 (3H, s), 2 47 (3H, s), 2 94 (3H, br), 3 90 (3H, s), 4 73 (2H, br), 6 79-6 87 (3H, m), 7 20 (1H,d), 7 86 (1H,d), 8 00 (1H, br), MS *m/z* ($ES^+$) 454 ($MNa^+$) |

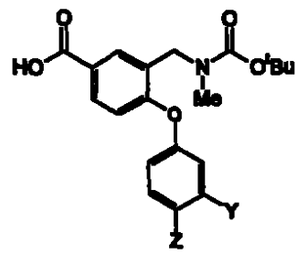
PREPARATION 55

3-[[(*tert*-Butoxycarbonyl)(methyl)amino]methyl]-4-(2,3-dihydro-1-benzothien-5-yloxy)benzoic acid



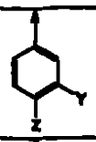
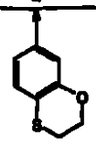
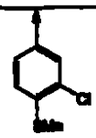
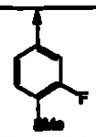
A solution of the ester of Preparation 50 (970 mg, 2 26 mmol) in THF (20 mL) and 1M LiOH (20 mL) was heated at reflux for 16 h After cooling to room temperature the THF was removed *in vacuo*, the residue was neutralised with sat aq $NH_4Cl$ and the mixture was extracted with DCM (100 mL) and then ether (100 mL) The combined organic layers were dried ($MgSO_4$) and evaporated to give a white foam (960 mg) which was used without further purification, $\delta_H$ ($CDCl_3$, 400 MHz) 1 30 (9H, s), 2.78 (3H, brs), 3 20 (2H, brs), 3 38 (2H, t), 4 41 (2H, m), 6.62 (2H, m), 6 78 (1H, m), 7 10 (1H, m), 7 84 (1H, m), 7 99 (1H, m), MS *m/z* ($ES^-$) 414 (M-H)

Compounds of formula XII shown in Table 22 were prepared according to Preparation 55 from the precursors indicated



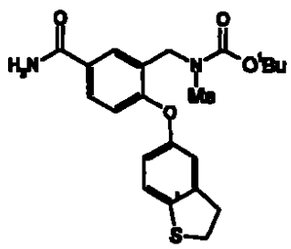
(XII)

Table 22

| Preparation | Precursor |  | data |
|---|---|---|---|
| 56 | Prep 51 |  | $\delta_H$ ($CDCl_3$, 400 MHz) 1 26 (9H, s), 2 74 (3H, s), 3 02 (2H, m), 4 31 (4H, m), 6 38 (2H, m), 6 64 (1H, d), 6.87 (1H, d), 7 68 (1H, brs), 7 78 (1H, brs), MS *m/z* ($ES^-$) 430 ($M-H^+$) |
| 57 | Prep 52 |  | $\delta_H$ ($CDCl_3$, 400 MHz) 1 44 (9H, brs), 2 49 (3H, s), 2 92 (3H, brd), 4 57 (2H, brd), 6 82 (1H, d), 6 94 (1H, d), 7 08 (1H, s), 7 21 (1H, d), 7 97 (1H, d), 8 04 (1H, brd), MS *m/z* ($ES^-$) 436 ($M-H^+$) |
| 58 | Prep 53 |  | $\delta_H$ ($CDCl_3$, 300 MHz) 1 46 (9H, brs), 2 49 (3H, s), 2 93 (3H, brs), 4 57 (2H, brs), 6 77 (2H, m), 6 92 (1H, d), 7 32 (1H, t), 7 99 (1H, d), 8 08 (1H, brs), MS *m/z* ($ES^-$) 420 ($M-H^+$) |

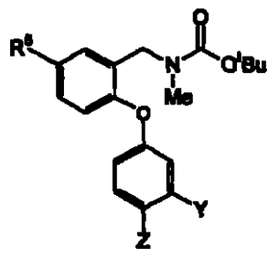
PREPARATION 59

*tert*-Butyl 5-(aminocarbonyl)-2-(2,3-dihydro-1-benzothien-5-yloxy)benzyl-(methyl)carbamate



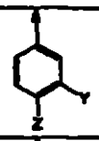
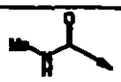
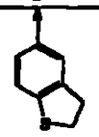
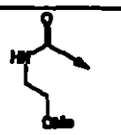
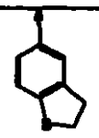
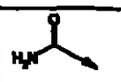
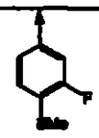
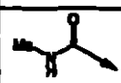
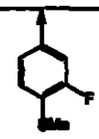
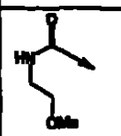
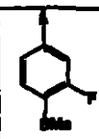
$Et_3N$ (267 µL, 1 92 mmol), $HOBt.H_2O$ (129 mg, 0 84 mmol) and WSCDI (191 mg, 1 0 mmol) were added to a solution of the acid of Preparation 55 (318 mg, 0 77 mmol) in DCM (10 mL) and the mixture was stirred for 1 h before the addition of a saturated solution of $NH_3$ in THF (2 mL) After stirring for a further 16 h the reaction was diluted with water (50 mL), 0 2M HCl (20 mL) and DCM (25 mL) The organic layer was separated and the aqueous layer was extracted with DCM (25 mL) The combined organic layers were dried ($MgSO_4$) and evaporated to give a white foam (assumed quantitative yield) which was used without further purification, $\delta_H$ ($CDCl_3$, 400 MHz) 1 44 (9H, s), 2 91 (3H, br), 3 27 (2H, t), 3 40 (2H, t), 4 54 (2H, br), 6 75-6 88 (3H, m), 7 18 (1H, d), 7 68 (1H, d), 7 74 (1H, s)

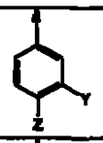
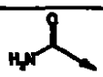
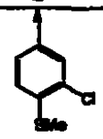
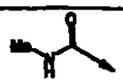
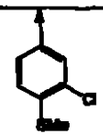
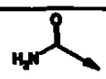
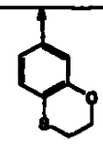
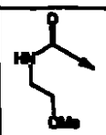
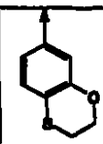
Compounds of formula XIII shown in Table 23 were prepared according to Preparation 59 from the precursors indicated



(XIII)

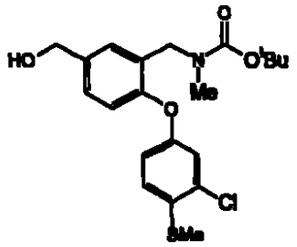
Table 23

| Preparation | Precursor | $R^6$ |  | data |
|---|---|---|---|---|
| 60 | Prep 55 |  |  | $\delta_H$ ($CDCl_3$, 400 MHz) 1 43 (9H, s), 2.83-3 00 (6H, m), 3 24 (2H, t), 3 39 (2H, t), 4 51 (2H, brs), 6 70-6 85 (3H, m), 7 15 (1H, d), 7 62 (1H, d), 7 68 (1H, s) |
| 61 | Prep 55 |  |  | $\delta_H$ ($CDCl_3$, 400 MHz) 1 46 (9H, s), 2 89 (3H, br), 3 24 (2H, t), 3 37-3 43 (5H, m), 3 56 (2H, t), 3 63 (2H, m), 4 54 (2H, br), 6 46 (1H, br), 6.75-6 86 (3H, m), 7.16 (1H, d), 7 62 (1H, d), 7 69 (1H, s) |
| 62 | Prep 58 |  |  | $\delta_H$ ($d_6$-DMSO, 400 MHz) 1 29 (9H, br), 2 40 (3H, s), 2 75 (3H, s), 4 39 (2H, s), 6 78 (1H, d), 6 91 (2H, m), 7 23 (1H, br), 7 36 (1H, t), 7 78 (2H, m), 7 90 (1H, br); MS *m/z* (TS$^+$) 438 ($MNH_4^+$) |
| 63 | Prep 58 |  |  | $\delta_H$ ($CDCl_3$, 400 MHz) 1 41 (9H, s), 2 40 (3H, s), 2 92 (3H, brs), 2 98 (3H, d), 4 45 (2H, brs), 6 10 (1H, brs), 6 67 (2H, m), 6 88 (1H, d), 7.27 (1H, obs), 7 63 (2H, m), MS *m/z* (TS$^+$) 452 ($MNH_4^+$) |
| 64 | Prep 58 |  |  | $\delta_H$ ($CDCl_3$, 400 MHz) 1 40 (9H, s), 2 40 (3H, s), 2 81 (3H, brs), 3 35 (3H, s), 3 53 (2H, m), 3 61 (2H, m), 4 44 (2H, brs), 6 45 (1H, brs), 6 66 (2H, m), 6 87 (1H, d), 7.29 (1H, d), 7 64 (1H, d), 7 72 (1H, s), MS *m/z* (TS$^+$) 479 ($MH^+$) |

| Preparation | Precursor | $R^5$ |  | data |
|---|---|---|---|---|
| 65 | Prep 57 |  |  | $\delta_H$ ($CDCl_3$, 400 MHz) 1 43 (9H, brs), 2 47 (3H, s), 2 90 (3H, brd), 4 52 (2H, brs), 6 87 (1H, d), 6 91 (1H, d), 7 03 (1H, s), 7 10 (1H, d), 7 72 (1H, d), 7 78 (1H, s), MS *m/z* ($ES^-$) 435 ($M-H^+$) |
| 66 | Prep 57 |  |  | $\delta_H$ ($CDCl_3$, 400 MHz) 1 42 (9H, brs), 2 47 (3H, s), 2 88 (3H, brd), 3 00 (3H, d), 4 48 (2H, brs), 6 18 (1H, brd), 6 85 (2H, m), 7 01 (1H, s), 7 19 (1H, d), 7 67 (2H, m), MS *m/z* ($ES^-$) 449 ($M-H^+$) |
| 67 | Prep 56 |  |  | $\delta_H$ ($CDCl_3$, 400 MHz) 1.42 (9H, s), 2 86 (3H, m), 3 08 (2H, m), 3 97 (2H, m), 4 48 (2H, brs), 5 86-6 27 (2H, brs), 6 45 (1H, s), 6 49 (1H, d), 6 82 (1H, d), 6 96 (1H, d), 7 64 (1H, d), 7 71 (1H, s), MS *m/z* ($TS^+$) 331 ($MH^+$-Boc) |
| 68 | Prep 56 |  |  | $\delta_H$ ($CDCl_3$, 400 MHz) 1 26 (9H, s), 2 74 (3H, s), 3 02 (2H, m), 4 31 (4H, m), 6 38 (2H, m), 6 64 (1H, d), 6 87 (1H, d), 7 68 (1H, brs), 7 78 (1H, brs), MS *m/z* ($ES^-$) 430 ($M-H^+$) |

PREPARATION 69

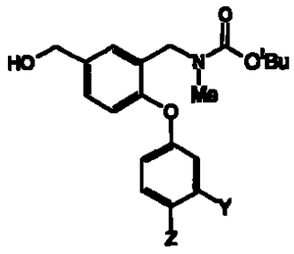
*tert*-Butyl 2-[3-chloro-4-(methylsulfanyl)phenoxy]-5-(hydroxymethyl)benzyl-(methyl)carbamate



A solution of $LiAlH_4$ in THF (1M, 2 mL, 2 mmol) was added dropwise to a solution of the ester of Preparation 52 (452 mg, 1 mmol) in THF (10 mL) under $N_2$ Once the reaction was judged complete by tlc analysis, ether (10 mL) was added and the excess $LiAlH_4$ was quenched by the cautious addition of 2M NaOH The organic layer was separated, washed with brine, dried ($MgSO_4$) and evaporated Purification of the residue by column chromatography [$SiO_2$, 39:1 (DCM/MeOH)] gave the desired alcohol (200 mg, 47%) as a

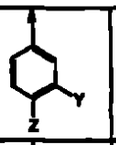
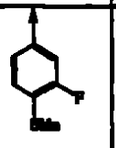
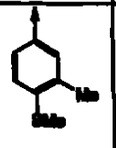
gummy white solid, $\delta_H$ ($CDCl_3$, 400 MHz) 1 41 (9H, brs), 1 80 (1H, brs), 2 43 (3H, s), 2 81 (3H, brd), 4 42 (2H, brd), 4 66 (2H, s), 6.82 (1H, d), 6 88 (1H, d), 6 96 (1H, s), 7 16 (1H, d), 7 27 (2H, obs), MS *m/z* ($ES^+$) 446 ($MNa^+$)

Compounds of formula XIV shown in Table 24 were prepared according to Preparation 69 starting from the precursors indicated



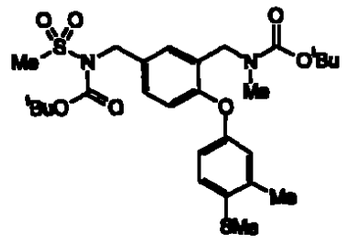
(XIV)

Table 24

| Preparation | Precursor |  | data |
|---|---|---|---|
| 70 | Prep 53 |  | $\delta_H$ ($CDCl_3$, 400 MHz) 1 39 (9H, brs), 1 99 (1H, brs), 2 39 (3H, s), 2 78 (3H, brd), 4 39 (2H, brs), 4 62 (2H, d), 6 61 (2H, t), 6.88 (1H, d), 7 20-7 30 (3H, m+$CHCl_3$), MS *m/z* ($TS^+$) 408 ($MH^+$) |
| 71 | Prep 54 |  | $\delta_H$ ($CDCl_3$, 300 MHz) 1 45 (9H, s), 2 34 (3H, s), 2 46 (3H, s), 2 90 (3H, br), 4 49 (2H, s), 4 67 (2H, s), 6 72-6 81 (2H, m), 6 85 (1H, d), 7 18 (1H, d), 7 21-7 30 (2H, obs), MS *m/z* ($TS^+$) 404 ($MH^+$) |

PREPARATION 72

*tert*-Butyl 3-{[(*tert*-butoxycarbonyl)(methyl)amino]methyl}-4-[3-methyl-4-(methylsulfanyl)phenoxy]benzyl(methylsulfonyl)carbamate

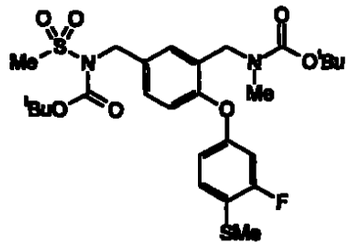


A solution of diethyl azodicarboxylate (505 µL, 3 21 mmol) in THF (5 mL) was added dropwise to a solution of *tert*-butyl methylsulfonylcarbamate (synthesised according to

*Tetrahedron Lett* 1994, 35, 379-380) (655 mg, 3 36 mmol), the alcohol of Preparation 71 (1 226 g, 3 04 mmol) and triphenylphosphine (880 mg, 3 36 mmol) in THF (15 mL) at 0°C The reaction was stirred at 0°C for 2 h then diluted with EtOAc (80 mL) and washed with 10% aq $K_2CO_3$ (100 mL) The organic layer was washed with brine, dried ($MgSO_4$) and evaporated The residue was purified by column chromatography [$SiO_2$, 1 4 EtOAc:pentane] to give the title compound (1 406 g, 80%) as a colourless oil, $\delta_H$ ($CDCl_3$, 300 MHz) 1 45 (9H, s), 1 52 (9H, s), 2 38 (3H, s), 2 44 (3H, s), 2 83 (3H, s), 3.22 (3H, s), 4 49 (2H, s), 4 85 (2H, s), 6 74-6 83 (3H, m), 7 18-7 29 (3H, obs), MS *m/z* ($TS^+$) 481 ($MH^+$-BOC)

PREPARATION 73

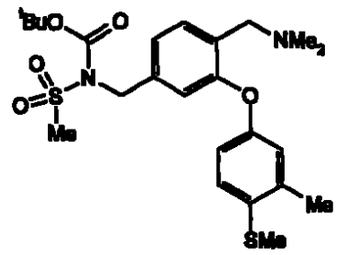
*tert*-Butyl 3-{[(*tert*-butoxycarbonyl)(methyl)amino]methyl}-4-[3-fluoro-4-(methylsulfanyl)phenoxy]benzyl(methylsulfonyl)carbamate



The title compound was prepared from the alcohol of Preparation 70 by the method of Preparation 72, $\delta_H$ ($CDCl_3$, 300 MHz) 1 44 (9H, s), 1 52 (9H, s), 2 44 (3H, s), 2 82 (3H, s), 3 23 (3H, s), 4 45 (2H, s), 4 87 (2H, s), 6 61-6 70 (2H, m), 6 90 (1H, d), 7 25-7 33 (3H, m), MS *m/z* ($ES^+$) 607 ($MNa^+$)

PREPARATION 74

*tert*-Butyl 4-[(dimethylamino)methyl]-3-[3-methyl-4-(methylsulfanyl)phenoxy]benzyl(methylsulfonyl)carbamate

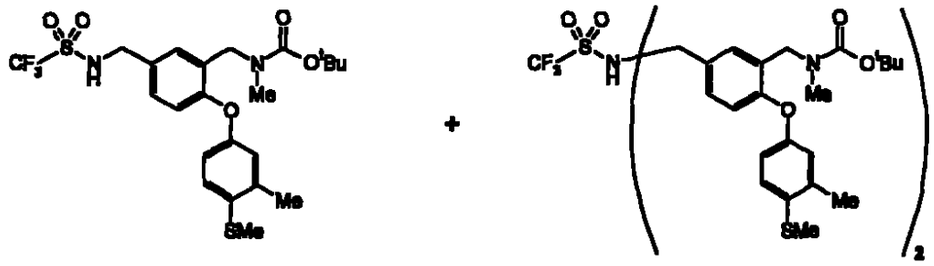


The title compound was prepared from the alcohol of Example 59 by the method of Preparation 72 The crude product was not purified by column chromatography but taken on directly to the next step, $\delta_H$ ($CDCl_3$, 400 MHz) 1 39 (9H, s), 2 22 (6H, s), 2 28 (3H, s),

2 38 (3H, s), 3 07 (3H, s), 3 42 (2H, s), 4 76 (2H, s), 6 72 (2H, m), 6 79 1H, s), 7 07 (1H, d), 7 12 (1H, d), 7 40 (1H, obs)

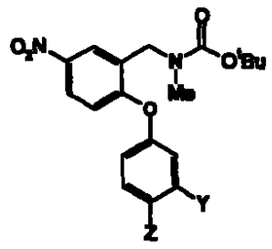
PREPARATION 75

*tert*-Butyl methyl[2-[3-methyl-4-(methylsulfanyl)phenoxy]-5-({[(trifluoromethyl)sulfonyl]amino}methyl)benzyl]carbamate



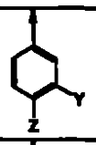
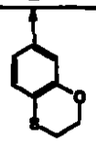
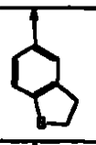
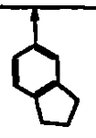
The title compound was prepared from the alcohol of Preparation 71 by the method of Preparation 72 using trifluoromethanesulfonamide instead of *tert*-butyl methylsulfonylcarbamate The desired product was contaminated with *tert*-butyl 5-({[3-{[(*tert*-butoxycarbonyl)(methyl)amino]methyl}-4-[3-methyl-4-(methylsulfanyl)phenoxy]benzyl][(trifluoromethyl)sulfonyl]amino}methyl)-2-[3-methyl-4-(methylsulfanyl)phenoxy]benzyl(methyl)carbamate and was taken on as a mixture, MS *m/z* ($ES^-$) 533 ($M-H^+$)

Compounds of formula XV shown in Table 25 were prepared according to Preparation 44 using the precursors indicated



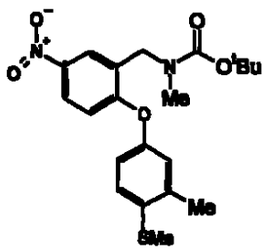
(XV)

Table 25

| Preparation | Precursor |  | data |
|---|---|---|---|
| 76 | Example 41 |  | $\delta_H$ ($CDCl_3$, 400 MHz) (major rotamer) 1 51 (9H, s), 2 92 (3H, s), 3 10 (2H, m), 4 40 (2H, m), 4 52 (2H, br), 6 53 (2H, m), 6 81 (1H, m), 7 03 (1H, d), 7 97-8 21 (2H, m), MS *m/z* ($TS^+$) 433 ($MH^+$) |
| 77 | Example 40 |  | $\delta_H$ ($CDCl_3$, 300 MHz) 1 50 (9H, br), 2 99 (3H, s), 3 29 (2H, m), 3 43 (2H, m), 4 60 (2H, br), 6 81 (2H, m), 6 91 (1H, s), 7 22 (1H, d), 8 04 (1H, d), 8 21 (1H, br) |
| 78 | Example 42 |  | $\delta_H$ ($CDCl_3$, 400 MHz) 1 56 (9H, s), 2 15 (2H, m), 2 85-3 00 (7H, m), 4 60 (2H, brd), 6 78 (2H, m), 6 87 (1H, s), 7 12 (1H, d), 8 03 (1H, d), 8 10 (1H, s), MS *m/z* ($TS^+$) 399 ($MH^+$) |

PREPARATION 79

*tert*-Butyl methyl[2-[3-methyl-4-(methylsulfanyl)phenoxy]-5-nitrobenzyl]carbamate



*N*-Methyl-*N*-[2-[3-methyl-4-(methylsulfanyl)phenoxy]-5-nitrobenzyl]amine and [2-[3-methyl-4-(methylsulfanyl)phenoxy]-5-nitrophenyl]methanol

To a suspension of the aldehyde of Preparation 39 (21 0 g, 69 2 mmol) in EtOH (100 mL) was added 8M methylamine in EtOH (86.5 ml, 692 mmol) A solution was given and after stirring for a short time a precipitate was observed This was re-dissolved by the addition of THF (100 mL), the solution was cooled to 0°C and $NaBH_4$ (7 85 g, 208 mmol) was then added The reaction was allowed to warm slowly to room temperature and stirred overnight before the solvent was removed *in vacuo* The residue was taken up in water (150 mL) and ether (150 mL), and 2M HCl was added cautiously until pH 1 The layers were separated and the aqueous layer was washed with ether (2×100 mL) The combined organic extracts were dried and evaporated to give [2-[3-methyl-4-(methylsulfanyl)phenoxy]-5-nitrophenyl]methanol (18 9 g, 89%) as a yellow solid, $\delta_H$

(CDCl$_3$, 400 MHz) 2 35 (3H, s), 2 48 (3H, s), 4 90 (2H, s), 6 79 (1H, d), 6 89 (1H, s), 6 91 (1H, d), 7 22 (1H, d), 8.07 (1H, dd), 8 41 (1H, d)

The aqueous layer from above was neutralised by pouring onto excess solid $K_2CO_3$. The basic solution was extracted with ether (2×100 mL) and these ether extracts were dried ($MgSO_4$) and evaporated to give *N*-methyl-*N*-{2-[3-methyl-4-(methylsulfanyl)phenoxy]-5-nitrobenzyl}amine (1.65 g, 7 5%) as an orange oil, MS *m/z* (ES$^+$) 319 (MH$^+$)

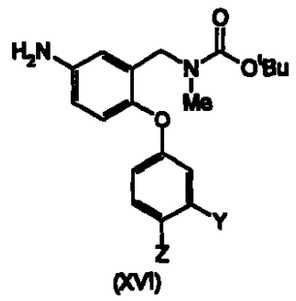
*N*-Methyl-*N*-[2-[3-methyl-4-(methylsulfanyl)phenoxy]-5-nitrobenzyl]amine from {2-[3-methyl-4-(methylsulfanyl)phenoxy]-5-nitrophenyl}methanol

Methanesulfonyl chloride (4 81 mL, 61 9 mmol) was added slowly to a solution of {2-[3-methyl-4-(methylsulfanyl)phenoxy]-5-nitrophenyl}methanol (18 9 g, 61 9 mmol) and $Et_3N$ (9 5 mL, 68 2 mmol) in DCM (60 mL) The mixture was stirred at room temperature for 3 h then poured into water and extracted with DCM (3 times). The combined organic extracts were dried ($MgSO_4$) and evaporated to give a dark, viscous oil This oil was taken up in DCM (50 mL) and 8M methylamine in EtOH (200 mL, 1 6 mol) was added followed by $Et_3N$ (10 mL, 71 7 mmol) After stirring for 18 h the mixture was concentrated *in vacuo* to give crude amine which was used without further purification

*tert*-Butyl methyl{2-[3-methyl-4-(methylsulfanyl)phenoxy]-5-nitrobenzyl}carbamate

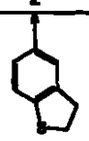
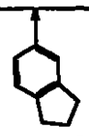
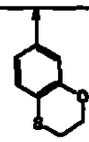
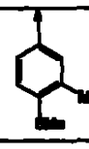
The crude amine from above was dissolved in DCM (100 mL) at 0°C and $Et_3N$ (11 4 mL, 81 8 mmol) was added, followed by di-*tert*-butyl dicarbonate (15 0 g, 68 7 mmol) The reaction was allowed to warm to room temperature and stirred for 16 h before being concentrated *in vacuo* The residue was partitioned between EtOAc and water and the aqueous layer was extracted with EtOAc (2 times) The combined organic layers were dried ($MgSO_4$) and evaporated The residue was purified by column chromatography ($SiO_2$, 1$^{st}$ column - 3% MeOH in DCM, 2$^{nd}$ column EtOAc pentane 1 3) to give the title compound (14 2 g, 54%) as a yellow oil, $\delta_H$ (CDCl$_3$, 400 MHz) 1 44 (9H, s), 2 32 (3H, s), 2 44 (3H, s), 2 95 (3H, s), 4 56 (2H, br), 6 75 (1H, d), 6 84 (2H, m), 7 17 (1H, d), 8 00 (1H, d), 8 18 (1H, br), MS *m/z* (TS$^+$) 419 (MH$^+$).

Compounds of formula XVI shown in Table 26 were prepared according to Example 103 from the precursors indicated



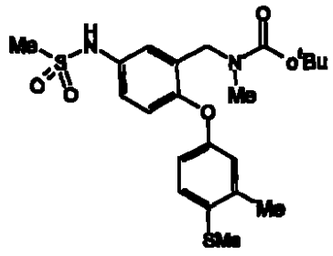
(XVI)

Table 26

| Preparation | Precursor | | data |
|---|---|---|---|
| 80 | Prep 77 |  | $\delta_H$ ($CDCl_3$, 300 MHz) 1 50 (9H, br), 2 80 (3H, br), 3 20 (2H, m), 2 37 (2H, m), 3 60 (2H, br), 4 40 (2H, s), 6 50-6 80 (5H, m), 7 05 (1H, d), MS *m/z* ($ES^+$) 387 ($MH^+$) |
| 81 | Prep 78 |  | $\delta_H$ ($CDCl_3$, 400 MHz) 1 42 (9H, s), 2 05 (2H, m), 2 80 (7H, m), 4 37 (2H, s), 6 50-6 65 (3H, m), 6 69 (1H, s), 6 78 (1H, d), 7 08 (1H, d), MS *m/z* ($TS^+$) 369 ($MH^+$) |
| 82 | Prep 76 |  | $\delta_H$ ($CDCl_3$, 400 MHz) 1 43 (9H, s), 2 86 (3H, br), 3 07 (2H, m), 3 59 (2H, br), 4 30 (2H, s), 4.36 (2H, m), 6 32 (1H, s), 6 40 (1H, d), 6 49-6 65 (2H, m), 6 75 (1H, d), 6 88 (1H, d), MS *m/z* ($TS^+$) 403 ($MH^+$) |
| 83 | Prep 79 |  | $\delta_H$ ($CDCl_3$, 300 MHz) 1.47 (9H, s), 2.33 (3H, s), 2.40 (3H, s), 2 82 (3H, br), 3 60 (2H, s), 4 35 (2H, s), 6 50-6 77 (4H, m), 6 80 (1H, d), 7 16 (1H, d), MS *m/z* ($TS^+$) 389 ($MH^+$) |

## PREPARATION 84

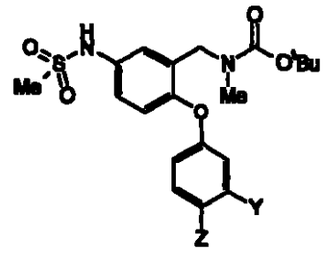
*tert*-Butyl methyl[2-[3-methyl-4-(methylsulfanyl)phenoxy]-5-[(methylsulfonyl)amino]benzyl]carbamate



Methanesulfonyl chloride (4 16 mL, 53 7 mmol) was added dropwise to a solution of the aniline of Preparation 83 (9 5 g, 24 5 mmol) and $Et_3N$ (7 5 mL, 53.8 mmol) in DCM (50 mL) at 0°C After stirring at 0°C for 30 min the reaction was allowed to warm to room

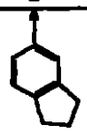
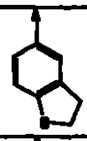
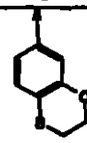
temperature before the solvent was removed *in vacuo* 2M NaOH (50 mL) was added to the residue and the mixture was stirred for 30 min The mixture was extracted with EtOAc and the organic layer was washed with brine, dried ($MgSO_4$) and evaporated to give an oil Purification by column chromatography [$SiO_2$, 97 5.2 5 0 25 (DCM/MeOH/880 $NH_3$)] gave the product (9 0 g, 79%) as a brown foam, $\delta_H$ ($CDCl_3$, 300 MHz) 1 43 (9H, brs), 2 35 (3H, s), 2 42 (3H, s), 2 88 (3H, brs), 3 01 (3H, s), 4 46 (2H, brs), 6 76 (2H, d+s), 6 83 (1H, d), 7 16 (1H, s), 7 20 (2H, brs), MS *m/z* ($ES^+$) 467 ($MH^+$)

Compounds of formula XVII shown in Table 27 were prepared according to Preparation 84 from the precursors indicated



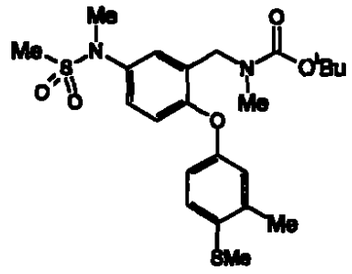
(XVII)

Table 27

| Preparation | Precursor | | data |
|---|---|---|---|
| 85 | Prep 81 |  | $\delta_H$ ($CDCl_3$, 400 MHz) (rotamers) 1 44 and 1.48 (9H, 2xs), 2 10 (2H, quintet), 2 88 (7H, m), 3.00 (3H, s), 4 49 (2H, br), 6 23 (1H, br), 6.72 (1H, d), 6 81 (1H, s), 6.83 (1H, d), 7 13 (3H, m), MS *m/z* ($TS^+$) 347 ($MH^+$-Boc) |
| 86 | Prep 80 |  | Product used without purification |
| 87 | Prep 82 |  | $\delta_H$ ($CDCl_3$, 400 MHz) (rotamers) 1 40 and 1 44 (9H, 2xs), 2 80 and 2 85 (3H, 2xs), 2 95 (3H, s), 3 07 (2H, m), 4 38 (2H, m), 6 36 (1H, s), 6 44 (1H, d), 6 84 (1H, d), 6.92 (1H, d), 7 12 (2H, m), MS *m/z* ($TS^+$) 498 ($MNH_4^+$) |

PREPARATION 88

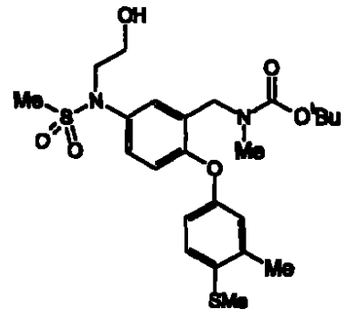
*tert*-Butyl methyl[2-[3-methyl-4-(methylsulfanyl)phenoxy]-5-[methyl(methylsulfonyl)amino]benzyl]carbamate



MeI (1 07 mL, 17 2 mmol) was added dropwise to a mixture of the sulfonamide of Preparation 84 (2 0 g, 4 3 mmol) and $K_2CO_3$ (592 mg, 4 3 mmol) in $CH_3CN$ (10 mL) under $N_2$. The mixture was stirred for 16 h and then partitioned between EtOAc (50 mL) and 2M NaOH (50 mL) The organic layer was washed with brine, dried ($MgSO_4$) and evaporated The residue was purified by column chromatography [$SiO_2$, 590 10 1 (DCM/MeOH/880 $NH_3$)] to give the product (1 23 g, 60%) as a yellow oil, $\delta_H$ ($CDCl_3$, 300 MHz) 1 45 (9H, s), 2 34 (3H, s), 2 42 (3H, s), 2 86 (3H, s), 2 90 (3H, s), 3 28 (3H, s), 4 49 (2H, s), 6 80 (3H, br), 7 18 (3H, m), MS *m/z* ($TS^+$) 498 ($MNH_4^+$)

PREPARATION 89

*tert*-Butyl 5-[(2-hydroxyethyl)(methylsulfonyl)amino]-2-[3-methyl-4-(methylsulfanyl)phenoxy]benzyl(methyl)carbamate

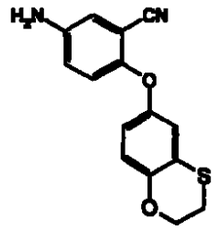


2-Bromoethanol (1 34 mL, 18 9 mmol) was added to a mixture of the sulfonamide of Preparation 84 (2 0 g, 4 3 mmol) and $K_2CO_3$ (2 605 g, 18 8 mmol) in $CH_3CN$ (10 mL) under $N_2$ The mixture was heated at reflux for 16 h, cooled and then partitioned between EtOAc (50 mL) and 2M NaOH (50 mL) The organic layer was washed with brine, dried ($MgSO_4$) and evaporated The residue was purified by column chromatography [$SiO_2$, 390 10 1 (DCM/MeOH/880 $NH_3$)] to give the product (524 mg, 24%) as a pink foam, $\delta_H$ ($CDCl_3$, 300 MHz) 1 42 (9H, s), 2 37 (3H, s), 2 43 (3H, s), 2 91

(3H, s), 2 98 (3H, s), 3 68 (2H, brs), 3 79 (2H, d), 4 49 (2H, s), 6 81 (3H, m), 7 19 (3H, m), MS *m/z* (TS$^+$) 528 ($MNH_4^+$)

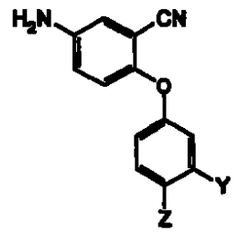
PREPARATION 90

5-Amino-2-(2,3-dihydro-1,4-benzoxathiin-6-yloxy)benzonitrile



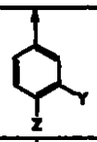
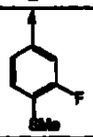
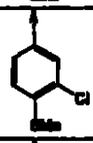
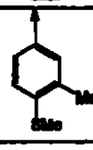
Fe powder (930 mg, 16 7 mmol) was added to the nitro compound of Preparation 41 (740 mg, 2 38 mmol) in AcOH (5 mL) and water (1 mL) and the mixture was stirred at room temperature for 16 h The solvent was removed *in vacuo*, the residue was taken up in EtOAc (50 mL) and 10% aq $K_2CO_3$ (50 mL) and filtered through Arbocel® The organic layer was separated and the aqueous layer was extracted with EtOAc (50 mL) The combined organic extracts were dried ($MgSO_4$) and evaporated to a brown foam (670 mg, 99%) which was used without further purification, $\delta_H$ ($CDCl_3$, 400 MHz) 3 18 (2H, m), 4 36 (2H, m), 6 60-6 70 (2H, m), 6 70-6 80 (3H, m), 6 85 (1H, s), MS *m/z* (TS$^+$) 302 ($MNH_4^+$)

Compounds of formula Vb, i e compounds of formula V where T is cyano, $R^4$ is hydrogen and $R^5$ is amino, shown in Table 28 were prepared according to Preparation 90 from the precursors indicated.



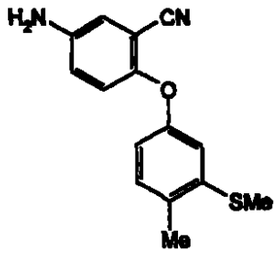
(Vb)

Table 28

| Preparation | Precursor |  | data |
|---|---|---|---|
| 91 | Prep 35 |  | $\delta_H$ ($CDCl_3$, 400 MHz) 2 40 (3H, s), 6 62-6 72 (2H, m), 6 80-6 90 (3H, m), 7 28 (1H, d) |
| 92 | Prep 37 |  | $\delta_H$ ($CDCl_3$, 300 MHz) 2 47 (3H, s), 3 83 (2H, br), 6 83-6 94 (4H, m), 7 01 (1H, s), 7 19 (1H, d), MS *m/z* ($TS^+$) 308 ($MNH_4^+$) |
| 93 | Prep 42 |  | $\delta_H$ ($CDCl_3$, 400 MHz) 2 30 (3H, s), 2 40 (3H, s), 3 84 (2H, br), 6 77 (4H, m), 6 85 (1H, s), 7 13 (3H, d), MS *m/z* ($TS^+$) 288 ($MNH_4^+$) |

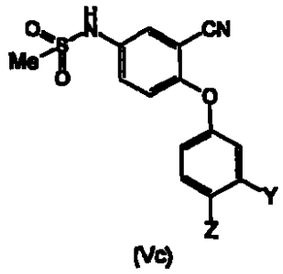
PREPARATION 94

5-Amino-2-[4-methyl-3-(methylsulfanyl)phenoxy]benzonitrile



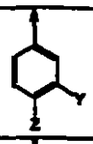
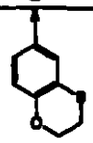
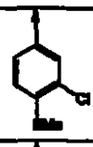
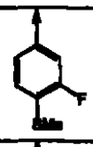
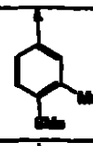
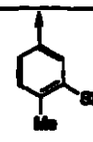
The title compound was prepared from the nitro compound of Preparation 43 by the method of Example 103, $\delta_H$ ($CDCl_3$, 400 MHz) 2.27 (3H, s), 2 41 (3H, s), 3 66 (2H, br), 6 62 (1H, d), 6 79 (2H, s), 6 82 (1H, s), 6 89 (1H, s), 7 08 (1H, d), MS *m/z* ($ES^+$) 293 ($MNa^+$), ($ES^-$) 269 ($M-H^+$)

Compounds of formula Vc, i e. compounds of formula V where T is cyano, $R^4$ is hydrogen and $R^5$ is $-NHSO_2Me$, shown in Table 29 were prepared according to Preparation 84 from the precursors indicated



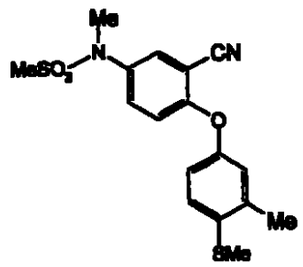
(Vc)

Table 29

| Preparation | Precursor |  | data |
|---|---|---|---|
| 95 | Prep 90 |  | $\delta_H$ ($CDCl_3$, 400 MHz) 2 98 (3H, s), 3 10 (2H, m), 4 39 (2H, m), 6 67 (1H, dd), 6 76 (1H, s), 6 81 (1H, d), 7 33 (1H, dd), 7 49 (1H, s), MS *m/z* ($TS^+$) 380 ($MNH_4^+$) |
| 96 | Prep 92 |  | $\delta_H$ ($CDCl_3$, 300 MHz) 2.51 (3H, s), 3 06 (3H, s), 6 52 (1H, br), 6 92 (1H, d), 7 02 (1H, dd), 7 14 (1H, d), 7 24 (1H, d), 7 41 (1H, dd), 7 57 (1H, d), MS *m/z* ($ES^+$) 391 ($MNa^+$) |
| 97 | Prep 91 |  | $\delta_H$ ($CDCl_3$, 400 MHz) 2 43 (3H, s), 3 02 (3h, S), 6.41 (1H, brs), 6.72-6.85 (2H, m), 6 92 (1H, d), 7 28 (1H, t), 7.38 (1H, d), 7 51 (1H, s), MS *m/z* ($ES^+$) 351 ($MH^+$) |
| 98 | Prep 93 |  | $\delta_H$ ($CDCl_3$, 400 MHz) 2 19 (3H, s), 2 42 (3H, s), 2 99 (3H, s), 6 81 (1H, d), 6 86 (2H, m), 7 15 (1H, d), 7 33 (1H, d), 7 51 (1H, s), MS *m/z* ($TS^+$) 366 ($MNH_4^+$) |
| 99 | Prep 94 |  | $\delta_H$ ($CDCl_3$, 400 MHz) 2 31 (3H, s), 2 43 (3H, s), 3 02 (3H, s), 6 61 (1H, s), 6 72 (1H, dd), 6 83 (1H, d), 6 88 (1H, s), 7 17 (1H, d), 7.37 (1H, dd), 7 55 (1H, s), MS *m/z* ($TS^+$) 366 ($MNH_4^+$) |

PREPARATION 100

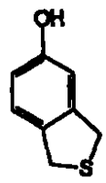
*N*-(3-Cyano-4-[3-methyl-4-(methylsulfanyl)phenoxy]phenyl)-*N*-methylmethanesulfonamide



The title compound was prepared from the sulfonamide of Preparation 98 by the method of Preparation 88, $\delta_H$ ($CDCl_3$, 400 MHz) 2.31 (3H, s), 2 44 (3H, s), 2 83 (3H, s), 3 27 (3H, s), 6 79 (1H, d), 6 88 (2H, m), 7 17 (1H, d), 7 44 (1H, dd), 7 58 (1H, d), MS *m/z* ($ES^+$) 385 ($MNa^+$)

PREPARATION 101

1,3-Dihydro-2-benzothiophen-5-ol



(i) Preparation of [4-(allyloxy)-2-(hydroxymethyl)phenyl]methanol

Dimethyl 4-(allyloxy)phthalate [prepared according to Inouye, M , Tsuchiya, K., Kitao, T *Angew Chem* 1992, 104, 198-200 (See also *Angew Chem , Int Ed Engl* , 1992, 204-205)] (9 9 g, 38 mmol) was dissolved in THF (40 mL) and cooled to 0°C before the dropwise addition of lithium aluminium hydride (1M in THF, 77 mL, 77 mmol) over 10 min The mixture was then allowed to stir at room temperature for 3 h before being quenched cautiously by the addition of water (1 4 mL) followed by 2M NaOH (1 4 mL) Excess $MgSO_4$ was then added followed by water until a granular precipitate formed (*ca* 5 mL) The mixture was then filtered and evaporated to a brown oil (7 1 g, ca. 95%). $^1H$ NMR showed the material to be of ca 85% purity It was used directly in the next stage without further purification, $\delta_H$ ($CDCl_3$, 400 MHz) 2 63 (1H, brs), 2.91 (1H, brs), 4 52 (2H, m), 4 67 (4H, m), 5 26 (1H, dd), 5 38 (1H, dd), 5 97-6 09 (1H, m), 6 80 (1H, dd), 6 92 (1H, d), 7 22 (1H, d)

(ii) Preparation of 5-(allyloxy)-1,3-dihydro-2-benzothiophene

Crude diol from stage (i) (3 5 g, 18 mmol) was dissolved in DCM (60 mL) and treated with $Et_3N$ (10 mL, 72 mmol) and the solution was cooled to 0°C Methanesulfonyl chloride (4 2 mL, 54 mmol) was added dropwise and the solution was stirred for 1 h being allowed to reach room temperature The reaction was then quenched by the addition of water followed by 2M HCl (50 mL) The DCM layer was separated and the aqueous layer was re-extracted with DCM (50 mL) The combined organic fractions were washed with water (50 mL), dried ($MgSO_4$) and concentrated to a volume of ca 30 mL Benzyltriethylammonium chloride (1 g) was added followed by a solution of sodium sulfide (5 g, 91 mmol) in water (50 mL) The mixture was stirred rapidly under a nitrogen atmosphere for 15 h The organic layer was separated and the aqueous layer was re-extracted with DCM (50 mL) The combined organic layers were dried ($MgSO_4$) and evaporated to a yellow oil Flash chromatography afforded two fractions, the first was pure product and the second product contaminated with dimeric material Trituration of the second fraction caused crystallisation of the dimeric material which was removed by filtration The filtrate was combined with the first chromatography fraction to afford the

desired product (800 mg, 23%), $\delta_H$ ($CDCl_3$, 400 MHz) 4 16 (2H, s), 4 19 (2H, s), 4 48 (2H, m), 5 26 (1H, d), 5 37 (1H, d), 5 95-6 06 (1H, m), 6 74 (2H, m), 7 09 (1H, d)

(iii) Preparation of 1,3-dihydro-2-benzothiophen-5-ol

The allyl ether from stage (ii) (800 mg, 4 16 mmol) was dissolved in THF (10 mL) and treated with palladium tetrakis(triphenylphosphine) (481 mg, 0 42 mmol) followed by sodium borohydride (944 mg, 25 mmol) The mixture was then heated to 45 °C and stirred at this temperature for 15 h After cooling to room temperature the THF was evaporated and the residue partitioned between 2M NaOH solution (25 mL) and diethyl ether (25 mL) The aqueous layer was separated and the organic layer re-extracted with 2M NaOH solution (25 mL) The combined aqueous layers were neutralised to pH 7-8 with concentrated hydrochloric acid and extracted with EtOAc (2 x 25 mL) The combined organic extracts were dried ($MgSO_4$) and evaporated to a clear oil of the title phenol which solidified upon standing (540 mg, 85%), 4 14 (2H, s), 4 17 (2H, s), 6 63-6 68 (2H, m), 7 04 (1H, d)

Biological Activity

A number of compounds were tested for biological activity by their ability to inhibit the uptake of serotonin by human serotonin transporters as follows

(i) Cell Culture

Human embryonic kidney cells (HEK-293) stably transfected with either the human serotonin transporter (hSERT), noradrenaline transporter (hNET) or dopamine transporter (hDAT) were cultured under standard cell culture techniques (cells were grown at 37°C and 5% $CO_2$ in DMEM-culture media (supplemented with 10% dialysed foetal calf serum (FCS), 2mM l-glutamine and 250µg/ml geneticin)) Cells were harvested for the assay to yield a cell suspension of 750,000 cells/ml

(i) Determination of inhibitor potency

All test compounds were dissolved in 100% DMSO and diluted down in assay buffer to give appropriate test concentrations Assays were carried out in 96-well filter bottom plates Cells (7500 cells/assay well) were pre-incubated in standard assay buffer containing either test compound, standard inhibitor or compound vehicle (1% DMSO) for 5 minutes Reactions were started by addition of either $^3$H-Serotonin, $^3$H-Noradrenaline or $^3$H-Dopamine substrates All reactions were

carried out at room temperature in a shaking incubator Incubation times were 5 minutes for the hSERT and hDAT assays and 15 minutes for the hNET assay Reactions were terminated by removal of the reaction mixture using a vacuum manifold followed by rapid washing with ice cold assay buffer The quantity of $^3$H-substrate incorporated into the cells was then quantified

Assay plates were dried in a microwave oven, scintillation fluid added, and radioactivity measured Potency of test compounds was quantified as $IC_{50}$ values (concentration of test compound required to inhibit the specific uptake of radiolabelled substrate into the cells by 50%)

(iii) Standard Assay Buffer Composition:

Trizma hydrochloride (26mM)
NaCl (124mM)
KCl (4 5mM)
$KH_2PO_4$ (1 2mM)
$MgCl_2$ $6H_2O$ (1 3mM)
Ascorbic acid (1 136mM)
Glucose (5 55mM)
*pH 7 40*
$CaCl_2$ (2 8mM)
Pargyline (100µM)

Note The pH of the buffer was adjusted to 7 40 with 1M NaOH before addition of $CaCl_2$ and pargyline

(iv) Summary of Assay Parameters

| | hSERT Assay | hDAT Assay | hNET Assay |
|---|---|---|---|
| Cell concentration per assay well | 75,000 | 75,000 | 75,000 |
| Substrate Concentration | $^3$H-5HT (50nM) | $^3$H-Dopamine (200nM) | $^3$H-Noradrenaline (200nM) |
| Incubation time (minutes) | 5 | 5 | 15 |

Compounds having a serotonin re-uptake inhibition (SRI) $IC_{50}$ value of less than or equal to 100nM include the title compounds of Examples 1-6, 8-23, 25, 26, 29-32, 34-36, 43, 45-49, 51, 56-102, 109-130

Compounds having an serotonin re-uptake inhibition (SRI) $IC_{50}$ value of less than or equal to 100nM and which are more than 10-fold as potent in the inhibition of serotonin re-uptake than in the inhibition of dopamine re-uptake or noradrenaline re-uptake include the title compounds of Examples 1-6, 9-13, 16-19, 21, 22, 25, 26, 29-32, 34-36, 43, 45, 47-49, 51, 57-88, 90-102, 109-121, 123, 124, 127, 129

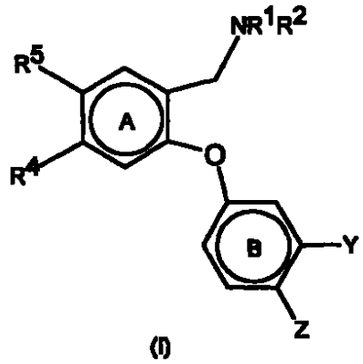
Compounds having an serotonin re-uptake inhibition (SRI) $IC_{50}$ value of less than or equal to 100nM and which are more than 100-fold as potent in the inhibition of serotonin re-uptake than in the inhibition of dopamine re-uptake or noradrenaline re-uptake include the title compounds of Examples 1, 2, 4, 5, 9, 12, 13, 16-19, 21, 22, 25, 26, 29-32, 34-36, 43, 45, 48, 49, 58-80, 83-88, 90, 92-97, 99-102, 111-113, 115-118, 120, 123, 124, 127

Compounds having an serotonin re-uptake inhibition (SRI) $IC_{50}$ value of less than or equal to 50nM and which are more than 100-fold as potent in the inhibition of serotonin re-uptake than in the inhibition of dopamine re-uptake and noradrenaline re-uptake include the title compounds of Examples 1, 2, 4, 9, 12, 17, 18, 26, 29, 30, 36, 43, 45, 48, 49, 60-66, 68-75, 78, 79, 90, 92-94, 100, 102, 116, 118, 124

In particular, the title compound of Example 16 had a serotonin re-uptake inhibition (SRI) $IC_{50}$ of 4 7 nM; the title compound of Example 29 had a serotonin re-uptake inhibition (SRI) $IC_{50}$ of 2 0 nM, and the title compound of Example 62 had a serotonin re-uptake inhibition (SRI) $IC_{50}$ of 3 7 nM

Claims

1 A compound of general formula (I), pharmaceutically acceptable salts, solvates or polymorphs thereof;




(I)

wherein,

$R^1$ and $R^2$, which may be the same or different, are H, $C_1$-$C_6$alkyl or $(CH_2)_d(C_3$-$C_6$cycloalkyl) wherein d = 0, 1, 2 or 3, or $R^1$and $R^2$ together with the nitrogen to which they are attached form an azetidine ring,

Z or Y is $-SR^3$ and the other Z or Y is halogen or $-R^3$; wherein $R^3$ is independently $C_1$-$C_4$ alkyl optionally substituted with fluorine, except that $R^3$ is not $CF_3$;

or Z and Y are linked so that, together with the interconnecting atoms, Z and Y form a fused 5 to 7-membered carbocyclic or heterocyclic ring which may be saturated, unsaturated or aromatic, and wherein when Z and Y form a heterocyclic ring, in addition to carbon atoms, the linkage contains one or two heteroatoms independently selected from oxygen, sulfur and nitrogen, with the proviso that when $R^5$ is fluorine and $R^2$ is methyl then the fused ring is not 1,3-dioxalane and Z and Y together do not form a fused phenyl ring;

$R^4$ and $R^5$, which may be the same or different, are

A-X, wherein A = -CH=CH- or $-(CH_2)_p$- where p is 0, 1 or 2, X is hydrogen, F, Cl, Br, I, $CONR^8R^7$, $SO_2NR^8R^7$, $SO_2NHC(=O)R^8$, OH, $C_{1-4}$alkoxy, $NR^8SO_2R^9$, $NO_2$, $NR^8R^{11}$, CN, $CO_2R^{10}$, CHO, $SR^{10}$, $S(O)R^9$ or $SO_2R^{10}$; $R^8$, $R^7$, $R^8$ and $R^{10}$ which may be the same or different, are hydrogen or $C_{1-6}$alkyl optionally substituted independently by one or more $R^{12}$, $R^9$ is $C_{1-6}$ alkyl optionally substituted independently by one or more $R^{12}$; $R^{11}$ is hydrogen, $C_{1-6}$ alkyl optionally substituted independently by one or more $R^{12}$, $C(O)R^8$, $CO_2R^9$, $C(O)NHR^8$ or $SO_2NR^8R^7$, $R^{12}$ is F, OH, $CO_2H$, $C_{3-6}$cycloalkyl, $NH_2$, $CONH_2$, $C_{1-6}$alkoxy, $C_{1-6}$alkoxycarbonyl or a 5- or 6-membered heterocyclic

ring containing 1, 2 or 3 heteroatoms selected from N, S and O optionally substituted independently by one or more $R^{13}$, or $R^6$ and $R^7$, together with the nitrogen to which they are attached, form a 4-, 5- or 6-membered heterocyclic ring optionally substituted independently by one or more $R^{13}$, or

a 5- or 6-membered heterocyclic ring containing 1, 2 or 3 heteroatoms selected from N, S and O, optionally substituted independently by one or more $R^{13}$;

wherein $R^{13}$ is hydroxy, $C_1$-$C_4$alkoxy, F, $C_1$-$C_6$alkyl, haloalkyl, haloalkoxy, $-NH_2$, $-NH(C_1$-$C_6$alkyl) or $-N(C_1$-$C_6$alkyl)$_2$

2 A compound according to claim 1, pharmaceutically acceptable salts, solvates or polymorphs thereof, wherein $R^1$ and $R^2$, which may be the same or different, are hydrogen or $C_1$-$C_6$alkyl

3 A compound according to claims 1 or 2, pharmaceutically acceptable salts, solvates or polymorphs thereof, wherein when Z or Y is $-SR^3$, $R^3$ is methyl or ethyl.

4 A compound according to claims 1 or 2, pharmaceutically acceptable salts, solvates or polymorphs thereof, wherein when Z and Y are linked to form a fused ring, the ring is a heterocyclic ring

5 A compound according to claim 4, pharmaceutically acceptable salts, solvates or polymorphs thereof, wherein in addition to carbon atoms, the linkage contains one or two sulfur atoms

6 A compound according to any preceding claim, pharmaceutically acceptable salts, solvates or polymorphs thereof, wherein $R^6$ and $R^7$, which may be the same or different, are hydrogen, $C_1$-$C_3$alkyl optionally substituted by hydroxy, $-CONH_2$ or $C_1$-$C_3$alkoxy

7 A compound according to any preceding claim, pharmaceutically acceptable salts, solvates or polymorphs thereof, wherein $R^6$ is hydrogen, hydroxyethyl or methyl.

8 A compound according to any preceding claim, pharmaceutically acceptable salts, solvates or polymorphs thereof, wherein $R^8$ is methyl, ethyl, isopropyl, trifluoromethyl or methoxyethyl

9 A compound according to any preceding claim, pharmaceutically acceptable salts, solvates or polymorphs thereof, wherein p is 1 or 0

10 A compound according to any preceding claim, pharmaceutically acceptable salts, solvates or polymorphs thereof, wherein $R^4$ and $R^5$, which may be the same or different, are

$-(CH_2)_p-X$, where p is 0, 1 or 2, X is hydrogen, hydroxy, $CONR^8R^7$, $SO_2NR^8R^7$, $NR^8SO_2R^8$, $SR^{10}$, $SOR^8$ or $SO_2R^{10}$ wherein $R^8$, $R^7$, $R^8$, $R^8$ and $R^{10}$ are as defined in claim 1, or

a 5- or 6-membered heterocyclic ring containing 1, 2 or 3 heteroatoms selected from N, S and O

11 A compound according to any preceding claim, pharmaceutically acceptable salts, solvates or polymorphs thereof, wherein $R^4$ and $R^5$, which may be the same or different, are

$-(CH_2)_p-X$, where p is 0 or 1, X is hydrogen, hydroxy, $CONR^8R^7$, $SO_2NR^8R^7$ or $NR^8SO_2R^8$; wherein $R^8$ and $R^7$, which may be the same or different, are hydrogen or $C_1$-$C_3$alkyl optionally substituted by hydroxy, $-CONH_2$ or $C_1$-$C_3$alkoxy (preferably methoxy), $R^8$ is hydrogen, hydroxyethyl or methyl, or $R^8$ is methyl, ethyl, isopropyl, trifluoromethyl or methoxyethyl, or

triazolyl, imidazolyl or pyrazolyl

12 A compound according to any preceding claim, pharmaceutically acceptable salts, solvates or polymorphs thereof, wherein $R^4$ and $R^5$ are not both hydrogen

13 A compound according to any preceding claim, pharmaceutically acceptable salts, solvates or polymorphs thereof, wherein $R^4$ is hydrogen

14 A compound according to claim 1, pharmaceutically acceptable salts, solvates or polymorphs thereof, selected from the group.

4-(2,3-dihydro-1-benzothien-5-yloxy)-3-[(methylamino)methyl]-benzenesulfonamide (Example 2),
3-[(dimethylamino)methyl]-4-[3-methyl-4-(methylsulfanyl)phenoxy]-benzenesulfonamide (Example 12),
4-(2,3-dihydro-1-benzothien-5-yloxy)-3-[(dimethylamino)methyl]-benzenesulfonamide (Example 16),
4-[3-chloro-4-(methylsulfanyl)phenoxy]-3-[(dimethylamino)methyl]-benzenesulfonamide (Example 17),
3-[(dimethylamino)methyl]-4-[3-fluoro-4-(methylsulfanyl)phenoxy]-benzenesulfonamide (Example 18),
*N*,*N*-dimethyl-*N*-[2-(6-quinolinyloxy)benzyl]amine (Example 29);
3-[(methylamino)methyl]-4-(6-quinolinyloxy)benzenesulfonamide (Example 35),
4-(2,3-dihydro-1-benzothien-5-yloxy)-3-[(methylamino)methyl]benzamide (Example 60),
4-(2,3-dihydro-1-benzothien-5-yloxy)-*N*-methyl-3-[(methylamino)methyl]-benzamide (Example 62),
*N*-[3-[(methylamino)methyl]-4-[3-methyl-4-(methylsulfanyl)phenoxy]benzyl]methanesulfonamide (Example 75),
3-[(methylamino)methyl]-4-[3-methyl-4-(methylsulfanyl)phenoxy]benzamide (Example 79),
4-(2,3-dihydro-1,4-benzoxathiin-7-yloxy)-3-[(dimethylamino)methyl]benzamide (Example 88),
{3-[(dimethylamino)methyl]-4-[3-fluoro-4-(methylsulfanyl)phenoxy]phenyl}-methanol (Example 90),
3-[(dimethylamino)methyl]-4-(6-quinolinyloxy)benzamide (Example 100),
3-[(methylamino)methyl]-4-(6-quinolinyloxy)benzamide (Example 102),
*N*-methyl-*N*-[3-[(methylamino)methyl]-4-[3-methyl-4-(methylsulfanyl)phenoxy]-phenyl]methanesulfonamide (Example 116) and
*N*-[4-(2,3-dihydro-1,4-benzoxathiin-7-yloxy)-3-[(dimethylamino)methyl]phenyl]-methanesulfonamide (Example 124)

15 A compound as defined in any preceding claim, pharmaceutically acceptable salts, solvates or polymorphs thereof, for use as a pharmaceutical

16 A pharmaceutical formulation containing a compound as defined in any one of claims 1 to 14, or pharmaceutically acceptable salts, solvates or polymorphs thereof, and a pharmaceutically acceptable adjuvant, diluent or carrier

17 The use of a compound as defined in any of claims 1 to 14, pharmaceutically acceptable salts, solvates or polymorphs thereof, in the manufacture of a medicament for the treatment or prevention of a disorder in which the regulation of monoamine transporter function is implicated.

18 The use according to claim 17 wherein the disorder is depression, attention deficit hyperactivity disorder, obsessive-compulsive disorder, post-traumatic stress disorder, substance abuse disorders or sexual dysfunction

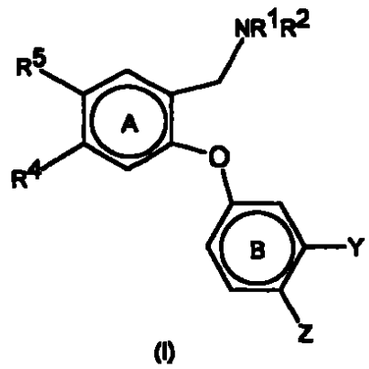
19 The use according to claim 18 wherein the disorder is premature ejaculation

20 A method of treatment or prevention of a disorder in which the regulation of monoamine transporter function is implicated, comprising the administration of an effective amount of a compound as defined in any one of claims 1 to 14, pharmaceutically acceptable salts, solvates or polymorphs thereof, to a patient in need of such treatment or prevention

21 A method of treatment or prevention of premature ejaculation, comprising the administration of an effective amount of a compound as defined in any one of claims 1 to 14, pharmaceutically acceptable salts, solvates or polymorphs thereof, to a patent in need of such treatment or prevention

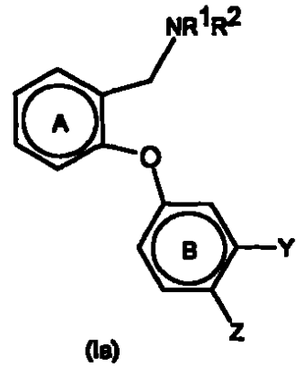
22 A method of increasing ejaculatory latency which comprises the administration of an effective amount of a compound as defined in any one of claims 1 to 14, pharmaceutically acceptable salts, solvates or polymorphs thereof, to a male desiring increased ejaculatory latency

23 A process for the preparation of a compound of general formula (I),




(I)

wherein $R^1$, $R^2$, $R^4$, $R^5$, X and Z are as defined in any one of claims 1 to 14 comprising reacting a compound of general formula Ia




(Ia)

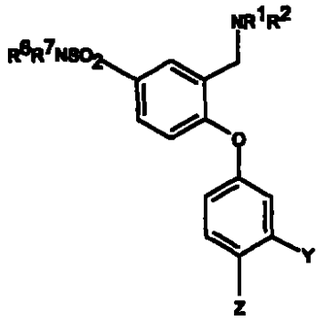
under suitable reaction conditions to form the compound of formula I, wherein the suitable reaction conditions are

i) where $R^4/R^5$ are halogen, by reaction of (Ia) with a suitable halogenating agent in an inert solvent which does not adversely affect the reaction,

ii) where $R^4/R^5$ are $-NO_2$, by reaction of (Ia) with a suitable nitrating agent in an inert solvent which does not adversely affect the reaction at, or below, room temperature, or

iii) where $R^4/R^5$ is $-SO_2NR^6R^7$ by reaction of an intermediate sulfonyl chloride with the requisite amine of formula $HNR^6R^7$ in a suitable solvent.

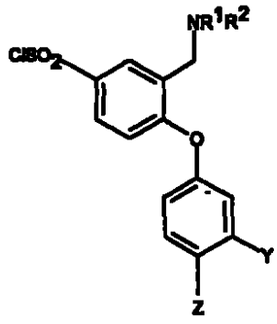
24 A process according to claim 23 for preparing a compound of formula (Iq), i e a compound of formula I where $R^5$ is $-SO_2NR^6R^7$ and $R^4$ is hydrogen,



(Iq)

comprising

a) reacting a compound of formula Ia, optionally in a suitable solvent, with chlorosulfonic acid to give a compound of formula XVIII



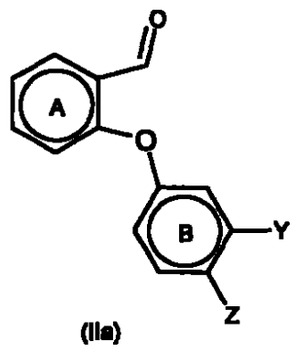
(XVIII)

followed by

b) reacting with $HNR^6R^7$ to give the compound of formula (Iq)

25 A process according to claim 24 wherein the compound of formula XVIII is generated *in situ* and reacted with $HNR^6R^7$ without isolation

26 A process according to any one of claims 23 to 25 which further comprises the step of preparing compounds of formula (Ia), by reacting compounds of formula (IIa)

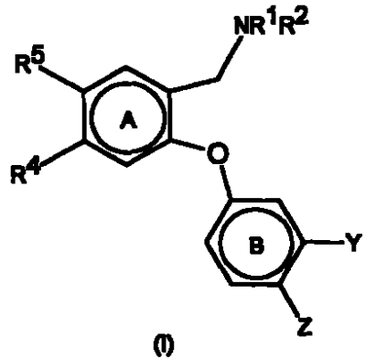


(IIa)

with a compound of formula $HNR^1R^2$, or with a suitable salt form thereof, together with a hydride reducing agent in a suitable solvent, to form the compound of formula (Ia)

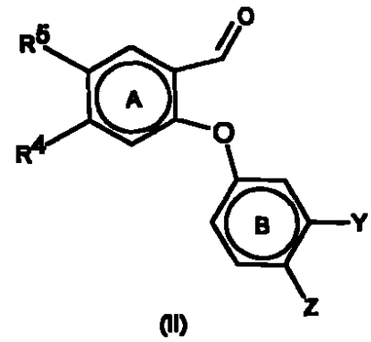
27 An intermediate compound of formula (IIa) or (XVIII) as defined in claims 23 to 26

28 A process for preparing a compound of formula I



(I)

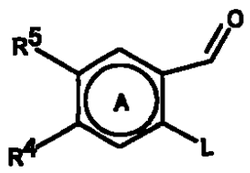
wherein $R^1$, $R^2$, $R^4$, $R^5$, X and Z are as defined in any one of claims 1 to 14, comprising reacting compounds of formula II



(II)

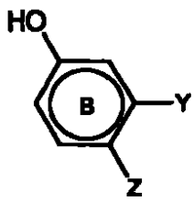
with a compound of formula $HNR^1R^2$ or with a suitable salt form thereof, together with a hydride reducing agent in a suitable solvent.

29 A process according to claim 28 which further comprises coupling under suitable reaction conditions a compound of formula III,




(III)

wherein L is a suitable leaving group such as halogen or a sulfonate ester such as trifluoromethanesulfonate or methanesulfonate, with a compound of formula IV




(IV)

to give the compound of formula II

30 An intermediate compound of formula II as defined in claim 28

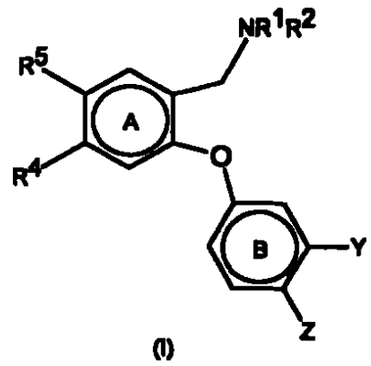
31 A compound of general formula (I), or pharmaceutically acceptable salts, solvates or polymorphs thereof, wherein $R^1$, $R^2$, Y and Z are as defined in claim 1, and $R^4$ and $R^5$, which may be the same or different, are $-(CH_2)_p-A'$, wherein p is 0, 1 or 2 and A' is a polar group

32 A compound according to claim 23, wherein the polar group has a δ-value more negative than -0 1

**Derivados de fenoxibencilamina como SSRI**

Esta invención se refiere a nuevos compuestos de éter difenílico que inhiben la reabsorción de monoaminas. En particular, los compuestos de la presente invención presentan actividad como inhibidores selectivos de la reabsorción de serotonina (SSRI, del inglés selective serotonin re-uptake inhibitors) y tienen utilidad, por tanto, en diversas áreas terapéuticas. Más notablemente, los compuestos de la presente invención son útiles en el tratamiento o prevención de diversos trastornos, incluidos aquellos en los que está implicada la regulación de la función de los transportadores de monoaminas, tales como depresión, trastorno de hiperactividad con déficit de atención, trastorno obsesivo compulsivo, trastorno de estrés post-traumático, trastornos de abuso de sustancias y disfunción sexual, incluida eyaculación precoz, y a las formulaciones farmacéuticas que contienen tales compuestos.

De acuerdo con un primer aspecto, la invención proporciona un compuesto de fórmula general (I), sus sales, solvatos o polimorfos farmacéuticamente aceptables:




(I)

en la que

$R^1$ y $R^2$, que pueden ser iguales o diferentes, son H, alquilo $C_1$-$C_6$ o $(CH_2)_d$-(cicloalquilo $C_3$-$C_6$), donde d es 0, 1, 2 ó 3, o $R^1$ y $R^2$ junto con el nitrógeno al que están unidos forman un anillo de azetidina,

uno de Z o Y es $-SR^3$ y el otro de Z o Y es halógeno o $-R^3$, donde $R^3$ es independientemente alquilo $C_1$-$C_4$ opcionalmente sustituido con flúor, excepto que $R^3$ no es $CF_3$,

o Z e Y están unidos de manera que, junto con los átomos de interconexión, Z e Y

forman un anillo carbocíclico o heterocíclico de 5 a 7 miembros, condensado, que puede ser saturado, insaturado o aromático, y donde, cuando Z e Y forman un anillo heterocíclico, además de átomos de carbono, el enlace contiene uno o dos heteroátomos seleccionados independientemente entre oxígeno, azufre y nitrógeno, con la condición de que cuando $R^5$ es flúor y $R^2$ es metilo, entonces el anillo condensado no es 1,3-dioxolano, y Z e Y juntos no forman un anillo de fenilo condensado,

$R^4$ y $R^5$, que pueden ser iguales o diferentes, son

A-X, donde A es -CH=CH- o $-(CH_2)_p-$, donde p es 0, 1 ó 2, X es hidrógeno, F, Cl, Br, I, $CONR^6R^7$, $SO_2NR^6R^7$, $SO_2NHC(=O)R^6$, OH, alcoxi $C_{1-4}$, $NR^8SO_2R^9$, $NO_2$, $NR^6R^{11}$, CN, $CO_2R^{10}$, CHO, $SR^{10}$, $S(O)R^9$ ó $SO_2R^{10}$, $R^6$, $R^7$, $R^8$ y $R^{10}$, que pueden ser iguales o diferentes, son hidrógeno o alquilo $C_{1-6}$ opcionalmente sustituido independientemente con uno o más $R^{12}$, $R^9$ es alquilo $C_{1-6}$ opcionalmente sustituido independientemente con uno o más $R^{12}$, $R^{11}$ es hidrógeno, alquilo $C_{1-6}$ opcionalmente sustituido independientemente con uno o más $R^{12}$, $C(O)R^6$, $CO_2R^9$, $C(O)NHR^6$ ó $SO_2NR^6R^7$, $R^{12}$ es F (preferiblemente hasta 3), OH, $CO_2H$, cicloalquilo $C_{3-6}$, $NH_2$, $CONH_2$, alcoxi $C_{1-6}$, alcoxi $C_{1-6}$-carbonilo o un anillo heterocíclico de 5 ó 6 miembros que contiene 1, 2 ó 3 heteroátomos seleccionados entre N, S y O, opcionalmente sustituido independientemente con uno o más $R^{13}$, o $R^6$ y $R^7$, junto con el nitrógeno al que están unidos, forman un anillo heterocíclico de 4, 5 ó 6 miembros opcionalmente sustituido independientemente con uno o más $R^{13}$, o

un anillo heterocíclico de 5 ó 6 miembros que contiene 1, 2 ó 3 heteroátomos seleccionados entre N, S y O, opcionalmente sustituido independientemente con uno o más $R^{13}$;

donde $R^{13}$ es hidroxi, alcoxi $C_1$-$C_4$, F, alquilo $C_1$-$C_6$, haloalquilo, haloalcoxi, $-NH_2$, -NH(alquilo $C_1$-$C_6$) o -N(alquilo $C_1$-$C_6$)$_2$

Salvo indicación en contrario, cualquier grupo alquilo puede ser lineal o ramificado y tiene de 1 a 6 átomos de carbono, preferiblemente de 1 a 4 y particularmente de 1 a 3 átomos de carbono

Salvo indicación en contrario, cualquier grupo carbociclilo contiene 3 a 8

átomos en el anillo, y puede ser saturado, insaturado o aromático. Los grupos carbocíclicos saturados preferidos son ciclopropilo, ciclopentilo o ciclohexilo Los grupos carbociclilo insaturados preferidos contienen hasta 3 dobles enlaces Un grupo carbociclilo aromático preferido es fenilo. El término carbocíclico deberá construirse similarmente Además, el término carbociclilo incluye cualquier combinación condensada de grupos carbociclilo, por ejemplo naftilo, fenantrilo, indanilo e indenilo.

Salvo indicación en contrario, cualquier grupo heterociclilo contiene 5 a 7 átomos en el anillo y hasta 4 de los mismos pueden ser heteroátomos tales como nitrógeno, oxígeno y azufre, y pueden ser saturados, insaturados o aromáticos Ejemplos de grupos heterociclilo son furilo, tienilo, pirrolilo, pirrolinilo, pirrolidinilo, imidazolilo, dioxolanilo, oxazolilo, tiazolilo, imidazolilo, imidazolinilo, imidazolidinilo, pirazolilo, pirazolinilo, pirazolidinilo, isoxazolilo, isotiazolilo, oxadiazolilo, triazolilo, tiadiazolilo, piranilo, piridilo, pipendinilo, dioxanilo, morfolino, ditianilo, tiomorfolino, piridazinilo, pirimidinilo, pirazinilo, piperazinilo, sulfolanilo, tetrazolilo, triazinilo, azepinilo, oxazepinilo, tiazepinilo, diazepinilo y tiazolinilo Además, el término heterociclilo incluye grupos heterociclilo condensados, por ejemplo bencimidazolilo, benzoxazolilo, imidazopiridinilo, benzoxazinilo, benzotiazinilo, oxazolopiridinilo, benzofuranilo, quinolinilo, quinazolinilo, quinoxalinilo, dihidroquinazolinilo, benzotiazolilo, ftalimido, benzofuranilo, benzodiazepinilo, indolilo e isoindolilo. El término heterocíclico deberá construirse de manera similar

Halo significa flúor, cloro, bromo o yodo

Preferiblemente, $R^1$ y $R^2$, que pueden ser iguales o diferentes, son hidrógeno o alquilo $C_1$-$C_6$. Más preferiblemente hidrógeno o metilo

Cuando Z o Y es -$SR^3$, $R^3$ es preferiblemente metilo o etilo

Cuando Z e Y forman un anillo condensado, el anillo es preferiblemente un anillo heterocíclico Más preferiblemente, el enlace contiene uno o dos átomos de azufre

Preferiblemente, $R^4$ y $R^5$ no son ambos hidrógeno

Preferiblemente, $R^4$ y $R^5$, que pueden ser iguales o diferentes, son

-$(CH_2)_p$-X, donde p es 0, 1 ó 2 (preferiblemente 0 ó 1), X es hidrógeno, hidroxi, $CONR^6R^7$, $SO_2NR^6R^7$, $NR^8SO_2R^9$, $SR^{10}$, $SOR^9$ ó $SO_2R^{10}$, donde $R^6$, $R^7$, $R^8$, $R^9$ y $R^{10}$ son como se han definido en el primer aspecto, o

un anillo heterocíclico de 5 ó 6 miembros que contiene 1, 2 ó 3 heteroátomos seleccionados entre N, S y O (preferiblemente oxadiazolilo, triazolilo,

imidazolilo, oxazolilo, pirazolilo, piridinilo o pirimidinilo)

Más preferiblemente, $R^4$ y $R^5$, que pueden ser iguales o diferentes, son. $-(CH_2)_p-X$, donde p es 0 ó 1, X es hidrógeno, hidroxi, $CONR^6R^7$, $SO_2NR^6R^7$ ó $NR^8SO_2R^9$, donde $R^6$ y $R^7$, que pueden ser iguales o diferentes, son hidrógeno o alquilo $C_1$-$C_3$ opcionalmente sustituido con hidroxi, $-CONH_2$ o alcoxi $C_1$-$C_3$ (preferiblemente metoxi), $R^8$ es hidrógeno, hidroxietilo o metilo, o $R^9$ es metilo, etilo, isopropilo, trifluorometilo o metoxietilo, o triazolilo, imidazolilo o pirazolilo

Más preferiblemente aún, $R^4$ es hidrógeno.

Preferiblemente, $R^6$ y $R^7$, que pueden ser iguales o diferentes, son hidrógeno, alquilo $C_1$-$C_3$ opcionalmente sustituido con hidroxi, $-CONH_2$ o alcoxi $C_1$-$C_3$ (preferiblemente metoxi) Más preferiblemente, $R^6$ y $R^7$, que pueden ser iguales o diferentes, son hidrógeno o metilo, más preferiblemente aún hidrógeno

Cuando está presente, $R^{12}$ es preferiblemente oxadiazolilo, triazolilo, imidazolilo, oxazolilo, pirazolilo, piridinilo o pirimidinilo. Más preferiblemente triazolilo, imidazolilo o pirazolilo

En el caso en que $R^6$ y $R^7$, junto con el nitrógeno al que están unidos, forman un anillo heterocíclico, los anillos preferidos son anillos de pirrolidina o piperidina, cada uno de los cuales puede estar sustituido con OH ó $CONH_2$ o un anillo de morfolina que puede estar sustituido con $CONH_2$

Preferiblemente, $R^{11}$ es hidrógeno o alquilo $C_{1-6}$

Preferiblemente, $R^8$ es hidrógeno, hidroxietilo o metilo Más preferiblemente hidrógeno

Preferiblemente, $R^9$ es metilo, etilo, isopropilo, trifluorometilo o metoxietilo Más preferiblemente metilo o etilo (preferiblemente metilo)

Preferiblemente, $R^{10}$ es metilo o etilo

Preferiblemente, p es 1 ó 0, más preferiblemente 0

Preferiblemente

$R^1$ y $R^2$, que pueden ser iguales o diferentes, son hidrógeno o metilo;

cuando está presente, $R^3$ es metilo o etilo; o Z e Y están unidos de modo que, junto con los átomos de interconexión, Z e Y forman un anillo carbocíclico o heterocíclico de 5 a 7 miembros, condensado, que puede ser saturado, insaturado o aromático, y donde cuando Z e Y forman un anillo heterocíclico, además de átomos de carbono, el enlace contiene uno o dos heteroátomos

seleccionados independientemente entre oxígeno, azufre y nitrógeno, y

$R^4$ y $R^5$, que pueden ser iguales o diferentes, son

$-(CH_2)_p-X$, donde p es 0 ó 1, X es hidrógeno, hidroxi, $CONR^6R^7$, $SO_2NR^6R^7$, $NR^8SO_2R^9$, $SR^{10}$, $SOR^9$ ó $SO_2R^{10}$ y donde $R^6$ y $R^7$, que pueden ser iguales o diferentes, son hidrógeno, alquilo $C_1$-$C_3$ opcionalmente sustituido con hidroxi, $-CONH_2$ o alcoxi $C_1$-$C_3$ (preferiblemente metoxi), o $R^6$ y $R^7$, junto con el nitrógeno al que están unidos, pueden formar un anillo de morfolina, pirrolidina o piperidina, cada uno de los cuales puede estar sustituido con OH ó $CONH_2$, $R^8$ es hidrógeno, hidroxietilo o metilo (preferiblemente hidrógeno), $R^9$ es metilo, etilo, isopropilo, trifluorometilo o metoxietilo, y $R^{10}$ es metilo o etilo; o

un grupo oxadiazolilo, triazolilo, imidazolilo, oxazolilo, pirazolilo, piridinilo o pirimidinilo

Más preferiblemente

$R^1$ y $R^2$, que pueden ser iguales o diferentes, son hidrógeno o metilo,

cuando está presente, $R^3$ es metilo o etilo, o Z e Y están unidos de modo que, junto con los átomos de interconexión, Z e Y forman un anillo heterocíclico condensado de 5 a 7 miembros que contiene 1 ó 2 átomos de azufre, y

$R^4$ y $R^5$, que pueden ser iguales o diferentes, son

$-(CH_2)_p-X$, donde p es 0 ó 1, X es hidrógeno, hidroxi, $CONR^6R^7$, $SO_2NR^6R^7$ o $NR^8SO_2R^9$, donde $R^6$ y $R^7$, que pueden ser iguales o diferentes, son hidrógeno, alquilo $C_1$-$C_3$ opcionalmente sustituido con hidroxi, $-CONH_2$ o alcoxi $C_1$-$C_3$ (preferiblemente metoxi), $R^8$ es hidrógeno, hidroxietilo o metilo; $R^9$ es metilo, etilo, isopropilo, trifluorometilo o metoxietilo, o

triazolilo, imidazolilo o pirazolilo

Más preferiblemente aún

$R^1$ y $R^2$, que pueden ser iguales o diferentes, son hidrógeno o metilo;

cuando está presente, $R^3$ es metilo o etilo, o Z e Y están unidos de modo que, junto con los átomos de interconexión, Z e Y forman un anillo heterocíclico saturado de 5 a 7 miembros, condensado, que contiene 1 ó 2 átomos de azufre,

$R^4$ es hidrógeno, y

$R^5$ es

$-(CH_2)_p-X$, donde p es 0 ó 1, X es hidrógeno, hidroxi, $CONR^6R^7$, $SO_2NR^6R^7$ o $NR^8SO_2R^9$, donde $R^6$ y $R^7$, que pueden ser iguales o diferentes, son

hidrógeno, alquilo $C_1$-$C_3$ opcionalmente sustituido con hidroxi, -$CONH_2$ o alcoxi $C_1$-$C_3$ (preferiblemente metoxi), $R^8$ es hidrógeno, hidroxietilo o metilo, $R^9$ es metilo, etilo, isopropilo, trifluorometilo o metoxietilo; o triazolilo, imidazolilo o pirazolilo

Más preferiblemente aun, $R^4$ y $R^5$ no son ambos hidrógeno

Compuestos preferidos son

4-(2,3-dihidro-1-benzotien-5-iloxi)-3-[(metilamino)metil]bencenosulfonamida (Ejemplo 2),

3-[(dimetilamino)metil]-4-[3-metil-4-(metilsulfanil)fenoxi]bencenosulfonamida (Ejemplo 12),

4-(2,3-dihidro-1-benzotien-5-iloxi)-3-[(dimetilamino)metil]bencenosulfonamida (Ejemplo 16),

4-[3-cloro-4-(metilsulfanil)fenoxi]-3-[(dimetilamino)metil]bencenosulfonamida (Ejemplo 17),

3-[(dimetilamino)metil]-4-[3-fluoro-4-(metilsulfanil)fenoxi]bencenosulfonamida (Ejemplo 18),

*N,N*-dimetil-*N*-[2-(6-quinoliniloxi)bencil]amina (Ejemplo 29)

3-[(metilamino)metil]-4-(6-quinoliniloxi)bencenosulfonamida (Ejemplo 35),

4-(2,3-dihidro-1-benzotien-5-iloxi)-3-[(metilamino)metil]benzamida (Ejemplo 60),

4-(2,3-dihidro-1-benzotien-5-iloxi)-*N*-metil-3-[(metilamino)metil]benzamida (Ejemplo 62),

*N*-{3-[(metilamino)metil]-4-[3-metil-4-(metilsulfanil)fenoxi]bencil}metanosulfonamida (Ejemplo 75),

3-[(metilamino)metil]-4-[3-metil-4-(metilsulfanil)fenoxi]benzamida (Ejemplo 79),

4-(2,3-dihidro-1,4-benzoxatiin-7-iloxi)-3-[(dimetilamino)metil]benzamida (Ejemplo 88);

{3-[(dimetilamino)metil]-4-[3-fluoro-4-(metilsulfanil)fenoxi]fenil}metanol (Ejemplo 90),

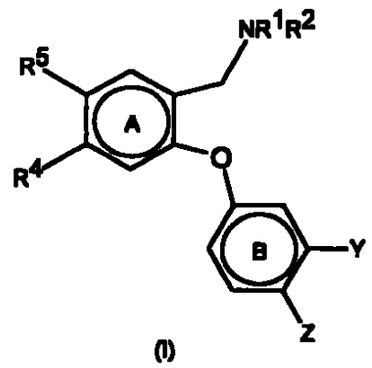
3-[(dimetilamino)metil]-4-(6-quinoliniloxi)benzamida (Ejemplo 100),

3-[(metilamino)metil]-4-(6-quinoliniloxi)benzamida (Ejemplo 102),

*N*-metil-*N*-{3-[(metilamino)metil]-4-[3-metil-4-(metilsulfanil)fenoxi]fenil}-metanosulfonamida (Ejemplo 116); y

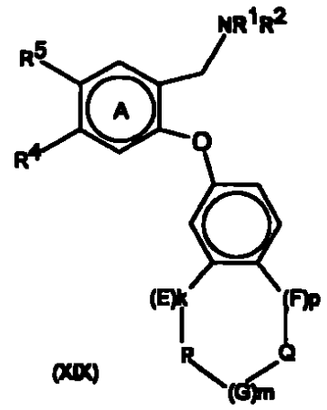
*N*-{4-(2,3-dihidro-1,4-benzoxatiin-7-iloxi)-3-[(dimetilamino)metil]fenil}metanosulfonamida (Ejemplo 124)

De acuerdo con un segundo aspecto, la invención proporciona un compuesto de fórmula (I) o (XIX)



(I)

y sus sales o solvatos farmacéuticamente aceptables, en las que (en este aspecto) $R^1$ y $R^2$, representan independientemente, H, alquilo $C_1$-$C_6$ o $(CH_2)_d$-(cicloalquilo $C_3$-$C_6$), donde d es 0, 1, 2 ó 3, o donde $NR^1R^2$, cuando se toman juntos, representan un anillo de 4 miembros en el que $R^1$ y $R^2$ juntos representan alquilo $C_3$, Z e Y representan ambos independientemente -$SR^3$ donde, cuando Z es $SR^3$, entonces Y es halógeno, -$OR^a$, -$R^a$ o -$SR^a$, o cuando Y es -$SR^3$, entonces Z es halógeno, -$OR^a$, $R^a$ o -$SR^a$, y $R^3$ y $R^a$ representan independientemente alquilo $C_1$-$C_4$ (opcionalmente sustituido con átomos de flúor, p ej , -$CF_3$), o Z e Y, cuando se toman juntos, pueden representar un anillo condensando de 5 a 7 miembros como se ilustra por la fórmula general XIX, donde dicho anillo de 5 a 7 miembros puede ser saturado, insaturado o aromático, y donde dicho anillo de 5 a 7 miembros puede contener opcionalmente uno o más heteroátomos P y Q, donde P y Q pueden ser independientemente O, S ó N, y donde E, F ó G representan independientemente CH o $CH_2$, y donde k y p pueden ser independientemente 0, 1, 2 ó 3, y m es 1, 2 ó 3, y




(XIX)

$R^4$ y $R^5$ representan independientemente A-X, donde A es $-(CH_2)_n-$, donde n representa 0, 1 ó 2 y donde X representa H, F, Cl, Br, I, $CONR^6R^7$ o $SO_2NR^6R^7$, OH, $NR^8SO_2R^9$, $NO_2$, $NR^6R^{11}$, CN, $CO_2R^{10}$, CHO, $S(O)_mR^{10}$, donde m es 0, 1 ó 2 y donde $R^6$, $R^7$, $R^8$ y $R^{10}$ representan independientemente H o alquilo $C_{1-6}$, donde $R^9$ representa alquilo $C_{1-6}$, $R^{11}$ representa H, alquilo $C_{1-6}$, $C(O)R^6$, $CO_2R^9$, $C(O)NHR^6$ ó $SO_2NR^6R^6$ y donde dicho grupo alquilo $C_{1-6}$ está opcionalmente sustituido con uno o más grupos seleccionados entre OH, $CO_2H$, cicloalquilo $C_{3-6}$, $NH_2$, $CONH_2$, alcoxi $C_{1-6}$, alcoxi $C_{1-6}$-carbonilo y un anillo heterocíclico de 5 ó 6 miembros que contiene 1, 2 ó 3 heteroátomos seleccionados entre N, S y O, o con la condición de que cuando P=Q= oxígeno, entonces tanto k como p son distintos de cero; con la condición de que Z e Y juntos no formen un anillo de fenilo condensado, $R^4$ o $R^5$ pueden ser representativos de un anillo heterocíclico de 5 ó 6 miembros que contiene 1, 2 ó 3 heteroátomos seleccionados entre N, S y O, y además, $R^6$ y $R^7$, junto con el átomo de N al que están unidos, pueden representar un anillo heterocíclico de 5 ó 6 miembros que puede estar opcionalmente sustituido, y sus sales o solvatos farmacéuticamente aceptables con la condición de que tanto $R^4$ como $R^5$ no sean H

Para evitar dudas, salvo indicación en contrario, el término sustituido significa sustituido con uno o más grupos definidos. En caso de que los grupos puedan seleccionarse entre cierto número de grupos alternativos, los grupos seleccionados pueden ser iguales o diferentes

Para evitar dudas, el término independientemente significa que cuando se selecciona más de un sustituyente entre cierto número de posibles sustituyentes, esos sustituyentes pueden ser iguales o diferentes

De acuerdo con un tercer aspecto, la invención proporciona un compuesto

de fórmula general I y sus sales farmacéuticamente aceptables, en la que $R^1$, $R^2$, $R^3$, Z e Y son como se han definido en el primer aspecto, y $R^4$ y $R^5$, que pueden ser iguales o diferentes, son $-(CH_2)_p-A'$, donde p es 0, 1 ó 2 y A' es un grupo polar En este aspecto, los grupos polares se pueden definir como aquellos que tienen un valor π negativo (véase C Hansch y A Leo, "Substituent Constants for Correlation Analysis in Chemistry and Biology", Wiley, Nueva York, 1979) En este sistema, H tiene un valor π de 0,00, $-OCH_3$ tiene un valor π de -0,02, y $-SO_2NH_2$ tiene un valor π de -1,82, por ejemplo [véase la Tabla VI-I, "Well-Characterized Aromatic Substituents", pág 49, ibid] Los grupos polares más preferidos tienen un valor π más negativo. así, los grupos preferidos tienen valores π de valor más negativo que -0,1, más preferiblemente un valor más negativo que -0,5, y lo más preferiblemente un valor más negativo que -1,0 Incluso cuando p es distinto de cero en la definición anterior, la definición de A' está basada en la anterior referencia como si p fuera cero

Salvo indicación en contrario, los compuestos del primero, segundo y tercer aspectos se definen aquí en lo sucesivo como compuestos de la invención

Los compuestos de la invención tienen la ventaja de que son inhibidores selectivos de la reabsorción de serotonina (SRI) (y también es probable que tengan menos efectos secundarios), tienen un rápido comienzo de acción (lo que los hace adecuados para la administración poco antes de requerir un efecto), tienen potencia deseable y propiedades asociadas Se prefieren los compuestos que inhiben selectivamente la reabsorción de serotonina, pero no noradrenalina o dopamina.

Se ha encontrado que los compuestos de fórmula I que poseen estas propiedades tienen un grupo relativamente polar en $R^4/R^5$.

Las sales farmacéutica o veterinariamente aceptables de los compuestos de la invención que contienen un centro básico son, por ejemplo, sales de adición de ácido no tóxicas formadas con ácidos inorgánicos tales como ácido clorhídrico, bromhídrico, yodhídrico, sulfúrico y fosfónco, con ácidos carboxílicos o con ácidos organosulfónicos Ejemplos incluyen las sales de HCl, HBr, HI, sulfato o bisulfato, nitrato, fosfato o hidrógenofosfato, acetato, benzoato, succinato, sacarato, fumarato, maleato, lactato, citrato, tartrato, gluconato, camsilato, metanosulfonato, etanosulfonato, bencenosulfonato, p-toluenosulfonato y pamoato. Los compuestos de la invención también pueden proporcionar sales metálicas farmacéutica o veterinariamente aceptables, en particular sales no tóxicas de metales alcalinos o alcalinotérreos, con bases Ejemplos incluyen las sales de sodio, potasio, aluminio, calcio, magnesio, zinc,

dıolamına, olamına, etılendıamına, trometamına, colına, megulamına y dıetanolamına. Para una revısıón sobre sales farmacéutıcas adecuadas véase Berge *y col* , J Pharm, Scı , 66, 1-19, 1977, P L Gould, International Journal of Pharmaceutıcs, 33 (1986), 201-217, y Bighley *y col* , Encyclopedıa of Pharmaceutical Technology, Marcel Deaker Inc , Nueva York 1996, volumen 13, páginas 453-497

Aquí en lo sucesivo, los compuestos, sus sales farmacéutıcamente aceptables, sus solvatos y polimorfos, definidos en cualquier aspecto de la invención (excepto los compuestos intermedios en los procedimientos químicos) se denominan "compuestos de la invención"

Los solvatos farmacéutıcamente aceptables de los compuestos de la invención incluyen sus hidratos

Los compuestos de la invención pueden poseer uno o más centros quirales y por tanto existir en diversas formas estereoisómeras Todos los estereoisómeros y sus mezclas están incluidos dentro del alcance de la presente invención Los compuestos racémicos o bien pueden separarse utilizando HPLC preparativa y una columna con una fase estacionaria quiral o bien pueden resolverse para proporcionar enantiómeros individuales utilizando métodos conocidos por los expertos en la técnica Además, los compuestos intermedios quirales pueden resolverse y utilizarse para preparar compuestos quirales de la invención

En los casos en que los compuestos de la invención existen como isómeros E y Z, la invención incluye los isómeros individuales, así como sus mezclas

En los casos en que los compuestos de la invención existen como isómeros tautómeros, la invención incluye tautómeros individuales, así como sus mezclas.

En los casos en que los compuestos de la invención existen como isómeros ópticos, la invención incluye isómeros individuales, así como sus mezclas.

En los casos en que los compuestos de la invención existen como diastereoisómeros, la invención incluye diastereoisómeros individuales, así como sus mezclas

La separación de diastereoisómeros o isómeros E y Z se puede conseguir por técnicas convencionales, p ej por cristalización fraccionada, cromatografía o HPLC Un enantiómero individual de un compuesto de la invención se puede preparar a partir de un correspondiente intermedio ópticamente puro o por resolución, tal como por HPLC, del correspondiente racemato utilizando un soporte quiral adecuado o por cristalización fraccionada de las sales diastereoisómeras formadas por reacción del

correspondiente racemato con un ácido o una base ópticamente activos adecuados, según sea apropiado

Los compuestos de la invención pueden existir en una o más formas tautómeras Todos los tautómeros y sus mezclas están incluidos dentro del alcance de la presente invención Por ejemplo, una reivindicación de 2-hidroxipiridinilo también abarcaría su forma tautómera, α-piridonilo

Se apreciará por los expertos en la técnica que ciertos derivados protegidos de los compuestos de la invención, que pueden prepararse antes de la etapa final de desprotección, pueden no poseer actividad farmacológica como tal, pero, en ciertos casos, pueden ser administrados oral o parenteralmente y ser metabolizados a continuación en el cuerpo para formar compuestos de la invención que son farmacológicamente activos Por lo tanto, tales derivados pueden describirse como "profármacos". Además, ciertos compuestos de la invención pueden actuar como profármacos de otros compuestos de la invención

Todos los derivados protegidos, y profármacos, de los compuestos de la invención están incluidos dentro del alcance de la invención Ejemplos de profármacos adecuados para los compuestos de la presente invención están descritos en Drugs of Today, volumen 19, número 9, 1983, págs 499-538 y en Topics in Chemistry, capítulo 31, págs 306-316 y en "Design of Prodrugs" por H Bundgaard, Elsevier, 1985, capítulo 1 (las descripciones de estos documentos se incorporan a la presente por referencia)

Será apreciado además por los expertos en la técnica, que ciertos restos, conocidos por los expertos en la técnica como "pro-restos", por ejemplo como describe H Bundgaard en "Design of Prodrugs" (la descripción de cuyo documento se incorpora a la presente por referencia) pueden ponerse en funcionalidades apropiadas cuando dichas funcionalidades están presentes dentro de compuestos de la invención

Los profármacos preferidos para los compuestos de la invención incluyen ésteres, ésteres de carbonato, hemiésteres, ésteres de fosfato, nitroésteres, ésteres de sulfato, sulfóxidos, amidas, carbamatos, azo-compuestos, fosfamidas, glicósidos, éteres, acetales y cetales

La invención también incluye todas las variaciones isotópicas adecuadas de los compuestos de la invención Una variación isotópica se define como una en la que al menos un átomo se reemplaza por un átomo que tiene el mismo número atómico

pero una masa atómica diferente de la masa atómica habitualmente encontrada en la naturaleza Ejemplos de isótopos que se pueden incorporar en los compuestos de la invención incluyen isótopos de hidrógeno, carbono, nitrógeno, oxígeno, fósforo, azufre, flúor y cloro tales como $^{2}H$, $^{3}H$, $^{13}C$, $^{14}C$, $^{15}N$, $^{17}O$, $^{18}O$, $^{31}P$, $^{32}P$, $^{35}S$, $^{18}F$ y $^{36}Cl$, respectivamente Ciertas variaciones isotópicas de la invención, por ejemplo, aquellas en las que se incorpora un isótopo radiactivo tal como $^{3}H$ o $^{14}C$, son útiles en los estudios de distribución de fármacos y/o substratos en tejidos Los isótopos tritio, es decir $^{3}H$, y carbono-14, es decir $^{14}C$, son particularmente preferidos por su facilidad de preparación y detectabilidad Además, la sustitución con isótopos tales como deuterio, es decir $^{2}H$, puede proporcionar ciertas ventajas terapéuticas que resultan de una mayor estabilidad metabólica, por ejemplo, requisitos más altos de semi-vida *in vivo* o más bajos de dosificación y por tanto se pueden preferir en algunas circunstancias Las variaciones isotópicas de los compuestos de la invención generalmente se pueden preparar por procedimientos convencionales tales como empleando los métodos o preparaciones descritas en los Ejemplos y Preparaciones aquí más adelante utilizando variaciones isotópicas apropiadas de reactivos adecuados

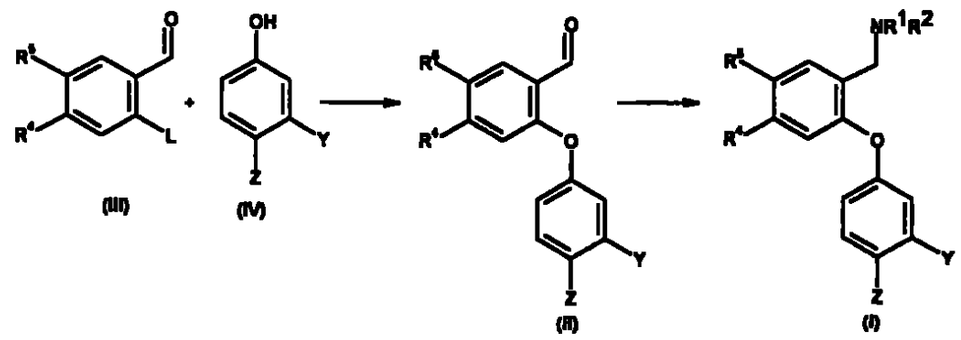
Los compuestos de la invención se pueden preparar de manera conocida de diversos modos En los Esquemas de reacción siguientes y más adelante, salvo indicación en contrario, $R^1$ a $R^{13}$, Z e Y son como se han definido en el primer aspecto Estos procedimientos forman aspectos adicionales de la invención

En toda la memoria, las fórmulas generales están designadas por números romanos I, II, III, IV, etc Los conjuntos de estas fórmulas generales se definen como Ia, Ib, Ic, etc IVa, IVb, IVc, etc

Los compuestos de fórmula general (I) se pueden preparar a partir de compuestos de fórmula (II) por reacción con una amina de fórmula general $HNR^1R^2$, o con una forma de sal adecuada de la misma, junto con un agente reductor de tipo hidruro en un disolvente adecuado (véase el Esquema 1) Cuando o bien $R^1$ o $R^2$ es hidrógeno, los disolventes adecuados incluyen disolventes próticos tales como etanol, y el borohidruro de sodio es un agente reductor apropiado como se ejemplifica en el Ejemplo 36 aquí más adelante Cuando ni $R^1$ ni $R^2$ son hidrógeno, un sistema disolvente adecuado es el formado por tetrahidrofurano/diclorometano y un agente reductor adecuado es el triacetoxiborohidruro de sodio En tales reacciones, es preferible el uso de una forma de sal de $HNR^1R^2$, tal como el hidrocloruro, y se puede

añadir opcionalmente una base auxiliar para mejorar la solubilidad de la sal de $HNR^1R^2$, tal como trietilamina, junto con ácido acético, como se ejemplifica en el Ejemplo 25 aquí

Esquema 1



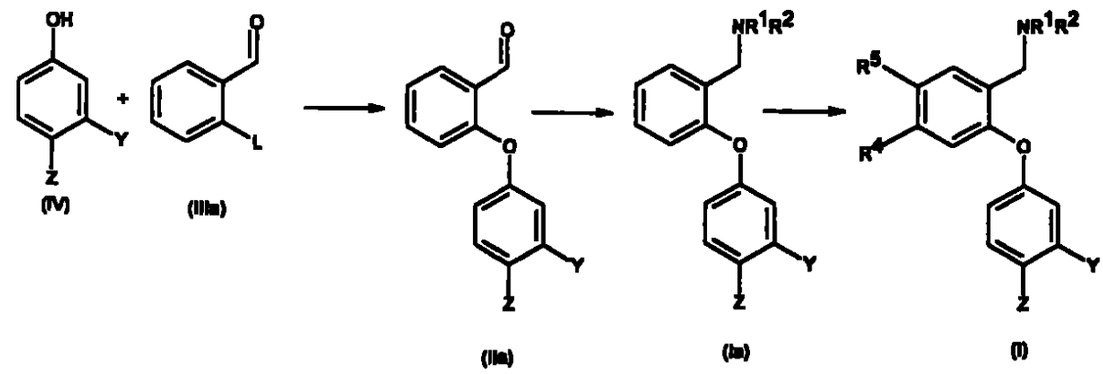
Los compuestos de fórmula (II) se pueden preparar a su vez a partir del acoplamiento de compuestos de fórmula general (IV) con compuestos de aldehído de fórmula general (III), en la que L es un grupo fácilmente eliminable adecuado tal como halógeno (F, Cl, Br o I) o un éster de sulfonato tal como trifluorometanosulfato o metanosulfonato, preferiblemente L es F o Cl Dicha reacción de acoplamiento se puede efectuar por técnicas conocidas en este campo, tal como por reacción con carbonato de potasio en un disolvente adecuado como dimetilformamida bajo condiciones de reacción adecuadas, tales como temperatura elevada y en una atmósfera inerte

Así, de acuerdo con un aspecto adicional, la invención proporciona un procedimiento para preparar compuestos de fórmula general (I) a partir de compuestos de fórmula general (II)

Alternativamente, $R^4$ y/o $R^5$ se pueden introducir después del acoplamiento con éter (véase el Esquema 2) Los compuestos de fórmula general (I) se pueden preparar a partir de compuestos de fórmula general (Ia), es decir compuestos de fórmula general (I) en la que $R^4$ y $R^5$ son hidrógeno Los compuestos de fórmula general (Ia) se pueden preparar a partir de (IIa) de una manera análoga a la preparación de (I) a partir de (II) (véase el Esquema 1), mientras que los compuestos de fórmula general (IIa) se pueden preparar a partir de (V) y (IIIa) de una manera análoga a la

preparación de (II) (véase el Esquema 1)

Esquema 2




Así, de acuerdo con un aspecto adicional, la invención proporciona un procedimiento para preparar compuestos de fórmula general (I) a partir de compuestos de fórmula general (Ia)

Las metodologías para introducir $R^4$ y/o $R^5$ en compuestos de fórmula (Ia) incluyen

i) Cuando $R^4/R^5$ son halógeno, por reacción de (Ia) con un agente halogenante adecuado en un disolvente inerte que no afecte adversamente a la reacción Agentes halogenantes adecuados incluyen ácido trifluorometanosulfónico y *N*-yodosuccinimida y disolventes inertes adecuados incluyen diclorometano

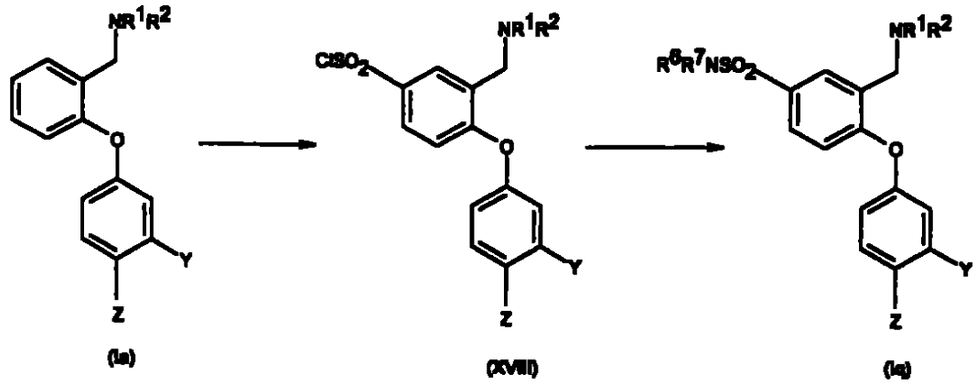
ii) Cuando $R^4/R^5$ son $-NO_2$, por reacción de (Ia) con un agente nitrante adecuado, tal como un nitrato de metal alcalino, en un disolvente que no afecte adversamente a la reacción a temperatura ambiente o más baja Agentes nitrantes adecuados incluyen ácido trifluorometanosulfónico/nitrato de potasio y disolventes adecuados incluyen ácido trifluoroacético

iii) Cuando $R^4/R^5$ es $-SO_2NR^6R^7$, por reacción de un cloruro de sulfonilo intermedio con la amina requerida de fórmula $HNR^6R^7$ en un disolvente adecuado Disolventes adecuados incluyen una mezcla de agua y diclorometano y las reacciones se efectúan generalmente a temperatura ambiente o

por debajo de ella Los cloruros de sulfonilo intermedios se pueden preparar a partir de compuestos de fórmula (Ia) por reacción con ácido clorosulfónico bajo condiciones de temperatura baja en presencia de un disolvente inerte que no afecte adversamente a la reacción, ya sea con o sin tratamiento subsiguiente con un agente clorante tal como oxicloruro de fósforo, pentacloruro de fósforo, cloruro de oxalilo o cloruro de tionilo en un disolvente que no afecte adversamente a la reacción Disolventes adecuados para la reacción con ácido clorosulfónico incluyen el ácido trifluoroacético y una temperatura típica de reacción es 0°C Disolventes adecuados para la reacción con agentes clorantes incluyen el acetonitrilo y las condiciones apropiadas incluyen reflujo, como se ilustra aquí en el Ejemplo 12

Por ejemplo, los compuestos de fórmula (Iq), en la que $R^5$ es $-SO_2NR^6R^7$, se pueden preparar a través de los cloruros de sulfonilo intermedios (XVIII) a partir de compuestos de fórmula (Ia) por reacción de (Ia) con ácido clorosulfónico, ya sea con o sin subsiguiente tratamiento con un agente clorante tal como un oxicloruro de fósforo, pentacloruro de fósforo, cloruro de oxalilo o cloruro de tionilo, seguido por reacción con $NHR^6R^7$ (véase el Esquema 2a) Típicamente, las condiciones de reacción comprenden bajas temperaturas La reacción puede tener lugar ya sea neta, es decir en ausencia de disolvente, o en presencia de un disolvente inerte que no afecte adversamente a la reacción El cloruro de sulfonilo intermedio (XVII) se puede aislar, purificar y después puede hacerse reaccionar con $HNR^6R^7$, alternativamente puede generarse *in situ*, sin aislamiento, y hacerse reaccionar después con $HNR^6R^7$

ESQUEMA 2a




Así, de acuerdo con un aspecto adicional, la invención proporciona un procedimiento para preparar compuestos de fórmula general (I) a partir de compuestos de fórmula general (II) En una realización preferida, se proporciona un procedimiento para preparar compuestos de fórmula (Iq) haciendo reaccionar compuestos de fórmula (Ia) en un disolvente adecuado, con ácido clorosulfónico, ya sea con o sin subsiguiente tratamiento con un agente clorante tal como oxicloruro de fósforo, pentacloruro de fósforo, cloruro de oxalilo o cloruro de tionilo, para dar compuestos de fórmula (XVIII) seguido por reacción con $HNR^6R^7$ para dar compuestos de fórmula (Iq) Preferiblemente, los compuestos de fórmula (XVIII) se generan *in situ* y se hacen reaccionar con $HNR^6R^7$ sin aislamiento

Alternativamente, los compuestos de fórmula general (I) que tienen un sustituyente $R^4/R^5$ particular se pueden convertir en otros compuestos de fórmula (I) utilizando técnicas conocidas Por ejemplo.

i) Cuando $R^4/R^5$ es halógeno tal como cloro, bromo o yodo, se pueden convertir en ciano por reacción con una sal de cianuro en presencia de un catalizador de Pd(0) o (II) en un disolvente de alto punto de ebullición a temperaturas elevadas Adecuados catalizadores de Pd incluyen tetraquis-(trifenilfosfina)paladio, las adecuadas sales de cianuro incluyen $Zn(CN)_2$ y los adecuados disolventes de alto punto de ebullición que no afectan adversamente a la reacción incluyen dimetilformamida, como se ejemplifica aquí en el Ejemplo 78,

ii) Cuando $R^4/R^5$ es halógeno tal como cloro, bromo o yodo, se puede convertir en el correspondiente éster $-CO_2R$ por tratamiento con monóxido de carbono a presión elevada con un catalizador de Pd(0) o (II), en un disolvente alcohólico (ROH en donde R es alquilo $C_1$-$C_4$), en presencia de una base a temperaturas elevadas Por ejemplo, la reacción se puede llevar a cabo a presiones en la región de aproximadamente 7 $kg/cm^2$, mientras que los catalizadores adecuados de Pd incluyen diclorobis(trifenilfosfina)paladio (II), bases adecuadas incluyen trietilamina y disolventes alcohólicos adecuados incluyen metanol como se ejemplifica aquí en la Preparación 50,

iii) Cuando $R^4/R^5$ es nitro, se puede reducir al correspondiente grupo $-NH_2$ por tratamiento con un agente reductor en un disolvente prótico a temperatura ambiente o por encima de ella Los agentes reductores adecuados incluyen polvo de hierro/cloruro de calcio, los disolventes próticos adecuados incluyen etanol acuoso y una temperatura de reacción típica es de aproximadamente 70°C a aproximadamente 100°C, preferiblemente alrededor de 90°C, como se ejemplifica en el Ejemplo 103 aquí más adelante;

iv) Cuando $R^4/R^5$ es $-NH_2$, se puede convertir en el correspondiente grupo $-NHSO_2R^9$ por reacción con un agente sulfonilante en presencia de una base en un disolvente inerte que no afecte adversamente a la reacción a temperatura ambiente o por debajo de ella Los agentes sulfonilantes adecuados incluyen cloruro de metanosulfonilo, las bases adecuadas incluyen trietilamina y los disolventes inertes adecuados incluyen diclorometano, como se ejemplifica en el Ejemplo 128 aquí más adelante;

v) Cuando $R^4/R^5$ es un grupo $-NHSO_2R^9$, se puede convertir en el correspondiente grupo $-NR^8SO_2R^9$ por tratamiento con un agente alquilante y una base en un disolvente inerte adecuado Ejemplos de agentes alquilantes adecuados incluyen yoduro de metilo, bases adecuadas incluyen carbonato de potasio y disolventes inertes adecuados incluyen acetonitrilo, como se ejemplifica en la Preparación 88 aquí más adelante,

vi) Cuando $R^4/R^5$ es un nitrilo -CN, se puede convertir en el correspondiente

grupo $-C(O)NH_2$ por hidrólisis en condiciones básicas, oxidantes o ácidas La hidrólisis básica se efectúa preferiblemente con una sal de hidróxido tal como hidróxido de potasio en un disolvente prótico tal como t-butanol a temperaturas elevadas, como se ejemplifica en el Ejemplo 79 aquí más adelante,

vii) Cuando $R^4/R^5$ es un éster $-CO_2R$, se puede reducir para formar el correspondiente grupo alcohólico $-CH_2OH$ por tratamiento con un agente reductor de tipo hidruro, tal como hidruro de litio y aluminio, como se ejemplifica en la Preparación 69 aquí más adelante,

viii) Cuando $R^4/R^5$ es un éster $-CO_2R$, se puede convertir en el correspondiente ácido $-CO_2H$ por tratamiento con una sal de hidróxido adecuada en presencia de agua y un co-disolvente adecuado Las sales de hidróxido adecuadas incluyen hidróxido de litio y co-disolventes adecuados incluyen tetrahidrofurano, como se ejemplifica en la Preparación 55 aquí más adelante,

ix) Cuando $R^4/R^5$ es un ácido $-CO_2H$, se puede convertir en la correspondiente amida $-CONR^6R^7$ por tratamiento con un agente de acoplamiento, una base y una amina $NHR^6R^7$ en un disolvente inerte adecuado que no afecte adversamente la reacción Agentes de acoplamiento adecuados incluyen hidrocloruro de 1-(3-dimetilaminopropil)-3-etilcarbodiimida en presencia de 1-hidroxibenzotriazol, bases adecuadas incluyen trietilamina y disolventes adecuados incluyen diclorometano, como se ejemplifica en la Preparación 59 aquí más adelante,

x) Cuando $R^4/R^5$ es halógeno tal como cloro, bromo o yodo, puede convertirse en una amida α,β-insaturada, por tratamiento con acrilamida, un catalizador de Pd(0) o (II) y una base adecuada, en un disolvente inerte que no afecte adversamente a la reacción, a temperaturas elevadas Catalizadores de paladio adecuados incluyen acetato de paladio (II) en presencia de tri(o-tolil)-fosfina, bases adecuadas incluyen trietilamina y disolvente inertes adecuados incluyen acetonitrilo como se ejemplifica en el Ejemplo 50 aquí más adelante;

xi) Cuando $R^4/R^5$ es una amida α,β-insaturada, se puede convertir en

$-CH_2CH_2CO_2NH_2$, por tratamiento con un agente reductor adecuado a una temperatura apropiada, en un disolvente adecuado que no afecte adversamente a la reacción Agentes reductores adecuados incluyen diyoduro de samario a temperatura ambiente y disolventes adecuados incluyen tetrahidrofurano que contiene una pequeña cantidad de agua, como se ejemplifica en el Ejemplo 51 aquí más adelante,

xii) Cuando $R^4/R^5$ es $-CH_2OH$, se puede convertir en $-CH_2NR^8SO_2R^9$ por medio de una reacción de Mitsunobu a una temperatura apropiada, en un disolvente adecuado que no afecte adversamente a la reacción Reactivos adecuados incluyen azodicarboxilato de dietilo, trifenilfosfina y metilsulfonilcarbamato de terc-butilo, 0°C es una temperatura de reacción adecuada y el tetrahidrofurano es un disolvente adecuado, como se ejemplifica en la Preparación 72 aquí más adelante

Alternativamente, los compuestos de fórmula general (I) que tienen un grupo $NR^1R^2$ particular se pueden convertir en otros compuestos de fórmula general (I) que tienen un grupo $NR^1R^2$ diferente Por ejemplo

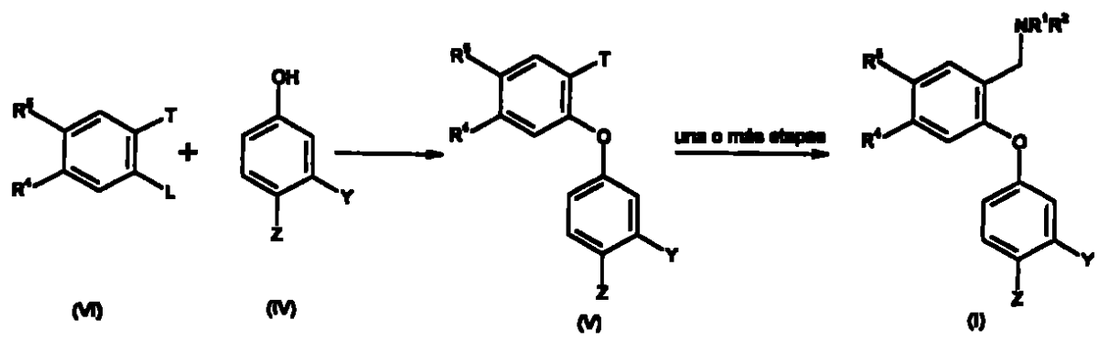
i) Los compuestos de fórmula (Ib) en la que o bien $R^1$ o $R^2$ es hidrógeno, se pueden convertir en un compuesto de fórmula (Ic) en la que ni $R^1$ ni $R^2$ son hidrógeno, por reacción del compuesto de fórmula (Ib) con un aldehído y un agente reductor de tipo hidruro Aldehídos adecuados incluyen formaldehído, agentes reductores adecuados incluyen tri(acetoxi)borohidruro de sodio y la reacción se lleva a cabo preferiblemente en un disolvente que no interfiera con la reacción, tal como diclorometano a temperatura ambiente o por debajo de ella, como se ejemplifica en el Ejemplo 12 aquí más adelante

ii) Los compuestos de fórmula (Ib) en la que $R^1$ o $R^2$ es hidrógeno, se pueden convertir en un compuesto de fórmula (Ic) en la que $R^1$ o $R^2$ es metilo, por reacción del compuesto de fórmula (Ib) con un agente formilante en un disolvente adecuado, seguida por una reducción subsiguiente del compuesto *N*-formilado intermedio con un agente reductor de tipo hidruro en un disolvente inerte, preferiblemente a temperatura elevada Agentes formilan-

tes adecuados incluyen formiato de pentafluorofenilo (formado a partir de ácido fórmico, pentafluorofenol y diciclohexilcarbodiimida) y disolventes adecuados para la formulación incluyen diclorometano Los agentes reductores adecuados incluyen el complejo de borano-tetrahidrofurano y los disolventes inertes adecuados para la reducción incluyen el tetrahidrofurano, como se ejemplifica en el Ejemplo 110 aquí más adelante.

Alternativamente, los compuestos de fórmula general (I) se pueden preparar a partir de compuestos de fórmula V (véase el Esquema 3) en la que L es como se ha definido para el Esquema 1 y T es un grupo que se puede convertir en $CH_2NR^1R^2$. Ejemplos de sustituyentes T adecuados incluyen. $-CO_2R^{10}$, -CN y $-C(O)NR^1R^2$.

Esquema 3




Las metodologías para convertir compuestos de fórmula (V) en (I), incluyen:

i) Cuando T es $-CO_2R^{10}$ y $R^{10}$ es metilo o etilo, por reacción con una amina de fórmula general $NHR^1R^2$ para formar una amida, seguida por reducción para proporcionar una amina.

ii) Cuando T es CN, por reducción para dar su correspondiente amina de fórmula $-CH_2NH_2$.

iii) Cuando T es $-C(O)NR^1R^2$, por reducción para proporcionar una amina.

Los compuestos de fórmula general (V) se pueden preparar a su vez por acoplamiento de compuestos de fórmula general (VI) y compuestos de fórmula general (IV) Los reactivos y condiciones para dichas reacciones de acoplamiento son como se han definido previamente para el acoplamiento de los compuestos de fórmulas generales (IV) y (III) en el Esquema 1

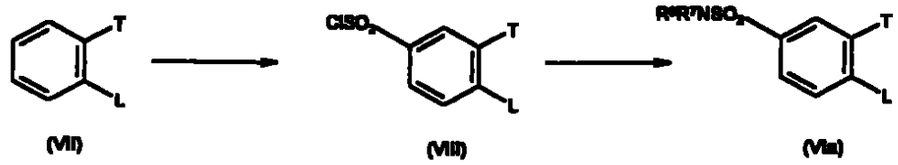
Los compuestos de fórmula general (VI) se pueden preparar a su vez a partir de compuestos de fórmula general (VII) (véase el Esquema 4)

Esquema 4


(VII) (VI)

Los compuestos de fórmula (VI) se pueden preparar por sustitución electrófila aromática de compuestos de fórmula (VII) para dar compuestos de fórmula (VI) directamente Alternativamente, los compuestos de fórmula (VI) se pueden preparar en dos o más etapas, sustitución electrófila aromática de compuestos de fórmula (VII) para dar compuestos intermedios que después experimentan otra reacción para dar compuestos de fórmula (VI) Los compuestos intermedios se pueden aislar o generar *in situ* sin aislamiento En el Esquema 5 se muestra una ruta preferida

Esquema 5




(VII) (VIII) (VIa)

Los compuestos de fórmula (VII) se hacen reaccionar con cloruro de sulfonilo para dar compuestos de fórmula (VIII) seguido por reacción con $NHR^6R^7$ para dar compuestos de fórmula (VIa)

De acuerdo con aspectos adicionales, la invención proporciona compuestos

de fórmulas (II), (IIa) y (V), como se ha definido anteriormente

Los compuestos de fórmulas (III), (IIIa), (IV), (VI) o (VII) o son compuestos conocidos y están disponibles a partir de fuentes comerciales o se pueden obtener a partir de materiales disponibles comercialmente utilizando técnicas conocidas (véanse los Ejemplos aquí más adelante)

Será evidente para los expertos en la técnica que puede ser necesario proteger y desproteger los grupos funcionales sensibles durante la síntesis de un compuesto de fórmula I Esto se puede efectuar por técnicas convencionales, por ejemplo como se describe en "Protective Groups in Organic Synthesis", 3ª edición, por T W Greene y P G M Wuts, John Wiley and Sons Inc, 1999. El Ejemplo 35 proporciona un ejemplo de una estrategia basada en grupos protectores empleada en la síntesis de un compuesto de la presente invención

Los químicos expertos en la técnica apreciarán que se pueden preparar éteres de diarilo utilizando diversas metodologías sintéticas Para una revisión de las metodologías véase J S Sawyer, *Tetrahedron*, 56 (2000) 5045-5065, que se incorpora aquí por referencia

Los compuestos de la presente invención son útiles ya que tienen actividad farmacológica en mamíferos, incluidos los seres humanos Más particularmente, son útiles en el tratamiento o prevención de un trastorno en el que está implicada la regulación de la función de los transportadores de monoaminas Estados de enfermedad que se pueden mencionar incluyen hipertensión, depresión (p ej , depresión en enfermos de cáncer, depresión en enfermos de Parkinson, depresión tras un infarto de miocardio, depresión sintomática subsindromal, depresión en mujeres infértiles, depresión pediátrica, depresión mayor, depresión en un solo episodio, depresión recurrente, depresión inducida por abusos en la infancia, depresión post-parto y síndrome de los ancianos malhumorados), trastorno de ansiedad generalizada, fobias (p ej , agorafobia, fobia social y fobias simples), síndrome de estrés post-traumático, trastorno de personalidad evasiva, eyaculación precoz, trastornos de la alimentación (p ej , anorexia nerviosa y bulimia nerviosa), obesidad, dependencia de productos químicos (p ej , adiciones al alcohol, cocaína, heroína, fenobarbital, nicotina y benzodiazepinas), cefaleas histamínicas, migrañas, dolor, enfermedad de Alzheimer, trastorno obsesivo compulsivo, trastorno de pánico, trastornos de la memoria (p ej , demencia, trastornos amnésicos y declinación cognitiva relacionada con la edad (ARCD)), enfermedades de Parkinson (p.ej , demencia en enfermedad de Parkinson,

parkinsonismo inducido por neurolépticos y disquinesias tardías), trastornos endocrinos (p ej , hiperprolactinemias), vasoespasmo (particularmente en la vasculatura cerebral), ataxia cereberal, trastornos del tracto gastrointestinal (que implican cambios en la motilidad y la secreción), síntomas negativos de la esquizofrenia, síndrome premenstrual, síndrome fibromiálgico, incontinencia por estrés, síndrome de Tourette, tricotilomanía, cleptomanía, impotencia masculina, trastorno de hiperactividad con déficit de atención (ADHD), hemicrania paroxismal crónica, cefaleas (asociadas con trastornos vasculares), debilidad emocional, llanto patológico, trastornos del sueño (cataplexia) y shock.

Trastornos de interés particular incluyen depresión, el trastorno de hiperactividad con déficit de atención, el trastorno obsesivo compulsivo, el trastorno de estrés post-traumático, los trastornos de abuso de sustancias y la disfunción sexual incluida (en particular) la eyaculación precoz La eyaculación precoz puede definirse como eyaculación persistente o recurrente antes de, en el momento de o poco después de la penetración peniana del compañero También puede definirse como la eyaculación que ocurre antes de que el individuo lo desee [véase "The Merck Manual", 16ª edición, pág 1576, publicado por Merck Research Laboratories, 1992]

Por lo tanto, de acuerdo con aspectos adicionales, la invención proporciona

i) un compuesto de la invención para uso como un fármaco,

ii) el uso de un compuesto de la invención, en la fabricación de un medicamento para el tratamiento o prevención de un trastorno en el que esté implicada la regulación de la función de los transportadores de monoaminas, por ejemplo depresión, trastorno de hiperactividad con déficit de atención, trastorno obsesivo compulsivo, trastorno de estrés post-traumático, trastornos de abuso de sustancias o disfunción sexual incluida la eyaculación precoz,

iii) el uso de un compuesto de la invención, en la fabricación de un medicamento para el tratamiento o prevención de eyaculación precoz,

iv) un método de tratamiento o prevención de depresión, trastorno de hiperactividad con déficit de atención, trastorno obsesivo compulsivo, trastorno de estrés post-traumático, trastornos de abuso de sustancias o disfunción

sexual, incluida la eyaculación precoz, que comprende administrar una cantidad terapéuticamente eficaz de un compuesto de la invención, a un paciente con necesidad de dicho tratamiento o prevención,

v) un método para incrementar la latencia eyaculatoria, que comprende la administración de una cantidad eficaz de un compuesto de la invención, a un varón que desea latencia eyaculatoria incrementada, y

vi) un compuesto de la invención, para el tratamiento o prevención de un trastorno en el que está implicada la regulación de la función de los transportadores de monoaminas, por ejemplo depresión, trastorno de hiperactividad con déficit de atención, trastorno obsesivo compulsivo, trastorno de estrés post-traumático, trastornos de abuso de sustancias o disfunción sexual, incluida la eyaculación precoz;

vii) un compuesto de la invención para el tratamiento de eyaculación precoz.

Se apreciará que todas las referencias hechas aquí a tratamiento incluyen tratamiento curativo, paliativo y profiláctico

Los compuestos de la invención se pueden administrar a solas o como parte de una terapia de combinación Si se administra una combinación de agentes activos, entonces se pueden administrar simultáneamente, separadamente o secuencialmente En particular, los compuestos de la invención se pueden combinar con lo siguiente para el tratamiento de PE

i) Alfa-bloqueantes (p ej , fentolamina, doxazasima, tamsulosina, terazazina, prazasina y el Ejemplo 19 del documento WO 98/30560) Una explicación razonada posible para el tratamiento de eyaculación precoz con alfa-bloqueantes es como sigue La actividad muscular de los músculos lisos (conducto diferente, vesículas espermáticas y uretra) son controlados por el sistema nervioso simpático a través de la liberación de noradrenalina La noradrenalina actúa en los adrenorreceptores alfa 1, que estimulan contracciones musculares, dando lugar a emisión espermática y subsiguiente eyaculación Por lo tanto, el bloqueo de estos receptores inhibirá la

eyaculación

ii) Apomorfina - las doctrinas del uso de apomorfina como fármaco pueden encontrarse en el documento US-A-5945117

iii) Agonistas de los receptores D2 de dopamina (p ej , Premiprixal, un compuesto de Pharmacia Upjohn con el número PNU95666)

iv) Agonistas de los receptores de melanocortina (p.ej., Melanotan II)

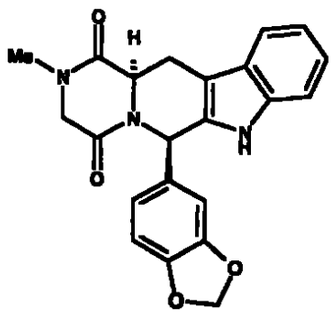
v) Agonistas de los receptores de PGE1 (p ej., alprostadil)

vi) Inhibidores del transporte de monoaminas, particularmente inhibidores de la reabsorción de noradrenalina (NRI) (p ej , Reboxetina), otros inhibidores de la reabsorción de serotonina (SRI) (p ej , paroxetina) o inhibidores de la reabsorción de dopamina (DRI)

vii) Antagonistas de 5-HT3 (p.ej , ondansetron y granisetron) Una explicación razonada posible para antagonistas de 5-HT3 para el tratamiento de eyaculación precoz es como sigue. Los receptores 5-HT3, que están presentes en la luz de la porción posterior de la uretra, son estimulados por 5-HT en el semen durante la emisión seminal, dando lugar a una sensibilización de la ruta del reflejo medular que facilita la eyaculación. Por lo tanto, un antagonista podría prevenir esta sensibilización y así retardar la eyaculación

viii) Inhibidores de PDE tales como PDE2 (p ej , eritro-9-(2-hidroxi-3-nonil)adenina) y el Ejemplo 100 del documento EP 0771799, que se incorpora aquí por referencia) y en particular un inhibidor de PDE5 (p ej , sildenafil, 1-{[3-(3,4-dihidro-5-metil-4-oxo-7-propilimidazo[5,1-f]astrazin-2-il)-4-etoxifenil]sulfonil}-4-etilpiperazina, es decir vardenafil / Bayer BA 38-9456 o IC351 (véase la estructura siguiente, Icos Lilly)) Una explicación razonada posible para inhibidores de PDE para tratamiento de eyaculación precoz es como sigue Los niveles de cAMP y CGMP en los músculos lisos eyaculatorios regulan el tono muscular de estos músculos eyaculatorios y por lo tanto retardan la

eyaculación



IC351 (Icos Lilly)

ix) Agentes que abren los canales del potasio.

x) Antagonistas de los receptores purinérgicos P2X.

xi) Antagonistas de los receptores de endotelina

Para uso humano, los compuestos de la invención se pueden administrar a solas, pero en terapia humana, generalmente se administrarán en mezcla con un excipiente, diluyente o vehículo farmacéutico adecuado seleccionado en relación con la ruta propuesta de administración y la práctica farmacéutica clásica

Por ejemplo, los compuestos de la invención se pueden administrar por vía oral, bucal o sublingual en forma de comprimidos, cápsulas (incluidas cápsulas de gelatina blanda), óvulos, elixires, soluciones o suspensiones, que pueden contener agentes aromatizantes o colorantes, para aplicaciones de liberación inmediata, retardada, modificada, sostenida, dual, de liberación controlada o de descarga pulsátil Los compuestos de la invención también se pueden administrar por inyección intracavernosa Los compuestos de la invención también se pueden administrar mediante formas de dosificación de dispersión rápida o disolución rápida.

Tales comprimidos pueden contener excipientes tales como celulosa microcristalina, lactosa, citrato sódico, carbonato cálcico, fosfato cálcico dibásico, glicina y almidón (preferiblemente almidón de maíz, patata o tapioca), disgregantes tales como sal sódica de glicolato de almidón, croscarmelosa sódica y ciertos silicatos complejos, y aglutinantes de la granulación tales como polinivinilpirrolidona, hidroxipropilmetilcelulosa (HPMC), hidroxipropilcelulosa (HPC), sacarosa, gelatina y

acacia Adicionalmente, se pueden incluir agentes lubricantes tales como estearato de magnesio, ácido esteárico, behenato de glicerilo y talco

También se pueden emplear composiciones sólidas de tipo similar como cargas en cápsulas de gelatina Excipientes preferidos a este respecto incluyen lactosa, almidón, una celulosa, azúcar de leche o polietilenglicoles de alto peso molecular Para suspensiones acuosas y/o elixires, los compuestos de la invención, y sus sales farmacéuticamente aceptables, se pueden combinar con diversos agentes edulcorantes o aromatizantes, materias colorantes o tintes, con agentes emulsionantes y/o suspensores y con diluyentes tales como tales como agua, etanol, propilenglicol y glicerina, y combinaciones de ellos

Las formas de dosificación de liberación modificada y de liberación pulsátil pueden contener excipientes tales como los detallados para las formas de dosificación de liberación inmediata, junto con excipientes adicionales que actúan como modificadores de la velocidad de liberación, estando éstos revestidos y/o incluidos en el cuerpo del dispositivo Los modificadores de la velocidad de liberación incluyen, pero no se limitan exclusivamente a, hidroxipropilmetilcelulosa, metilcelulosa, carboximetilcelulosa sódica, etilcelulosa, acetato de celulosa, poli(óxido de etileno), goma xantana, Carbomer, copolímero de metacrilato de amonio, aceite de ricino hidrogenado, cera de carnauba, cera de parafina, acetato-ftalato de celulosa, ftalato de hidroxipropilmetilcelulosa, copolímero de ácido metacrílico y mezclas de los mismos. Las formas de dosificación de liberación modificada y liberación pulsátil pueden contener uno o una combinación de excipientes modificadores de la velocidad de liberación Los excipientes modificadores de la velocidad de liberación pueden estar presentes tanto dentro de la forma de dosificación, es decir dentro de la matriz, y/o sobre la forma de dosificación, es decir en la superficie o el revestimiento.

Las formulaciones de dosificación de dispersión o disolución rápida (FDDF) pueden contener los ingredientes siguientes aspartamo, acesulfamo potásico, ácido cítrico, croscarmelosa sódica, crospovidona, ácido diascórbico, acrilato de etilo, etilcelulosa, gelatina, hidroxipropilmetilcelulosa, estearato de magnesio, manitol, metacrilato de metilo, aroma de menta, polietilenglicol, sílice pirolizada, dióxido de silicio, sal sódica de glicolato de almidón, sal sódica de fumarato de estearilo, sorbitol, xilitol Los términos dispersión o disolución que se utilizan aquí para describir FDDF dependen de la solubilidad de la sustancia farmacológica utilizada, es decir cuando la sustancia farmacológica es insoluble se puede preparar una forma de dosificación de

dispersión rápida y cuando la sustancia la sustancia farmacológica es soluble se puede preparar una forma de dosificación de disolución rápida

Los compuestos de la invención también se pueden administrar parenteralmente, por ejemplo, por vía intravenosa, intraarterial, intraperitoneal, intratecal, intraventricular, intrauretral, intraesternal, intracraneal, intramuscular o subcutánea, o se puede administrar por técnicas de infusión Para tal administración parenteral, lo mejor es utilizarlos en forma de una solución acuosa estéril que puede contener otras sustancias, por ejemplo, suficientes sales o glucosa para hacer la solución isotónica con la sangre Las soluciones acuosas tendrán que tamponarse adecuadamente (preferiblemente a un pH de 3 a 9), si es necesario La preparación de formulaciones parenterales adecuadas en condiciones estériles se lleva a cabo fácilmente por técnicas farmacéuticas clásicas bien conocidas por los expertos en la técnica

Los siguientes niveles de dosificación y otros niveles de dosificación expresados aquí son para un ser humano de tamaño medio que tiene un peso en el intervalo de aproximadamente 65 a 70 kg. Los expertos en la técnica serán capaces de determinar fácilmente los niveles de dosificación requeridos para un individuo cuyo peso caiga fuera de este intervalo, como es el caso de los niños y los ancianos.

Para la administración oral y parenteral a pacientes humanos, el nivel diario de dosificación de los compuestos de la invención o sales o solvatos de los mismos será habitualmente de 10 a 500 mg (en una sola dosis o en dosis fraccionadas)

Así, por ejemplo, los comprimidos o cápsulas de los compuestos de la invención o sus sales o solvatos contendrán de 5 mg a 250 mg de compuesto activo para administración individual o dos o más a un tiempo, según sea apropiado El facultativo será el que determine en último caso la dosificación real que será adecuada para cualquier paciente individual y que variará con la edad, peso y respuesta del paciente particular Las dosificaciones anteriores son ilustrativas del caso medio. Por supuesto, puede haber casos que precisen dosis más altas o más bajas, y también están dentro del alcance de esta invención El experto en la técnica apreciará que, en el tratamiento de ciertas condiciones (incluida PE), los compuestos de la invención se pueden tomar como una sola dosis en una base de "según se requiera" (es decir según se necesite o se desee)

**Ejemplo de formulación de comprimidos**

En general, una formulación de comprimidos podría contener típicamente

entre aproximadamente 0,01 mg y 500 mg de un compuesto de acuerdo con la presente invención mientras que los pesos de cargas del comprimido pueden variar de 50 mg a 1 000 mg Una formulación ilustrativa para un comprimido de 10 mg es la siguiente

| Ingrediente | % en peso |
|---|---|
| Compuesto de la invención | 10,000* |
| Lactosa | 64,125 |
| Almidón | 21,375 |
| Croscarmelosa sódica | 3,000 |
| Estearato de magnesio | 1,500 |

*Esta cantidad se ajusta típicamente de acuerdo con la actividad del fármaco.

Los compuestos de la invención también se pueden administrar por vía intranasal o por inhalación y convenientemente son descargados en forma de un inhalador de polvo seco o una presentación de aerosol contenida en un envase presurizado, bomba, pulverizador o nebulizador con el uso de un propelente adecuado, p ej , diclorodifluorometano, triclorofluorometano, diclorotetrafluoroetano, un hidrofluoroalcano tal como 1,1,1,2-tetrafluoroetano (HFA 134A [marca comercial]) o 1,1,1,2,3,3,3-heptafluoropropano (HFA 227EA [marca comercial]), dióxido de carbono u otro gas adecuado En el caso de un aerosol presurizado, la unidad de dosificación puede determinarse proporcionando una válvula para descargar una cantidad medida El envase presurizado, la bomba, el pulverizador o el nebulizador pueden contener una solución o suspensión del compuesto activo, p ej , usando una mezcla de etanol y propelente como disolvente, que puede contener adicionalmente un lubricante, p ej., trioleato de sorbitán Las cápsulas y los cartuchos (hechos, por ejemplo, de gelatina) para uso en un inhalador o insuflador pueden formularse para contener una mezcla en polvo de un compuesto de la invención y una base de polvo adecuada tal como lactosa o almidón

Las formulaciones de aerosol o polvo seco se disponen preferiblemente de modo que cada dosis medida o "disparada" contenga de 1 a 50 mg de un compuesto de la invención para descarga al paciente. La dosis diana global con un aerosol estará en el intervalo de 1 a 50 mg, que se pueden administrar en una sola dosis o más

habitualmente en dosis fraccionadas a lo largo del día

Los compuestos de la invención también se pueden formular para descarga mediante un atomizador Las formulaciones para dispositivos atomizadores pueden contener los siguientes ingredientes como solubilizantes, emulsionantes o agentes de suspensión agua, etanol, glicerol, propilenglicol, polietilenglicoles de bajo peso molecular, cloruro de sodio, fluorocarbonos, éteres de polietilenglicol, trioleato de sorbitán, ácido oleico

Alternativamente, los compuestos de la invención se pueden administrar en forma de un supositorio o pesario, o se puede aplicar tópicamente en forma de un gel, hidrogel, loción, solución, crema, pomada o polvo para espolvorear Los compuestos de la invención también se pueden administrar dérmica o transdérmicamente, por ejemplo por el uso de un parche cutáneo También se pueden administrar por ruta ocular, pulmonar o rectal

Para uso oftálmico, los compuestos se pueden formular como suspensiones micronizadas en solución salina estéril isotónica y con pH ajustado o, preferiblemente, como soluciones salinas estériles isotónicas y con pH ajustado, opcionalmente en combinación con un agente conservante tal como cloruro de bencilalconio Alternativamente, se pueden formular en una pomada tal como vaselina.

Para la aplicación tópica a la piel, los compuestos de la invención se pueden formular como una pomada adecuada que contiene el compuesto activo suspendido o disuelto en, por ejemplo, una mezcla con uno o más de lo siguiente. aceite mineral, vaselina líquida, vaselina blanca, propilenglicol, compuesto de polioxietileno-polioxipropileno, cera emulsionante y agua Alternativamente, se pueden formular como una loción o crema adecuada, suspendida o disuelta en, por ejemplo, una mezcla de uno o más de lo siguiente aceite mineral, monoestearato de sorbitán, un polietilenglicol, parafina líquida, polisorbato 60, ésteres cetílicos, cera, alcohol cetearílico, 2-octildodecanol, alcohol bencílico y agua

Los compuestos de la invención también se pueden usar en combinación con una ciclodextrina Se conocen ciclodextrinas que forman complejos de inclusión y no inclusión con moléculas de fármacos La formación de un complejo de fármaco-ciclodextrina puede modificar las propiedades de solubilidad, régimen de disolución, biodisponibilidad y/o estabilidad de una molécula del fármaco. Los complejos de fármaco-ciclodextrina son útiles generalmente para mayores formas de dosificación y rutas de administración Como alternativa a la complejación directa con el fármaco,

la ciclodextrina se puede utilizar como un aditivo auxiliar, p ej , como un vehículo, diluyente o solubilizante Las ciclodextrinas alfa, beta y gamma son las más comunmente utilizadas y se describen ejemplos adecuados en los documentos WO-A-91/11172, WO-A-94/02518 y WO-A-98/55148

Para la administración oral o parenteral a pacientes humanos, los niveles de dosificación diarios de los compuestos de la invención serán de 0,01 a 30 mg/kg (en una sola dosis o en dosis fraccionadas) y preferiblemente estará en el intervalo de 0,01 a 5 mg/kg Así, los comprimidos contendrán de 1 mg a 0,4 mg de compuesto para administración una sola vez o dos o más veces, según sea apropiado El facultativo será el que determine en último caso la dosificación real que será adecuada para cualquier paciente en particular y variará con la edad, peso y respuesta del paciente particular Las dosificaciones anteriores, por supuesto, son sólo ilustrativas del caso medio y puede haber casos que precisen dosis más altas o más bajas, y tales casos están dentro del alcance de la invención

Se prefiere la administración oral Preferiblemente, la administración tiene lugar poco antes de necesitar un efecto.

Para uso veterinario, un compuesto de la invención, o una de sus sales veterinariamente aceptables, o un solvato o pro-fármaco del mismo veterinariamente aceptable, se administra como una formulación aceptable adecuadamente de acuerdo con las prácticas veterinarias habituales y será el veterinario el que determine el régimen de dosificación y la ruta de administración que será la más apropiada para un animal particular.

Por lo tanto, de acuerdo con un aspecto adicional, la invención proporciona una formulación farmacéutica que contiene un compuesto de la invención y un coadyuvante, diluyente o vehículo farmacéuticamente aceptable

La invención se ilustra por los siguientes Ejemplos no limitativos, en los que se utilizan las siguientes abreviaturas y definiciones

| | |
|---|---|
| Arbacel® | agente filtrante |
| br | ancho |
| Boc | terc-butoxicarbonilo |
| CDI | carbonildiimidazol |
| δ | desplazamiento químico |
| d | doblete |

| | |
|---|---|
| Δ | calor |
| DCCI | diciclohexilcarbodiimida |
| DCM | diclorometano |
| DMF | *N,N*-dimetilformamida |
| DMSO | dimetilsulfóxido |
| $ES^+$ | exploración de iones positivos por electropulverización |
| $ES^-$ | exploración de iones negativos por electropulverización |
| h | horas |
| HOBt | 1-hidroxibenzotriazol |
| HPLC | cromatografía de líquidos a presión elevada |
| m/z | pico en espectro de masas |
| min | minutos |
| MS | espectro de masas |
| NMR | resonancia magnética nuclear |
| Prec | precursor |
| Prep | preparación |
| q | cuartete |
| s | singlete |
| t | triplete |
| Tf | trifluorometanosulfonilo |
| TFA | ácido trifluoroacético |
| THF | tetrahidrofurano |
| TLC | cromatografía en capa fina |
| $TS^+$ | exploración de ionización positiva por termopulverización |
| WSCDI | hidrocloruro de 1-(3-dimetilaminopropil)-3-etilcarbodiimida |

Los espectros de resonancia magnética nuclear (NMR) $^1H$ fueron en todos los casos concordantes con las estructuras propuestas Los desplazamientos químicos característicos (δ) se dan en partes por millón campo abajo de tetrametilsilano utilizando abreviaturas convencionales para la designación de los picos principales· p ej s, singlete, d, doblete, t, triplete; q, cuartete, m, multiplete, br, ancho.

Para disolventes comunes, se han utilizado las siguientes abreviaturas $CDCl_3$, deuterocloroformo, DMSO, dimetilsulfóxido La abreviatura psi significa libras/pulgada al cuadrado y LRMS significa espectrometría de masas de baja

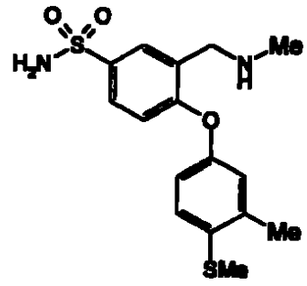
resolución Cuando se ha utilizado cromatografía en capa fina (TLC) se refiere a TLC sobre gel de sílice utilizando placas de gel de sílice 60 $F_{254}$ $R_f$ es la distancia recorrida por un compuesto dividida por la distancia recorrida por el frente de disolvente en una placa de TLC Los puntos de fusión se determinaron utilizando un instrumento Perkin Elmer DCS7 a un régimen de calentamiento de 20°C/minuto)

Como se ha indicado, los compuestos se caracterizaron como sus sales de hidrocloruro. Un procedimiento típico para la formación de sales de hidrocloruro se da en el Ejemplo 12. El procedimiento se puede llevar a cabo con otros disolventes, p ej , éter dietílico o DCM

Los materiales de partida comercialmente disponibles se obtuvieron de Aldrich Chemical Co, Lancaster Synthesis Ltd o Acros Organics

**EJEMPLO 1**

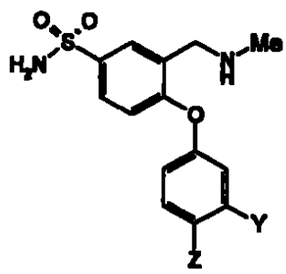
**3-[(Metilamino)metil]-4-[3-metil-4-(metilsulfanil)fenoxi]bencenosulfonamida**



La amida de la Preparación 8 (760 mg, 2,07 mmol) se suspendió en THF (10 ml) y la suspensión resultante se trató con complejo de borano-tetrahidrofurano (solución 1 M en THF, 6,22 ml, 6,22 mmol) a temperatura ambiente La solución resultante se calentó a reflujo durante 5 horas en una atmósfera de nitrógeno seco. La reacción se enfrió a temperatura ambiente y se trató cuidadosamente con solución de HCl 6 M (6 ml) La mezcla resultante se calentó a reflujo durante 30 min. Después de enfriar a temperatura ambiente, la mezcla se diluyó con agua (10 ml) y se alcalinizó por adición cuidadosa de carbonato de potasio sólido La capa acuosa se extrajo con acetato de etilo (20 ml) que dio un precipitado en la capa orgánica, y la capa acuosa se extrajo adicionalmente con DCM (2 x 20 ml) La fracción de acetato de etilo se lavó con NaOH 2 M (20 ml) dando una separación bifásica clara y la capa básica se extrajo

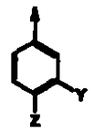
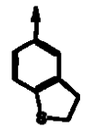
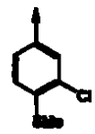
con DCM (4 x 25 ml) Todas las fracciones orgánicas se combinaron y lavaron con salmuera (20 ml), se secaron con sulfato de magnesio y se evaporaron para dar un aceite incoloro La purificación por cromatografía instantánea [$SiO_2$, (acetato de etilo/metanol/$NH_3$ 880) 95 5 0,5 a 90 10 1] proporcionó un polvo blanco de la amina deseada (646 mg, 89%) $\delta_H$ (300 MHz, d6-DMSO) 2,26 (3H, d), 2,32 (3H, d), 2,45 (3H, d), 3,75 (2H, d), 6,90 (3H, m), 7,25 (3H, bs), 7,67 (1H, t), 7,98 (1H, d), MS $MH^+$ 353

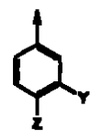
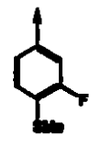
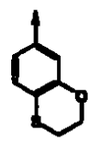
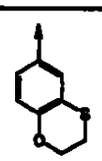
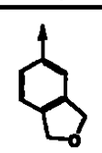
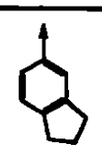
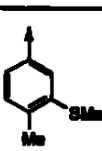
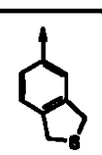
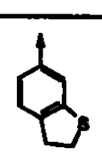
Los compuestos de fórmula Id, es decir los compuestos de fórmula general I en la que $R^1$ es metilo, $R^2$ es hidrógeno y $R^5$ es -$SO_2NH_2$, mostrados en la Tabla 1, se prepararon de una manera análoga al Ejemplo 1 a partir de los precursores indicados.



(Id)

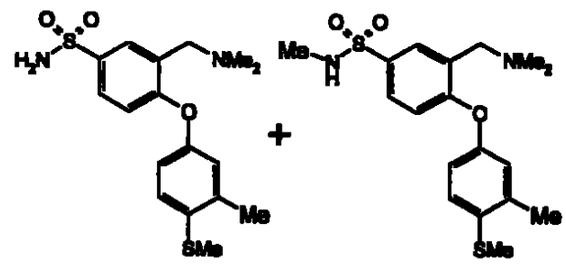
Tabla 1

| Ejemplo | Precursor |  | Datos |
|---|---|---|---|
| 2 | Prep 9 |  | Sal de HCl $\delta_H$ ($CD_3OD$, 400 MHz) 2,80 (3H, s), 3,42 (2H, m), 4,41 (2H, s), 6,86-7,00 (2H, m),7,09 (1H, s), 7,23 (1H, d), 7,90 (1H, d), 8,05 (1H, s), MS *m/z* ($TS^+$) 351 ($MH^+$) |
| 3 | Prep. 12 |  | Sal de HCl $\delta_H$ ($CD_3OD$, 300 MHz) 2,54 (3H, s), 2,82 (3H, s), 4,43 (2H, s), 7,00 (1H, d), 7,20 (1H, d), 7,34 (1H, s), 7,42 (1H, d), 7,95 (1H, d), 8,11 (1H, s), MS *m/z* ($TS^+$) 373 ($MH^+$) |

| Ejemplo | Precursor |  | Datos |
|---|---|---|---|
| 4 | Prep. 11 |  | Sal de HCl. $\delta_H$ ($CD_3OD$, 400 MHz) 2,45 (3H, s), 2,73 (3H, s), 5,44 (2H, s), 6,97 (3H, m), 7,42 (1H, m), 7,89 (1H, m), 8,03 (1H, s), MS *m/z* ($ES^+$) 357 ($MH^+$) |
| 5 | Prep 10 |  | Sal de HCl $\delta_H$ ($CD_3OD$, 400 MHz) 2,79 (3H, s), 3,18 (2H, m), 4,38 (2H, s), 4,41 (2H, m), 6,68 (2H, m), 6,97 (1H, d), 7,13 (1H, d), 7,91 (1H, d), 8 03 (1H, s), MS *m/z* ($TS^+$) 367 ($MH^+$) |
| 6 | Prep 13 |  | Sal de HCl. $\delta_H$ ($CD_3OD$, 400 MHz) 2,78 (3H, s), 3,15 (2H, m), 4,38 (4H, m), 6,79 (1H, d), 6,85 (3H, m), 7,84 (1H, d), 8,00 (1H, s), MS *m/z* ($ES^+$) 367 ($MH^+$) |
| 7 | Prep 14 |  | Sal de HCl $\delta_H$ ($CD_3OD$, 400 MHz) 2,81 (3H, s), 4,43 (2H, s), 5,09 (4H, s), 6,93 (1H, d), 7,12 (2H, s+d), 7,40 (1H, d), 7,90 (1H, d), 8,08 (1H, s), MS *m/z* ($TS^+$)335 ($MH^+$) |
| 8 | Prep 15 |  | Sal de HCl $\delta_H$ ($CD_3OD$, 400 MHz) 2,16 (2H, m), 2,80 (3H, s), 2,92 (4H, t), 4,40 (2H, s), 6,86 (1H, d), 6,94 (1H, d), 7,03 (1H, s), 7,30 (1H, d), 7,88 (1H, d), 8,03 (1H, s), MS *m/z* ($TS^+$) 333 ($MH^+$) |
| 9 | Prep 16 |  | Sal de HCl $\delta_H$ ($CD_3OD$, 400 MHz) 2,32 (3H, s), 2,43 (3H, s), 2,81 (3H, s), 4,41 (2H, s), 6,84 (1H, d), 6,91 (1H, d), 7,06 (1H, s), 7,24 (1H, d), 7,89 (1H, d), 8,05 (1H, s), MS *m/z* ($ES^+$) 352 ($MH^+$) |
| 10 | Prep 17 |  | Sal de HCl $\delta_H$ ($CD_3OD$, 400 MHz) 2,78 (3H, s), 4,21 (4H, s), 4,39 (2H, s), 6,89 (1H, d), 7,01 (1H, d), 7,08 (1H, s), 7,38 (1H, d), 7,85 (1H, d), 8,02 (1H, s), MS *m/z* ($TS^+$) 351 ($MH^+$) |
| 11 | Prep 18 |  | $\delta_H$ ($CD_3OD$, 400 MHz) 2,76 (3H, s), 3,30 (2H, m), 3,42 (2H, m), 4,33 (2H, s), 6,90 (1H, d), 6,94 (1H, d), 7,00 (1H, s), 7,29 (2H, d), 7,89 (1H, d), 8,04 (1H, s), MS *m/z* ($ES^+$) 351 ($MH^+$), ($ES^-$) 349 ($M-H^+$) |

**EJEMPLOS 12 y 13**

**3-[(Dimetilamino)metil]-4-[3-metil-4-(metilsulfanil)fenoxi]bencenosulfonamida (Ejemplo 12) y 3-[(dimetilamino)metil]-*N*-metil-4-[3-metil-4-(metilsulfanil)fenoxi]benceno-sulfonamida (Ejemplo 13)**



Se añadió formaldehído (solución acuosa al 37%, 282 µl, 3,76 mmol) a una suspensión de la amina secundaria del Ejemplo 1 (409 mg, 1,16 mmol) en DCM (20 ml) a temperatura ambiente en nitrógeno. La mezcla resultante se agitó durante 15 minutos antes de añadir triacetoxiborohidruro de sodio (984 mg, 4,64 mmol). La mezcla de reacción resultante se agitó durante 5 horas antes de alcalinizarla con una solución saturada de $NaHCO_3$ (10 ml) y se extrajo con DCM (3 x 20 ml). Las capas orgánicas se lavaron con salmuera (10 ml), se secaron ($MgSO_4$) y se evaporaron para dar un aceite amarillo. Éste se purificó por HPLC (columna de $C_{18}$ de 75 x 4,6 mm de Phenomonex Luna, $CH_3CN$, $H_2O$, TFA). Las fracciones que contenían el producto mayoritario se evaporaron y el residuo se trató con solución saturada de $NaHCO_3$ (5 ml) y se extrajo con DCM (3 x 30 ml). Las fracciones orgánicas combinadas se lavaron con salmuera (30 ml), se secaron ($MgSO_4$) y se evaporaron para dar un espuma blanca (155 mg, 36%) del Ejemplo 12 $\delta_H$ (300 MHz, $CDCl_3$) 2,30 (6H, s), 2,35 (3H, s), 2,48 (3H, s), 3,60 (2H, s), 6,83 (3H, m), 7,20 (1H, m), 7,28 (2H, s), 7,74 (1H, d), 8,08 (1H, s), MS *m/z* (TS+) 367 $MH^+$.

También se obtuvo un producto minoritario después de purificación por HPLC. Las fracciones relevantes se evaporaron y el residuo se trató con solución saturada de $NaHCO_3$ (5 ml), y se extrajo con DCM (2 x 30 ml). Las fracciones orgánicas combinadas se lavaron con salmuera (30 ml), se secaron ($MgSO_4$) y se evaporaron para dar una goma. Ésta se recogió en DCM (5 ml), se trató con HCl etéreo 1 M (2 ml) y se evaporó para dar un polvo blanco (39 mg, 9%) del Ejemplo 13, sal de HCl $\delta_H$ ($CDCl_3$, 300 MHz) 2,30 (6H, s), 2,35 (3H, s), 2,48 (3H, s), 3,60 (2H,

s), 6,83 (3H, m), 7,20 (1H, m), 7,28 (2H, s), 7,74 (1H, d), 8,08 (1H, s), MS *m/z* ($TS^+$) 381 ($MH^+$)

En una reacción repetida, utilizando 1 equivalente de formaldehído a la amina del Ejemplo 1, se obtuvo el Ejemplo 12 con un 78% de rendimiento después de la cromatografía en columna [$SiO_2$, (EtOAc/MeOH/$NH_3$ 880) 95 5 0,5 a 9 10 1] Esto se recogió en EtOAc y se convirtió en la sal de HCl por adición de HCl etéreo 1 M El precipitado resultante se filtró y se secó a vacío para dar la sal de HCl del Ejemplo 12, p f. 188°C

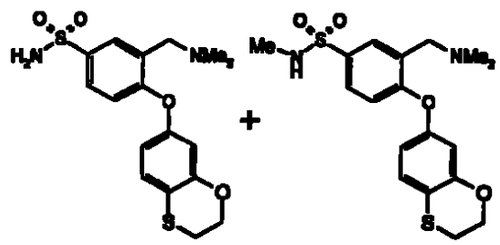
Alternativamente, también se puede formar el Ejemplo 12 a partir de la amina del Ejemplo 1 por el método del Ejemplo 110.

El Ejemplo 12 también se preparó como sigue

Se añadió lentamente una solución de la sal de hidrocloruro del Ejemplo 94 (20 g) en ácido trifluoroacético (100 ml) a una solución de ácido clorosulfónico (72 g) manteniendo la temperatura entre 0 y 5°C. Después de 1 h, la mezcla de reacción se inactivó lentamente en agua (200 ml) a 0-20°C Luego la mezcla se extrajo con diclorometano (200 ml) y se separó Luego la capa acuosa se extrajo con diclorometano (60 ml) y se separó Las capas orgánicas combinadas se lavaron con agua (200 ml) Las capas se separaron y el diclorometano se separó a vacío para dar un sólido Se añadió acetonitrilo (240 ml) y a esta suspensión se añadió oxicloruro de fósforo (28,8 ml) Luego la solución se calentó a reflujo durante una noche La mezcla de reacción se enfrió a temperatura ambiente y se inactivó en una mezcla agitada de amoníaco (90 ml), diclorometano (240 ml) y agua (100 ml), manteniendo la temperatura entre 0°C y 10°C La mezcla se ajustó con amoníaco (en caso necesario) para dar un pH mayor que 8 Después de 15 minutos, la mezcla de reacción se dejó calentar a temperatura ambiente y se separaron las capas La capa orgánica se concentró a vacío para dar un aceite pardo espeso Éste se disolvió en acetona (100 ml) y se suspendió con carbono (Norit SX plus, 50% en peso), se filtró y se trató con otra carga de carbono (Norit SX plus, 50% en peso) Esta mezcla se filtró de nuevo y la solución se concentró, reponiendo el volumen con agua (200 ml) La suspensión se granuló, se filtró y se secó a vacío durante una noche para dar el producto del título como un sólido blanco crema (rendimiento 40%)

**EJEMPLOS 14 y 15**

**4-(2,3-Dihidro-1,4-benzoxatiin-7-iloxi)-3-[(dimetilamino)metil]bencenosulfonamida y 4-(2,3-dihidro-1,4-benzoxatiin-7-iloxi)-3-[(dimetilamino)metil]-*N*-metilbencenosulfonamida**

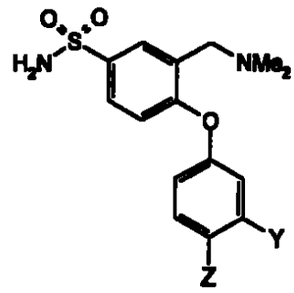


Estos compuestos se formaron de una manera análoga a los Ejemplos 12 y 13 a partir de la amina secundaria del Ejemplo 5

**EJEMPLO 14.** Sal de HCl $\delta_H$ ($CD_3OD$, 400 MHz) 2,97 (6H, s), 3,18 (2H, m), 4,42 (2H, m), 4,52 (2H, s), 6,68 (2H, d), 6,99 (1H, d), 7,14 (1H, d), 7,94 (1H, d), 8,07 (1H, s), MS *m/z* ($ES^+$) 381 ($MH^+$)

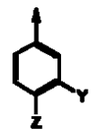
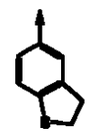
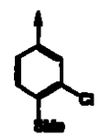
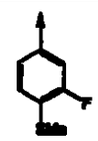
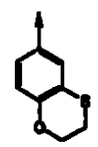
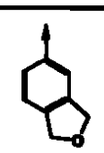
**EJEMPLO 15** Sal de HCl. $\delta_H$ ($CD_3OD$, 400 MHz) 2,56 (3H, s), 2,80 (6H, s), 3,17 (2H, m), 4,35 (2H, s), 4,41 (2H, m), 6,68 (2H, m), 6,98 (1H, d), 7,13 (1H, d), 7,81 (1H, d), 8,00 (1H, s), MS *m/z* ($ES^+$) 395 ($MH^+$)

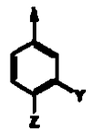
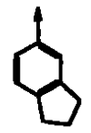
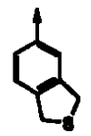
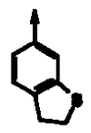
Los compuestos de fórmula Ie, es decir, los compuestos de fórmula general I en la que $R^1$ y $R^2$ son metilo y $R^5$ es $-SO_2NH_2$, mostrados en la Tabla 2, se prepararon de acuerdo con el Ejemplo 12 a partir de los precursores indicados Las N-metil-sulfonamidas análogas al Ejemplo 13 no se aislaron en estas reacciones y no fue necesaria la purificación por HPLC



(Ie)

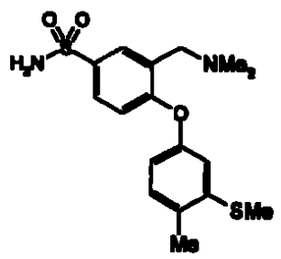
Tabla 2

| Ejemplo | Precursor |  | Datos |
|---|---|---|---|
| 16 | Ejemplo 2 |  | Sal de HCl. $\delta_H$ ($CD_3OD$, 400 MHz) 2,98 (6H, s), 3,41 (2H, m), 4,58 (2H, s), 6,95 (2H, m), 7,08 (1H, s), 7,25 (1H, d), 7,95 (1H, d), 8,05 (1H, s), MS *m/z* ($ES^+$) 365 ($MH^+$) |
| 17 | Ejemplo 3 |  | Sal de HCl $\delta_H$ ($CD_3OD$, 300 MHz) 2,54 (3H, s), 2,98 (6H, s), 4,53 (2H, s), 7,01 (1H, d), 7,20 (1H, dd), 7,33 (1H, s), 7,42 (1H, d), 7,99 (1H, d), 8,04 (1H, s), MS *m/z* ($TS^+$) 387 ($MH^+$) |
| 18 | Ejemplo 4 |  | Sal de HCl. $\delta_H$ ($CD_3OD$, 400 MHz) 2,43 (3H, s), 2,88 (6H, s), 4,42 (2H, s), 6,99 (3H, m), 7,42 (1H, t), 7,92 (1H, d), 8,06 (1H, s); MS *m/z* ($ES^+$) 371 ($MH^+$) |
| 19 | Ejemplo 6 |  | Sal de HCl $\delta_H$ ($CD_3OD$, 400 MHz) 2,89 (3H, s), 3,17 (2H, m), 4,39 (2H, m), 4,47 (2H, s), 6,78 (1H, d), 6,87 (3H, m), 7,89 (1H, d), 8,01 (1H, s); MS *m/z* ($TS^+$) 367 ($MH^+$) |
| 20 | Ejemplo 7 |  | Sal de TFA $\delta_H$ ($CDCl_3$, 400 MHz) 2,22 (6H, s), 2,60 (2H, t), 5,05 (4H, d), 6,75-6,90 (3H, m), 7,20 (1H, d), 7,60 (1H, m), 8,00 (1H, m), MS *m/z* 349 ($MH^+$) |

| Ejemplo | Precursor |  | Datos |
|---|---|---|---|
| 21 | Ejemplo 8 |  | Sal de HCl $\delta_H$ ($CD_3OD$, 400 MHz) 2,10 (2H, m), 2,85-3,00 (10H, m), 4,30 (1H, brs), 4,50 (2H, s), 6,80-6,95 (2H, m), 7,05 (1H, s), 7,25 (1H, d), 7,80 (1H, d), 8,10 (1H, s), MS *m/z* ($ES^+$) 347 ($MH^+$) |
| 22 | Ejemplo 10 |  | Sal de HCl $\delta_H$ ($CD_3OD$, 400 MHz) 2,93 (6H, s), 4,21 (4H, s), 4,50 (2H, s), 6,91 (1H, d), 7,02 (1H, d), 7,09 (1H, s), 7,37 (1H, d), 7,91 (1H, d), 8,05 (1H, s), MS *m/z* ($TS^+$) 365 ($MH^+$) |
| 23 | Ejemplo 11 |  | Sal de HCl. $\delta_H$ (DMSO-$d_6$, 400 MHz) 2,76 (6H, s), 3,21 (2H, t), 3,38 (2H, t), 4,39 (2H, s), 6,80 (1H, d), 6,86 (1H, d), 7,10 (1H, s), 7,28 (3H, m), 7,80 (1H, d), 8,06 (1H, s), 10,23 (1H, br), MS *m/z* ($TS^+$) 365 ($MH^+$) |

**EJEMPLO 24**

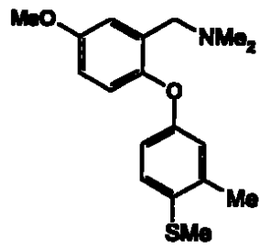
**3-[(Dimetilamino)metil]-4-[4-metil-3-(metilsulfanil)fenoxi]bencenosulfonamida**



El compuesto del título se preparó a partir de la amina secundaria del Ejemplo 9 por el método del Ejemplo 110, $\delta_H$ ($CD_3OD$, 400 MHz) 2,27 (3H, s), 2,41 (3H, s), 2,61 (6H, s), 4,19 (2H, s), 6,76 (1H, d), 6,86-6,93 (2H, m), 7,20 (1H, d), 7,82 (1H, d), 8,03 (1H, d), MS *m/z* ($TS^+$) 367 ($MH^+$)

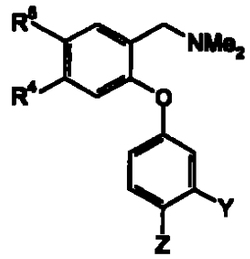
**EJEMPLO 25**

***N*-{5-Metoxi-2-[3-metil-4-(metilsulfanil)fenoxi]bencil}-*N,N*-dimetilamina**



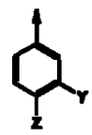
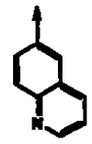
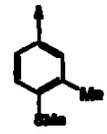
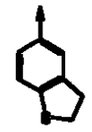
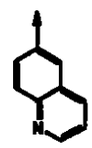

Se añadieron hidrocloruro de dimetilamina (424 mg, 5,2 mmol), $Et_3N$ (725 µl, 5,2 mmol), AcOH (298 µl, 5,2 mmol) y triacetoxiborohidruro de sodio (1,10 g, 5,2 mmol) a una solución del aldehído de la Preparación 24 (1,00 g, 3,47 mmol) en THF (15 ml) y DCM (15 ml) y la mezcla se agitó a temperatura ambiente durante 16 h Después de separar el disolvente a vacío, el residuo se recogió en HCl 2 M (20 ml) y se lavó con éter (2 x 15 ml) La capa acuosa se alcalinizó con lentejas de NaOH y se extrajo con DCM (4 x 20 ml) Los extractos combinados en DCM se lavaron con salmuera, se secaron ($MgSO_4$) y se evaporaron El residuo se recogió en una pequeña cantidad de DCM y se trató con HCl etéreo 1 M para precipitar la sal de HCl Ésta se filtró, se lavó con éter y se secó para dar un sólido blanco (936 mg) contaminado con hidrocloruro de trietilamina Éste se disolvió en NaOH 1 M (10 ml) y se extrajo con EtOAc (3 x 15 ml) Los extractos orgánicos se lavaron con salmuera (10 ml), se secaron ($MgSO_4$) y se evaporaron antes de redisolverse en EtOAc y evaporarse de nuevo El residuo se recogió en DCM y se trató con HCl etéreo 1 M para precipitar la sal de HCl, que se filtró, se lavó con éter y se secó para dar un sólido blanco (635 mg, 52%), $\delta_H$ ($CDCl_3$, 300 MHz) 2,35 (3H, s), 2,45 (3H, s), 2,79 (6H, s), 3,90 (3H, s), 4,21 (2H, s), 6,70 (1H, d), 6,73 (1H, s), 6,90 (2H, m), 7,18 (1H, d), 7,65 (1H, s), 12,83 (1H, brs); MS *m/z* ($TS^+$) 318 ($MH^+$)

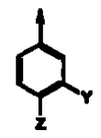
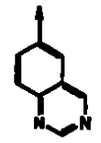
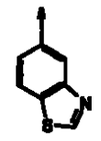
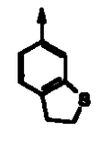
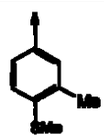
Los compuestos de fórmula If, es decir los compuestos de fórmula general I en la que $R^1$ y $R^2$ son metilo, mostrados en la Tabla 3, se prepararon de acuerdo con el Ejemplo 25 a partir de los precursores indicados



(II)

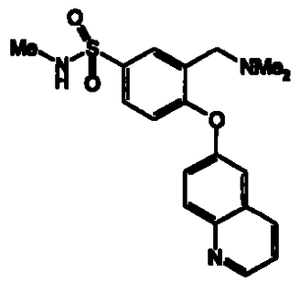
Tabla 3

| Ejemplo | Precursor | $R^4$ | $R^5$ |  | Datos |
|---|---|---|---|---|---|
| 26 | Prep 25 | H | F |  | Sal de HCl $\delta_H$ ($CDCl_3$, 300 MHz) 2,23 (6H, s), 3,41 (2H, s), 6,98 (2H, m), 7,34 (2H, m), 7,48 (1H, dd), 7,98 (1H, d), 8,08 (1H, d), 8,80 (1H, s), MS *m/z* ($TS^+$) 297 ($MH^+$) |
| 27 | Prep. 39 | H | $-NO_2$ |  | $\delta_H$ ($CDCl_3$, 300 MHz) 2,32 (6H, s), 2,36 (3H, s), 2,47 (3H, s), 3,60 (2H, s), 6,80 (1H, d), 6,87 (2H, d), 7,19 (1H, d), 8,03 (1H, d), 8,40 (1H, d), MS *m/z* ($ES^+$) 333 ($MH^+$) |
| 28 | Prep. 38 | H | $-NO_2$ |  | Tomado en bruto a una pureza de ~75%, $\delta_H$ ($CDCl_3$, 400 MHz) 2,33 (6H, s), 3,24 (2H, m), 3,38 (2H, m), 3,66 (2H, s), 6,76 (2H, m), 6,86 (1H, m), 7,17 (1H, d), 8,00 (1H, dd), 8,37 (1H, d) |
| 29 | Prep 26 | H | H |  | $\delta_H$ ($CDCl_3$, 300 MHz) 2,28 (6H, s), 3,50 (2H, s), 7,03 (2H, m), 7,20-7,40 (3H, m), 7,52 (2H, m), 7,98 (1H, d), 8,09 (1H, d), 8,81 (1H, m), MS *m/z* ($TS^+$) 279 ($MH^+$) |

| Ejemplo | Precursor | $R^4$ | $R^5$ |  | Datos |
|---|---|---|---|---|---|
| 30 | Prep 27 | H | H |  | Sal de HCl $\delta_H$ ($d_6$-DMSO, 300 MHz) 2,77 (6H, d), 4,38 (2H, d), 7,08 (1H, d), 7,36 (1H, t), 7,52 (1H, t), 7,62 (1H, s), 7,80 (1H, d), 7,91 (1H, dd), 8,10 (1H, d), 9,25 (1H, s), 9,52 (1H, s), MS *m/z* ($TS^+$) 280 ($MH^+$) |
| 31 | Prep 29 | H | H |  | Sal maleato: $\delta_H$ ($d_6$-DMSO, 300 MHz) 2,77 (6H, s), 4,33 (2H, s), 5,98 (2H, s), 6,87 (1H, d), 7,21 (1H, dt), 7,30 (1H, dd), 7,41 (1H, dt), 7,58 (1H, dd), 7,88 (1H, d), 8,11 (1H, d), 9,32 (1H, s), MS *m/z* 285 ($MH^+$) |
| 32 | Prep 33 | H | Br |  | Sal de HCl. $\delta_H$ (DMSO-$d_6$, 400 MHz) 2,77 (6H, d), 3,23 (3H, m), 3,39 (2H, m), 4,32 (2H, d), 6,75 (2H, m), 7,03 (1H, s), 7,26 (1H, d), 7,57 (1H, dd), 7,87 (1H, s), 10,06 (1H, br, s), MS *m/z* ($ES^+$) 366 ($MH^+$) |
| 33 | Prep 32 | Br | H |  | $\delta_H$ ($CDCl_3$, 400 MHz) 2,22 (6H, s), 2,30 (3H, s), 2,41 (3H, s), 3,41 (2H, s), 6,76 (2H, m), 6,94 (1H, s), 7,18 (1H, s), 7,21 (1H, obs), 7,30 (1H, d), MS *m/z* ($TS^+$) 366/368 ($MH^+$) |

**EJEMPLO 34**

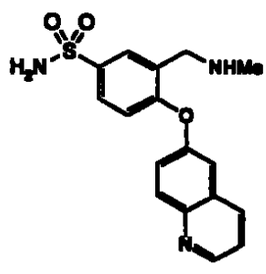
**3-[(Dimetilamino)metil]-*N*-metil-4-(6-quinolinoxi)bencenosulfonamida**



Se añadió ácido clorosulfónico (106 µl, 1,6 mmol) a una solución del Ejemplo 29 (50 mg, 0,16 mmol) en DCM (2 ml) y la mezcla se agitó durante 3 h a temperatura ambiente Se añadió agua (2 ml), la mezcla se ajustó a pH 6 con $NaHCO_3$ acuoso saturado y se extrajo con DCM (2 x 5 ml) Los extractos orgánicos se secaron ($MgSO_4$) y se filtraron y se añadió metilamina 8 M en EtOH (0,3 ml) Después de dejar estar durante 1 h, el disolvente se separó a vacío y el residuo se purificó por cromatografía en columna [$SiO_2$, (DCM/MeOH/$NH_3$ 880) 95.5 0,5] El producto se recogió en EtOAc y se convirtió en la sal de HCl por adición de HCl etéreo Ésta dio el producto deseado como un sólido higroscópico (3 mg, 5%), $\delta_H$ ($CD_3OD$, 300 MHz) 2,60 (3H, s), 2,99 (2H, s), 4,60 (2H, s), 7,21 (1H, d), 7,96 (1H, d), 8,04 (3H, m), 8,19 (1H, s), 8,38 (1H, d), 9,03 (1H, d), 9,18 (1H, d), MS *m/z* ($TS^+$) 371 ($MH^+$)

**EJEMPLO 35**

**3-[(Metilamino)metil]-4-(6-quinolinoxi)bencenosulfonamida**

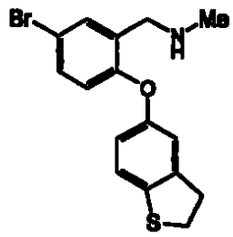


Se añadió anhídrido trifluoroacético (0,96 ml, 6,8 mmol) a una solución de la amina del Ejemplo 48 (900 mg, 3,4 mmol) y trietilamina (1,9 ml, 13,6 mmol) en

$CH_2Cl_2$ (15 ml) a 0°C y la mezcla se agitó durante 5 min El disolvente se separó a vacío y el residuo se repartió entre $CH_2Cl_2$ y agua La capa orgánica se lavó con salmuera, se secó ($MgSO_4$) y se evaporó para dar un aceite amarillo, que se utilizó sin más purificación Este aceite bruto se recogió en $CH_2Cl_2$ (20 ml), se enfrió a 0°C y se añadió gota a gota $ClSO_3H$ (2,4 ml, 36,1 mmol) La mezcla se dejó calentar a temperatura ambiente y se agitó durante 4 h antes de verterla en agua helada La mezcla se extrajo con $CH_2Cl_2$ (50 ml) y la capa orgánica se trató con una solución saturada de $NH_3$ en MeOH (10 ml) Después de agitar durante 4 h, se añadió LiOH 1 M (20 ml) y se continuó agitando durante una noche El análisis por tlc indicó que la reacción era incompleta, de modo que se añadió más LiOH 1 M (50 ml) y la mezcla se agitó durante 2 h La mezcla se acidificó a pH 8 con HCl 2 M y se extrajo con $CH_2Cl_2$ (3 x 200 ml) Los extractos orgánicos combinados se secaron ($MgSO_4$) y se evaporaron y el residuo se trituró con éter para dar el compuesto del título (500 mg, 43%) como un sólido amarillo, $\delta_H$ ($CDCl_3$, 400 MHz) 2,46 (3H, s), 3,87 (2H, s), 6,93 (1H, d), 7,25 (1H, s), 7,39 (1H, t), 7,42 (1H, d), 7,78 (1H, d), 8,00-8,08 (2H, m), 8,12 (1H, d), 8,86 (1H, s), MS *m/z* ($ES^+$) 344 ($MH^+$)

**EJEMPLO 36**

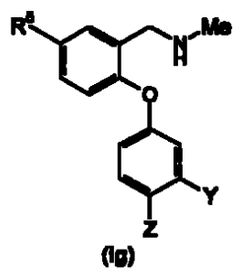
***N*-[5-Bromo-2-(2,3-dihidro-1-benzotien-5-iloxi)bencil]-*N*-metilamina**




El aldehído de la Preparación 19 (1,10 g, 3,28 mmol) se disolvió en metilamina 8 M en EtOH (4,1 ml, 32,8 mmol) y se agitó durante 5 h antes de la adición en porciones de $NaBH_4$ (372 mg, 9,83 mmol) a lo largo de 30 min. Se añadió EtOH (100 ml) y la reacción se agitó durante 16 h antes de ser concentrada a vacío. El residuo se inactivó con HCl 6 M hasta pH 1 y la sal de HCl precipitada se recogió por filtración, se lavó con agua (100 ml) y se secó a vacío para dar un sólido cristalino (1,04 g, 82%), $\delta_H$ ($CDCl_3$, 400 MHz) 2,62 (3H, s), 3,26 (2H, t), 3,41 (2H, t), 4,18 (2H, s), 6,66 (1H, d), 6,90 (1H, d), 7,03 (1H, s), 7,19 (1H, d), 7,39 (1H, d), 7,80

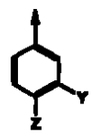
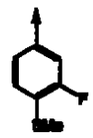
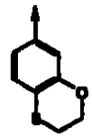
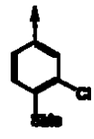
(1H, s), MS *m/z* ($ES^+$) 350, 352 ($MH^+$)

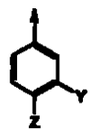
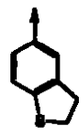
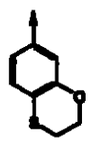
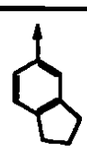
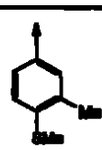
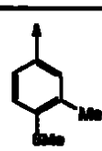
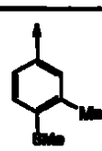
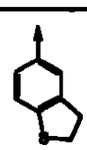
Los compuestos de fórmula Ig, es decir los compuestos de fórmula general I en la que $R^1$ y $R^2$ son hidrógeno y $R^2$ es metilo, mostrados en la Tabla 4, se prepararon de acuerdo con el Ejemplo 36 a partir de los precursores indicados Para aquellos compuestos que se aislaron como la base libre, la mezcla de reacción se repartió entre HCl 2 M y éter después de separar el disolvente de reacción a vacío Luego la capa acuosa se alcalinizó y se extrajo con DCM, siendo la capa de DCM secada ($MgSO_4$) y evaporada para dar la amina secundaria deseada.

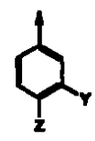
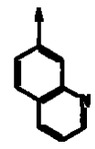
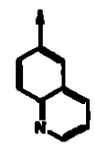
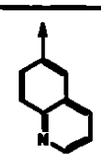


(Ig)

Tabla 4

| Ejemplo | Precursor | $R^5$ |  | Datos |
|---|---|---|---|---|
| 37 | Prep 20 | Br |  | Sal de HCl $\delta_H$ ($d_6$-DMSO, 300 MHz) 2,48 (3H, s), 2,59 (3H, s), 4,18 (2H, s), 6,88 (1H, d), 7,01 (1H, d), 7,16 (1H, d), 7,45 (1H, t), 7,59 (1H, d), 7,91 (1H, s), MS *m/z* ($TS^+$) 356, 358 ($MH^+$) |
| 38 | Prep 21 | Br |  | $\delta_H$ ($CDCl_3$, 400 MHz) 2,43 (3H, s), 3,11 (2H, t), 3,78 (2H, s), 4,41 (2H, t), 6,44 (1H, s), 6,51 (1H, d), 6,77 (1H, d), 6,98 (1H, d), 7,31 (1H, d), 7,55 (1H, s); MS *m/z* ($ES^+$) 366, 368 ($MH^+$) |
| 39 | Prep 22 | Br |  | $\delta_H$ ($CDCl_3$, 400 MHz) 2,41 (3H, s), 2,45 (3H, s), 3,72 (2H, s), 6,77 (1H, d), 6,85 (1H, d), 6,99 (1H, s), 7,18 (1H, d), 7,36 (1H, d), 7,59 (1H, s), MS *m/z* ($TS^+$) 372, 374 ($MH^+$) |

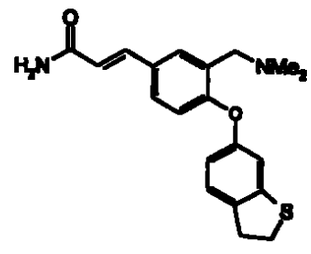
| Ejemplo | Precursor | $R^5$ |  | Datos |
|---|---|---|---|---|
| 40 | Prep 38 | $-NO_2$ |  | $\delta_H$ ($CDCl_3$, 300 MHz) 2,55 (3H, s), 3,20 (2H, m), 3,43 (2H, m), 3,95 (2H, s), 6,80 (2H, m), 6,91 (1H, s), 7,22 (1H, d), 8,05 (1H, d), 8,40 (1H, s); MS *m/z* ($ES^+$) 317 ($MH^+$) |
| 41 | Prep 36 | $-NO_2$ |  | $\delta_H$ ($CDCl_3$, 400 MHz) 2,45 (3H, s), 3,10 (2H, m), 3,86 (2H, s), 4,40 (2H, m), 6,53 (2H, m), 6,80 (1H, d), 7,01 (1H, d), 8,00 (1H, d), 8,27 (1H, s); MS *m/z* ($TS^+$) 333 ($MH^+$) |
| 42 | Prep 40 | $-NO_2$ |  | $\delta_H$ ($CDCl_3$, 400 MHz) 2,14 (2H, m), 2,52 (3H, s), 2,93 (4H, t), 3,92 (2H, s), 6,78 (1H, d), 6,81 (1H, d), 6,91 (1H, s), 7,22 (1H, d), 8,02 (1H, dd), 8,29 (1H, s), MS *m/z* ($TS^+$) 299 ($MH^+$) |
| 43 | Prep 24 | -OMe |  | Sal de HCl $\delta_H$ ($CDCl_3$, 300 MHz) 2,35 (3H, s), 2,45 (3H, s), 2,60 (3H, s), 3,84 (3H, s), 4,17 (2H, s), 6,80 (1H, d), 6,82 (1H, s), 6,88 (2H, s), 7,15 (1H, d), 7,42 (1H, s), 9,85 (2H, brs); MS *m/z* ($TS^+$) 304 ($MH^+$) |
| 44 | Prep 23 | Br |  | $\delta_H$ ($CDCl_3$, 300 MHz) 2,35 (3H, s), 2,45 (6H, s), 3,77 (2H, s), 6,73 (2H, m), 6,80 (1H, s), 7,19 (1H, d), 7,32 (1H, d), 7,57 (1H, s), MS *m/z* ($TS^+$) 352, 354 ($MH^+$) |
| 45 | Prep 30 | H |  | Sal de HCl. $\delta_H$ ($d_6$-DMSO, 400 MHz) 2,22 (3H, s), 2,42 (3H, s), 2,58 (3H, s), 4,18 (2H, s), 6,78 (1H, d), 6,96 (1H, d), 6,99 (1H, s), 7,18 (1H, t), 7,25 (1H, d), 7,38 (1H, t), 7,60 (1H, d), MS *m/z* ($ES^+$) 274 ($MH^+$) |
| 46 | Prep 31 | H |  | Sal de HCl: $\delta_H$ ($CDCl_3$, 400 MHz) 2,55 (3H, brs), 3,21 (2H, t), 3,32 (2H, m), 4,17 (2H, s), 6,76 (1H, d), 6,84 (1H, d), 6,99 (1H, s), 7,04 (1H, m), 7,12 (1H, d), 7,28 (1H, obs), 7,61 (1H, d), MS *m/z* ($ES^+$) 272 ($MH^+$) |

| Ejemplo | Precursor | $R^5$ |  | Datos |
|---|---|---|---|---|
| 47 | Prep 28 | H |  | Sal maleato $\delta_H$ (DMSO-$d_6$, 400 MHz) 2,60 (3H, s), 4,19 (2H, s), 5,99 (2H, s), 7,03 (1H, d), 7,29 (1H, m), 7,37 (1H, s), 7,45 (3H, m), 7,60 (1H, d), 8,06 (1H, d), 8,37 (1H, d), 8,74 (2H, br), 8,83 (1H, dd), MS *m/z* 264 ($MH^+$) |
| 48 | Prep. 26 | H |  | $\delta_H$ ($CDCl_3$, 300 MHz) 2,64 (3H, s), 4,25 (2H, s), 6,89 (1H, d), 7,19 (1H, t), 7,30-7,41 (2H, m), 7,45 (1H, s), 7,49 (1H, d), 7,69 (1H, d), 8,08 (1H, d), 8,16 (1H, d), 8,87 (1H, d), MS *m/z* ($ES^+$) 529 ($2M+H^+$) |
| 49 | Prep 34 | -CN |  | Sal de HCl $\delta_H$ ($CD_3OD$, 400 MHz) 2,81 (3H, s), 3,30 (1H, br), 4,42 (2H, s), 7,17 (1H, br), 7,82 (1H, br), 8,06 (1H, br), 8,11 (3H, br), 8,39 (1H, br), 9,18 (1H, br), 9,21 (1H, br), MS *m/z* ($ES^+$) 290 ($MH^+$) |

[a] Se utilizó metilamina 2 M en MeOH (2 equivalentes) y $Ti(O^iPr)_4$ (2 equivalentes) en EtOH (solución ~0,1 M de aldehído) en lugar de metilamina en EtOH Después del aislamiento de la base libre, se convirtió en la sal de maleato por métodos clásicos

**EJEMPLO 50**

**(2*E*)-3-{4-(2,3-Dihidro-1-benzotien-6-iloxi)-3-[(dimetilamino)metil]fenil}-2-propenamida**

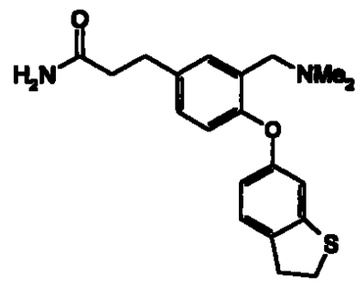


Una mezcla del bromuro del Ejemplo 32 (400 mg, 1,10 mmol), acrilamida (156 mg, 2,19 mmol), trietilamina (0,38 ml, 2,74 mmol), acetato de paladio II (12,5 mg, 0,06 mmol) y tri-*o*-tolilfosfina (33,4 mg, 0,11 mmol) en acetonitrilo (15 ml) se

calentó a reflujo durante 72 h Después de enfriar a temperatura ambiente, el disolvente se separó a vacío y el residuo se repartió entre EtOAc (50 ml) y HCl 2 M (50 ml) La fase acuosa se alcalinizó con NaOH 2 M y se extrajo con EtOAc (3 x 50 ml) Los extractos básicos combinados se secaron ($MgSO_4$) y se evaporaron El residuo se purificó por cromatografía en columna [$SiO_2$, (DCM/MeOH/$NH_3$ 880) 96.4 0,5 aumentando la polaridad a 90 10 1] para dar el compuesto del título (196 mg, 50%) como una espuma beige, $\delta_H$ ($CDCl_3$, 400 MHz) 2,28 (6H, s), 3,24 (2H, t), 3,38 (2H, t), 3,51 (2H, s), 5,73 (2H, br), 6,42 (1H, d), 6,59 (1H, dd), 6,82 (2H, m), 7,10 (1H, d), 7,32 (1H, d), 7,60 (1H, d), 7,69 (1H, s); MS *m/z* ($ES^+$) 355 ($MH^+$)

**EJEMPLO 51**

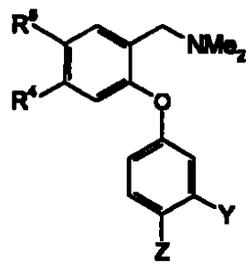
**3-{4-(2,3-Dihidro-1-benzotien-6-iloxi)-3-[(dimetilamino)metil]fenil}propanamida**



Se añadió una solución de $SmI_2$ en THF (0,1 M, 21,9 ml, 2,19 mmol) a una solución del alqueno del Ejemplo 50 (194 mg, 0,55 mmol) en THF (5 ml) en nitrógeno, seguido por agua (1 ml) Después de agitar a temperatura ambiente durante 10 min, la reacción se inactivó con NaOH 6 M (10 ml) y se agitó durante 30 min Se separó la fase orgánica y la fase acuosa se extrajo con EtOAc (2 x 20 ml) Las capas orgánicas combinadas se secaron ($MgSO_4$) y se evaporaron para dar un aceite, que se purificó por cromatografía en columna [$SiO_2$, (DCM/MeOH/$NH_3$ 880) 93 7 1 aumentando la polaridad a 90 90 10:1] para dar el compuesto del título (90 mg, 46%); $\delta_H$ ($CDCl_3$, 400 MHz) 2,25 (6H, s), 2,54 (2H, t), 2,97 (2H, t), 3,22 (2H, t), 3,36 (2H, t), 3,42 (2H, s), 5,20-5,46 (2H, br), 6,54 (1H, d), 6,73 (1H, s), 6,81 (1H, d), 7,05 (2H, m), 7,31 (1H, s), MS *m/z* ($TS^+$) 357 ($MH^+$)

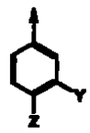
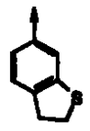
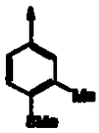
Los compuestos de fórmula If, es decir los compuestos de fórmula general I en la que $R^1$ y $R^2$ son metilo, mostrados en la Tabla 5, se prepararon de acuerdo con

la Preparación 50 a partir de los precursores indicados



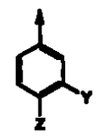
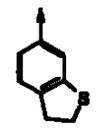
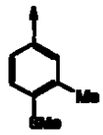
(If)

Tabla 5

| Ejemplo | Precursor | $R^4$ | $R^5$ |  | Datos |
|---|---|---|---|---|---|
| 52 | Ejemplo 32 | H | $-CO_2Me$ |  | $\delta_H$ ($CDCl_3$, 400 MHz) 2,29 (6H, s), 3,26 (3H, m), 3,39 (2H, m), 3,54 (2H, s), 3,89 (3H, s), 6,62 (1H, d), 6,84 (2H, m), 7,13 (1H, d), 7,86 (1H, d), 8,12 (1H, s), MS *m/z* ($TS^+$) 344 ($MH^+$) |
| 53 | Ejemplo 33 | $-CO_2Me$ | H |  | $\delta_H$ ($CDCl_3$, 400 MHz) 2,24 (6H, s), 2,33 (3H, s), 2,42 (3H, s), 3,48 (2H, s), 3,82 (3H, s), 6,73 (2H, m), 7,14 (1H, d), 7,50 (1H, s), 7,55 (1H, d), 7,78 (1H, d), MS *m/z* ($TS^+$) 346 ($MH^+$) |

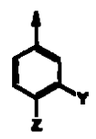
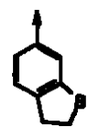
Los compuestos de fórmula If, es decir los compuestos de fórmula general I en la que $R^1$ y $R^2$ son metilo, mostrados en la Tabla 6, se prepararon de acuerdo con la Preparación 55 a partir de los precursores indicados

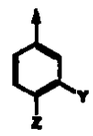
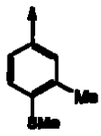
Tabla 6

| Ejemplo | Precursor | $R^4$ | $R^5$ |  | Datos |
|---|---|---|---|---|---|
| 54 | Ejemplo 52 | H | $-CO_2H$ |  | $\delta_H$ ($CD_3OD$, 400 MHz) 2,95 (6H, s), 3,29 (2H, m), 3,42 (2H, m), 4,52 (2H, s), 6,80 (1H, d), 6,89 (1H, d), 7,03 (1H, s), 7,29 (1H, d), 8,06 (1H, d), 8,23 (1H, s), MS *m/z* ($TS^+$) 330 ($MH^+$) |
| 55 (~80% de pureza) | Ejemplo 55 | $-CO_2H$ | H |  | $\delta_H$ ($CD_3OD$, 400 MHz) 2,27 (3H, s), 2,42 (3H, s), 2,88 (6H, s), 4,43 (2H, s), 6,95 (2H, m), 7,26 (1H, m), 7,42 (2H, m), 7,72 (1H, m) |

Los compuestos de fórmula If, es decir los compuestos de fórmula general I en la que $R^1$ y $R^2$ son metilo, mostrados en la Tabla 7, se prepararon de acuerdo con la Preparación 59 a partir de los precursores indicados

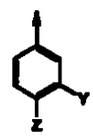
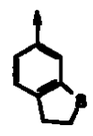
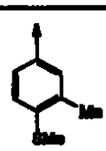
Tabla 7

| Ejemplo | Precursor | $R^4$ | $R^5$ |  | Datos |
|---|---|---|---|---|---|
| 56 | Ejemplo 54 | H | $-CONH_2$ |  | $\delta_H$ ($CDCl_3$, 400 MHz) 2,27 (6H, s), 3,25 (2H, m), 3,38 (2H, m), 3,54 (2H, s), 5,90-6,38 (2H, br), 6,59 (1H, d), 6,80 (1H, s), 6,86 (1H, d), 7,11 (1H, d), 7,71 (1H, d), 7,92 (1H, s), MS *m/z* ($TS^+$) 329 ($MH^+$) |

| Ejemplo | Precursor | $R^4$ | $R^5$ |  | Datos |
|---|---|---|---|---|---|
| 57 | Ejemplo 55 | $-CONH_2$ | H |  | Sal de HCl $\delta_H$ ($CD_3OD$, 400 MHz) 2,32 (3H, s), 2,43 (3H, s), 2,94 (6H, s), 4,47 (2H, s), 6,98 (2H, br), 7,27 (1H, br), 7,36 (1H, br), 7,62 (1H, br), MS *m/z* ($TS^+$) 331 ($MH^+$) |

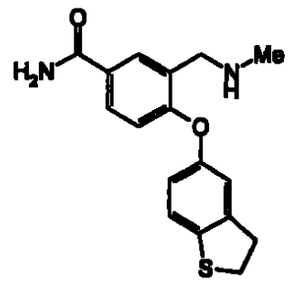
Los compuestos de fórmula If, es decir los compuestos de fórmula general I en la que $R^1$ y $R^2$ son metilo, mostrados en la Tabla 8, se prepararon de acuerdo con la Preparación 69 a partir de los precursores indicados.

Tabla 8

| Ejemplo | Precursor | $R^4$ | $R^5$ |  | Datos |
|---|---|---|---|---|---|
| 58 | Ejemplo 52 | H | $-CH_2OH$ |  | Sal de HCl $\delta_H$ (DMSO-$d_3$, 400 MHz) 2,76 (6H, s), 3,22 (2H, m), 3,40 (2H, m), 4,30 (2H, s), 4,49 (2H, s), 5,27 (1H, br, s), 6,68 (1H, d), 6,83 (1H, d), 6,97 (1H, s), 7,25 (1H, d), 7,37 (1H, d), 7,60 (1H, s), 10,07 (1H, br), MS *m/z* ($TS^+$) 316 ($MH^+$) |
| 59 | Ejemplo 53 | $-CH_2OH$ | H |  | Sal de HCl $\delta_H$ ($CD_3OD$, 400 MHz) 2,34 (3H, s), 2,46 (3H, s), 2,90 (6H, s), 4,40 (2H, s), 4,55 (2H, s), 6,89 (1H, s), 6,95 (2H, m), 7,18 (1H, d), 7,28 (1H, d), 7,50 (1H, d), MS *m/z* ($TS^+$) 318 ($MH^+$) |

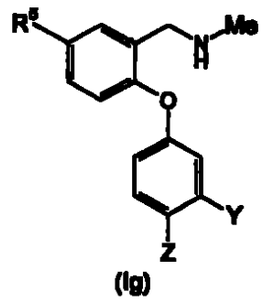
**EJEMPLO 60**

**4-(2,3-Dihidro-1-benzotien-5-iloxi)-3-[(metilamino)metil]benzamida**



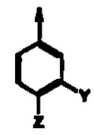
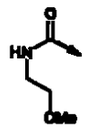
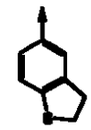
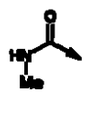
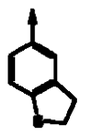
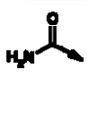
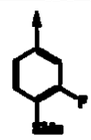
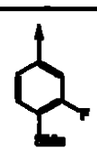
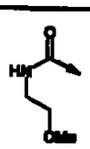
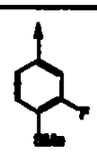
La amina protegida de la Preparación 59 (317 mg, 0,76 mmol) se disolvió en una solución saturada de HCl en DCM (25 ml) a 0°C y se dejó durante 1 h antes de ser neutralizada por la adición de $K_2CO_3$ acuoso al 10% (25 ml) Se añadió agua (50 ml) y las capas se separaron La capa acuosa se extrajo con DCM (25 ml) y las capas orgánicas combinadas se secaron ($MgSO_4$) y se evaporaron El aceite resultante se disolvió en EtOAc (10 ml) y se trató con HCl etéreo 1 M (1 ml) El precipitado blanco se recogió por filtración y se secó a vacío para dar el producto deseado (211 mg, 77%), $\delta_H$ ($CD_3OD$, 400 MHz) 2,77 (3H, s), 3,35 (2H, obs), 3,39 (2H, t), 4,34 (2H, s), 6,79 (1H, d), 6,90 (1H, dd), 7,02 (1H, s), 7,21 (1H, d), 7,83 (1H, d), 8,00 (1H, s), MS *m/z* ($TS^+$) 315 ($MH^+$)

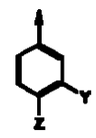
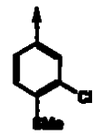
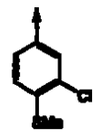
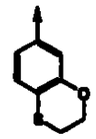
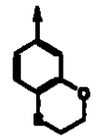
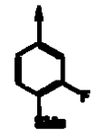
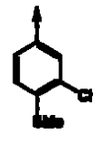
Los compuestos de fórmula Ig, es decir los compuestos de fórmula general I, en la que $R^1$ y $R^4$ son hidrógeno y $R^2$ es metilo, mostrados en la Tabla 9, se prepararon de acuerdo con el Ejemplo 60 a partir de los precursores indicados

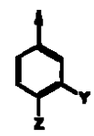
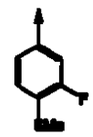
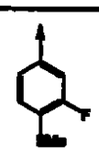
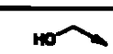
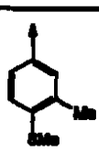
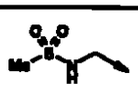
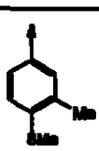
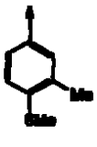


(Ig)

Tabla 9

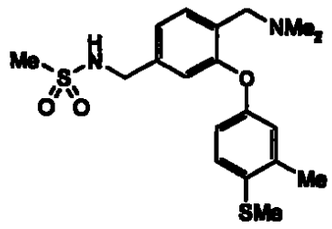
| Ejemplo | Precursor | $R^5$ |  | Datos |
|---|---|---|---|---|
| 61 | Prep 61 |  |  | Sal de HCl $\delta_H$ ($CDCl_3$, 400 MHz) 2,77 (3H, d), 3,35 (2H, obs), 3,36 (3H, s), 3,39 (2H, t), 3,51 (4H, s), 4,35 (2H, s), 6,80 (1H, d), 6,90 (1H, dd), 7,01 (1H, s), 7,21 (1H, d), 7,79 (1H, d), 7,96 (1H, s), MS *m/z* ($TS^+$) 373 ($MH^+$) |
| 62 | Prep 60 |  |  | Sal de HCl $\delta_H$ ($CD_3OD$, 400 MHz) 2,77 (3H, s), 2,88 (3H, s), 3,35 (2H, obs), 3,39 (2H, t), 4,35 (2H, s), 6,79 (1H, d), 6,90 (1H, dd), 7,01 (1H, s), 7,20 (1H, d), 7,78 (1H, d), 7,96 (1H, s), MS *m/z* ($TS^+$) 329 ($MH^+$) |
| 63 | Prep 62 |  |  | Sal de HCl $\delta_H$ ($d_6$-DMSO, 300 MHz) 2,52 (3H, obs), 2,61 (3H, s), 4,21 (3H, s), 6,90 (1H, d), 7,07 (1H, d), 7,19 (1H, d), 7,40 (1H, brs), 7,48 (1H, t), 7,92 (1H, d), 7,96 (1H, s), 8,21 (1H, s), MS *m/z* ($TS^+$) 321 ($MNH_4^+$) |
| 64 | Prep 63 |  |  | Sal de HCl. $\delta_H$ ($d_6$-DMSO, 300 MHz) 2,52 (3H, obs), 2,60 (3H, s), 2,79 (3H, d), 4,21 (2H, s), 6,89 (1H, d), 7,07 (1H, d), 7,19 (1H, d), 7,48 (1H, t), 7,85 (1H, d), 8,19 (1H, s), 8,48 (1H, d), MS *m/z* ($TS^+$) 335 ($MH^+$) |
| 65 | Prep 64 |  |  | Sal de HCl $\delta_H$ ($d_6$-DMSO, 300 MHz) 2,52 (3H, obs), 2,60 (3H, s), 3,27 (3H, s), 3,46 (4H, m), 4,22 (2H, s), 6,91 (1H, d), 7,08 (1H, d), 7,20 (1H, d), 7,50 (1H, t), 7,89 (1H, d), 8,10 (1H, s), 8,58 (1H, brs); MS *m/z* ($TS^+$) 379 ($MH^+$) |

| Ejemplo | Precursor | $R^5$ |  | Datos |
|---|---|---|---|---|
| 66 | Prep 65 |  |  | Sal de HCl $\delta_H$ ($d_6$-DMSO, 300 MHz) 2,52 (3H, obs), 2,60 (3H; t), 4,11 (2H, s+$H_2O$), 6,82 (1H, d), 7,21 (1H, d), 7,40 (3H, s+d), 7,88 (1H, d), 7,96 (1H, brs), 8,21 (1H, s), MS *m/z* ($ES^+$) 337 ($MH^+$) |
| 67 | Prep 66 |  |  | Sal de HCl $\delta_H$ ($d_6$-DMSO, 300 MHz) 2,52 (3H, obs), 2,60 (3H, t), 2,79 (3H, d), 4,22 (2H, t), 6,94 (1H, d), 7,22 (1H, d), 7,40 (2H, s+d), 7,83 (1H, d), 8,19 (1H, d), 8,46 (1H, d), MS (*m/z* ($ES^+$) 351 ($MH^+$) |
| 68 | Prep 67 |  |  | $\delta_H$ ($CDCl_3$, 400 MHz) 2,41 (3H, s), 3,08 (2H, m), 3,80 (2H, s), 4,37 (2H, m), 5,94-6,36 (2H, brd), 6,46 (1H, s), 6,49 (1H, d), 6,81 (1H, d), 6,96 (1H, d), 7,65 (1H, d), 7,86 (1H, s), MS *m/z* ($TS^+$) 331 ($MH^+$) |
| 69 | Prep 68 |  |  | Sal de HCl $\delta_H$ ($CDCl_3$, 400 MHz) 2,42 (3H, s), 3,08 (2H, m), 3,44-3,50 (4H, m), 3,80 (2H, s), 4,40 (2H, m), 6,45 (1H, s), 6,49 (1H, d), 6,62 (1H, brs), 6,83 (1H, d), 6,96 (1H, d), 7,62 (1H, d), 7 78 (1H, s), MS *m/z* ($TS^+$) 390 ($MH^+$) |
| 70 | Prep 70 |  |  | Sal de HCl $\delta_H$ ($d_6$-DMSO, 300 MHz) 2,48 (3H, s), 2,58 (3H, s), 4,12 (2H, s), 4,50 (2H, d), 5,32 (1H, t), 6,92 (2H, m), 7,03 (1H, dd), 7,39 (1H, dd), 7,46 (1H, d), 7,60 (1H, s), MS *m/z* ($TS^+$) 308 ($MH^+$) |
| 71 | Prep. 69 |  |  | Sal de HCl $\delta_H$ ($d_6$-DMSO, 300 MHz) 2,52 (3H, obs), 2,58 (3H, t), 4,10 (2H, s+$H_2O$), 4,48 (2H, s), 6,94 (1H, d), 7,11 (1H, d), 7,21 (1H, s), 7,25 (2H, m), 7,57 (1H, s); MS *m/z* ($ES^+$) 324 ($MH^+$) |

| Ejemplo | Precursor | $R^5$ |  | Datos |
|---|---|---|---|---|
| 72 | Prep 49 | -C≡N |  | Sal de HCl· $\delta_H$ ($d_6$-DMSO, 300 MHz) 2,52 (3H, s), 2,60 (3H, s), 4,24 (2H, s), 6,94 (1H, d), 7,04 (1H, d), 7,28 (1H, d), 7,50 (1H, t), 7,86 (1H, d), 8,08 (1H, s), MS *m/z* ($TS^+$) 303 ($MH^+$) |
| 73 | Prep 73 |  |  | Sal de HCl· $\delta_H$ ($CDCl_3$, 300 MHz) 2,48 (3H, s), 2,64 (3H, s), 2,99 (3H, s), 4,23 (2H, s), 4,30 (2H, d), 6,40 (1H, br), 6,81-6,89 (3H, m), 7,26-7,35 (2H, obs), 7,92 (1H, s); MS *m/z* ($ES^+$) 385 ($MH^+$), ($ES^-$) 383 ($M-H^+$) |
| 74 | Prep 71 |  |  | Sal de HCl· $\delta_H$ ($CD_3OD$, 400 MHz) 2,30 (3H, s), 2,44 (3H, s), 2,73 (3H, s), 4,25 (2H, s), 4,59 (2H, s), 6,81 (1H, d), 6,88-6,92 (2H, m), 7,24 (1H, d), 7,37 (1H, d), 7,46 (1H, s), MS *m/z* ($ES^+$) 304 ($MH^+$) |
| 75 | Prep 72 |  |  | Sal de HCl. $\delta_H$ ($CD_3OD$, 300 MHz) 2,37 (3H, s), 2,48 (3H, s), 2,78 (3H, s), 2,96 (3H, s), 4,27 (2H, s), 4,31 (2H, s), 6,85 (1H, d), 6,92-7,00 (2H, m), 6,31 (1H, d), 7,41 (1H, d), 7,57 (1H, s); MS *m/z* ($ES^+$) 381 ($MH^+$) , ($ES^-$) 379 ($M-H^+$) |
| 76 | Prep 75 |  |  | Sal de HCl $\delta_H$ ($CD_3OD$, 400 MHz) 2,29 (3H, s), 2,41 (3H, s), 2,43 (3H, s), 3,76 (2H, s), 4,30 (2H, s), 6,72-6,79 (3H, m), 7,12 (1H, br), 7,27 (2H, obs), MS *m/z* ($ES^+$) 435 ($MH^+$), ($ES^-$) 433 ($M-H^+$) |

**EJEMPLO 77**

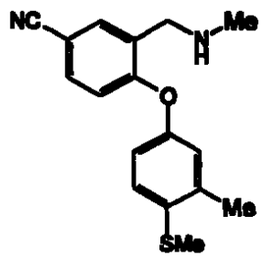
***N*-{4-[(Dimetilamino)metil]-3-[3-metil-4-(metilsulfanil)fenoxi]bencil}metanosulfonamida**



El Ejemplo 77 se preparó a partir de la sulfonamida protegida con Boc de la Preparación 74 por el método del Ejemplo 60; sal de HCl: $\delta_H$ ($CD_3OD$, 400 MHz) 2,29 (3H, s), 2,42 (3H, s), 2,82 (3H, s), 2,89 (6H, s), 4,17 (2H, s), 4,39 (2H, s), 6,39 (3H, m), 7,19 (1H, d), 7,24 (1H, d), 7,48 (1H, d), MS *m/z* ($TS^+$) 395 ($MH^+$)

**EJEMPLO 78**

**3-[(Metilamino)metil]-4-[3-metil-4-(metilsulfanil)fenoxi]benzonitrilo**

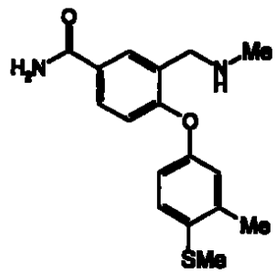


Se añadieron $Zn(CN)_2$ (700 mg, 5,96 mmol) y $Pd(PPh_3)_4$ (1,97 g, 1,7 mmol) a una solución del bromuro del Ejemplo 44 (3,0 g, 8,52 mmol) en DMF (20 ml) y la mezcla se calentó a 100°C durante 17 h La reacción se enfrió a temperatura ambiente, se diluyó con agua (100 ml) y se extrajo con éter (2 x 100 ml y después 3 x 50 ml) Las capas orgánicas combinadas se lavaron con agua (3 x 50 ml), se secaron ($MgSO_4$) y se evaporaron para dar un aceite amarillo. La purificación inicial por cromatografía en columna [$SiO_2$, (DCM/MeOH/$NH_3$ 880) 95 5 0,5] no tuvo éxito así que el material se volvió a cromatografiar [$SiO_2$, 50% de pentano en (DCM/MeOH/$NH_3$ 880) 95 5 0,5 aumentando la polaridad hasta 0% de pentano] para dar el producto (1,275 g, 50%) como un aceite amarillo pálido Se recogió una

muestra en DCM (5 ml) y se trató con HCl etéreo 1 M para dar la sal de HCl como un polvo blanco que se recogió por filtración, $\delta_H$ ($CDCl_3$, 300 MHz) 2,35 (3H, s), 2,47 (6H, s), 3,88 (2H, s), 6,79 (1H, d), 6,87 (2H, m), 7,20 (1H, d), 7,46 (1H, d), 7,72 (1H, s), MS *m/z* ($TS^+$) 299 ($MH^+$)

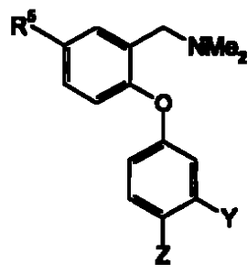
**EJEMPLO 79**

**3-[(Metilamino)metil]-4-[3-metil-4-(metilsulfanil)fenoxi]benzamida**



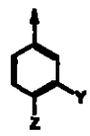
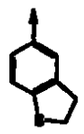
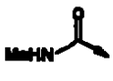
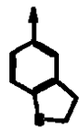
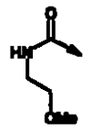
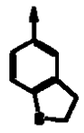
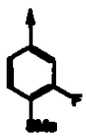

Una mezcla del nitrilo del Ejemplo 78 (404 mg, 1,35 mmol) y KOH (304 mg, 5,42 mmol) en terc-butanol (10 ml) se calentó a reflujo durante 1 h en atmósfera de nitrógeno Después de enfriar a temperatura ambiente, el disolvente se separó a vacío y el residuo se repartió entre agua (10 ml) y DCM (10 ml) La capa acuosa se extrajo con DCM (4 x 20 ml) y las capas orgánicas combinadas se lavaron con salmuera, se secaron ($MgSO_4$) y se evaporaron. El residuo se purificó por cromatografía en columna [$SiO_2$, (DCM/MeOH/$NH_3$ 880) 93.7 1] para dar el producto deseado (376 mg, 88%) como una espuma blanca, $\delta_H$ ($CDCl_3$, 300 MHz) 2,35 (3H, s), 2,47 (3H, s), 2,49 (3H, s), 3,88 (2H, s), 5,90-6,30 (2H, brs), 6,82 (3H, m), 7,19 (1H, d), 7,70 (1H, d), 7,90 (1H, s), MS *m/z* ($TS^+$) 317 ($MH^+$)

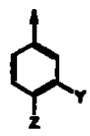
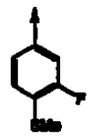
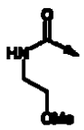
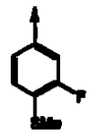
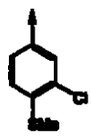
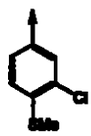
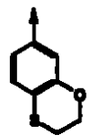
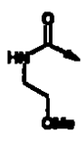
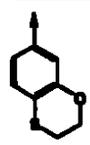
Los compuestos de fórmula Ih, es decir, los compuestos de fórmula general I en la que $R^1$ y $R^2$ son metilo y $R^4$ es hidrógeno, mostrados en la Tabla 10, se prepararon de acuerdo con el Ejemplo 12 a partir de los precursores indicados

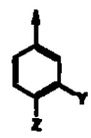
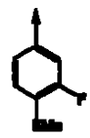
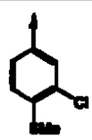
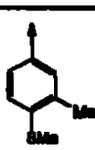
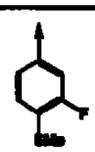
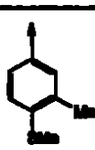
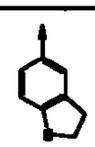


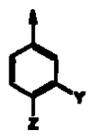
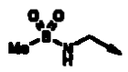
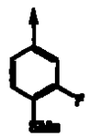
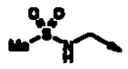
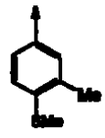
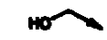
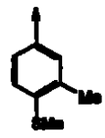
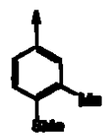
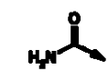
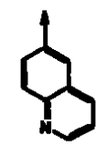
(Ih)

Tabla 10

| Ejemplo | Precursor | $R^5$ |  | Datos |
|---|---|---|---|---|
| 80 | Ejemplo 60 |  |  | $\delta_H$ ($CD_3OD$, 400 MHz) 2,91 (6H, s), 3,35 (2H, obs), 3,38 (2H, t), 4,45 (2H, s), 6,81 (1H, d), 6,90 (1H, d), 7,03 (1H, s), 7,21 (1H, d), 7,86 (1H, d), 8,03 (1H, s), MS *m/z* ($TS^+$) 329 ($MH^+$) |
| 81 | Ejemplo 62 |  |  | $\delta_H$ ($CD_3OD$, 400 MHz) 2,90-2,99 (9H, m), 3,35 (2H, obs), 3,43 (2H, t), 4,50 (2H, s), 6,88 (1H, d), 6,97 (1H, d), 7,07 (1H, s), 7,28 (1H, d), 7,85 (1H, d), 8,03 (1H, s), MS *m/z* ($TS^+$) 343 ($MH^+$) |
| 82 | Ejemplo 61 |  |  | $\delta_H$ ($CDCl_3$, 400 MHz) 2,90 (6H, brm), 3,35 (2H, obs), 3,37 (2H, brm), 3,51 (4H, brm), 4,43 (2H, brs), 6,80-6,94 (2H, brd), 7,01 (1H, brs), 7,20 (1H, brs), 7,82 (1H, brs), 7,98 (1H, brs), MS *m/z* ($TS^+$) 387 ($MH^+$) |
| 83 | Ejemplo 63 |  |  | $\delta_H$ ($CDCl_3$, 300 MHz) 2,29 (6H, s), 2,47 (3H, s), 3,51 (2H, s), 6,73 (2H, s), 6,97 (1H, d), 7,30 (1H, t), 7,79 (1H, d), 7,97 (1H, s), MS *m/z* ($TS^+$) 335 ($MNH_4^+$) |

| Ejemplo | Precursor | $R^5$ |  | Datos |
|---|---|---|---|---|
| 84 | Ejemplo 64 |  |  | $\delta_H$ ($CDCl_3$, 300 MHz) 2,29 (6H, s), 2,46 (3H, s), 3,02 (3H, d), 3,54 (2H, s), 6,20 (1H, brs), 6,69 (2H, m), 6,97 (1H, d), 7,30 (1H, t), 7,75 (1H, d), 7,91 (1H, s), MS *m/z* ($TS^+$) 349 ($MH^+$) |
| 85 | Ejemplo 65 |  |  | Sal de HCl. $\delta_H$ ($CDCl_3$, 300 MHz) 2,49 (3H, s), 2,94 (6H, s), 3,42 (3H, s), 3,65 (4H, m), 4,33 (2H, s), 6,79 (2H, d), 6,96 (1H, d), 7,35 (1H, t), 7,39 (1H, brs), 7,98 (1H, d), 8,68 (1H, s), MS *m/z* ($TS^+$) 393 ($MH^+$) |
| 86 | Ejemplo 66 |  |  | $\delta_H$ ($CDCl_3$, 400 MHz) 2,38 (6H, s), 2,47 (3H, s), 3,53 (2H, s), 6,88 (2H, d), 7,03 (1H, s), 7,19 (1H, d), 7,77 (1H, d), 7,95 (1H, s), MS *m/z* ($ES^+$) 351 ($MH^+$) |
| 87 | Ejemplo 67 |  |  | $\delta_H$ ($CDCl_3$, 400 MHz) 2,27 (6H, s), 2,46 (3H, s), 3,01 (3H, d), 3,50 (2H, s), 6,19 (1H, brs), 6,88 (2H, m), 7,00 (1H, s), 7,19 (1H, d), 7,72 (1H, d), 7,85 (1H, s), MS *m/z* ($ES^+$) 365 ($MH^+$) |
| 88 | Ejemplo 68 |  |  | Sal de HCl $\delta_H$ ($CDCl_3$, 400 MHz) 2,25 (6H, s), 3,07 (2H, s), 3,49 (2H, s), 4,37 (2H, m), 5,47-6,22 (2H, brd), 6,44 (1H, s), 6,49 (1H, d), 6,86 (1H, d), 6,95 (1H, d), 7,68 (1H, d), 7,87 (1H, s); MS *m/z* ($TS^+$) 346 ($MH^+$) |
| 89 | Ejemplo 69 |  |  | Sal de HCl $\delta_H$ ($CD_3OD$, 400 MHz) 2,91 (6H, s), 3,13 (2H, s), 3,27 (3H, s), 4,39 (2H, s), 4,46 (2H, s), 6,64 (2H, s+d), 6,87 (1H, d), 7,08 (1H, d), 7,95 (1H, d), 8,00 (1H, s), MS *m/z* ($TS^+$) 403 ($MH^+$) |

| Ejemplo | Precursor | $R^5$ |  | Datos |
|---|---|---|---|---|
| 90 | Ejemplo 70 |  |  | Sal de HCl $\delta_H$ ($d_6$-DMSO, 300 MHz) 2,46 (3H, s), 2,74 (6H, s), 4,29 (2H, s), 4,51 (2H, s), 5,32 (1H, brs), 6,93 (2H, d), 7,08 (1H, d), 7,41 (2H, m),7,63 (1H, s); MS *m/z* ($TS^+$) 322 ($MH^+$) |
| 91 | Ejemplo 71 |  |  | Sal de HCl $\delta_H$ ($d_6$-DMSO, 400 MHz) 2,52 (3H, obs), 2,76 (6H, s), 4,09 (2H, s), 4,49 (2H, s), 5,32 (1H, brs), 6,87 (1H, d), 7,08 (1H, d), 7,26 (1H, s), 7,38 (2H, m), 7,60 (1H, s), MS *m/z* ($ES^+$) 338 ($MH^+$) |
| 92 | Ejemplo 78 | -C≡N |  | Sal de HCl $\delta_H$ ($CDCl_3$, 400 MHz) 2,35 (3H, s), 2,48 (3H, s), 2,87 (6H, d), 4,39 (2H, d), 6,85 (1H, d), 6,90 (1H, d), 6,93 (1H, dd), 7,21 (1H, d), 7,60 (1H, d), 8,17 (1H, s), MS *m/z* ($TS^+$) 313 ($MH^+$) |
| 93 | Ejemplo 72 | -C≡N |  | Sal de HCl. $\delta_H$ ($d_6$-DMSO, 300 MHz) 2,49 (3H, obs), 2,79 (6H, s), 4,41 (2H, s), 6,97 (1H, d), 7,14 (1H, d), 7,32 (1H, d), 7,49 (1H, t), 7,87 (1H, d), 8,22 (1H, s), MS *m/z* ($TS^+$) 317 ($MH^+$) |
| 94 | Ejemplo 45 | H |  | Sal de HCl $\delta_H$ ($d_6$-DMSO, 400 MHz) 2,23 (3H, s), 2,42 (3H, s), 2,76 (6H, s), 4,34 (2H, s), 6,80 (1H, d), 7,97 (1H, dd), 7,00 (1H, s), 7,19 (1H, t), 7,24 (1H, d), 7,40 (1H, t), 7,67 (1H, d), MS *m/z* ($ES^+$) 288 ($MH^+$) |
| 95 | Ejemplo 46 | H |  | Sal de HCl $\delta_H$ ($CDCl_3$, 400 MHz) 2,74 (6H, s), 3,22 (2H, m), 3,38 (2H, m), 4,26 (2H, s), 6,71 (1H, d), 6,80 (2H, brm), 7,15 (2H, brm), 7,32 (1H, d), 7,79 (2H, d); MS *m/z* ($ES^+$) 286 ($MH^+$) |

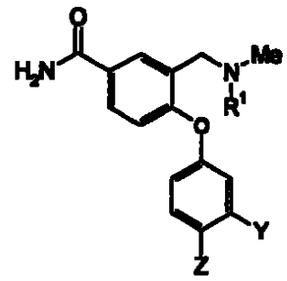
| Ejemplo | Precursor | $R^5$ |  | Datos |
|---|---|---|---|---|
| 96 | Ejemplo 73 |  |  | Sal de HCl $\delta_H$ ($CD_3OD$, 300 MHz) 2,46 (3H, s), 3,93 (6H, s), 3,97 (3H, s), 4,24 (2H, s), 4,42 (2H, s), 6,91-7,00 (3H, m), 7,41-7,54 (2H, m), 7,61 (1H, s), MS *m/z* ($TS^+$) 399 ($MH^+$), ($ES^-$) 397 ($M-H^+$) |
| 97 | Ejemplo 75 |  |  | Sal de HCl $\delta_H$ ($CD_3OD$, 400 MHz) 2,31 (3H, s), 2,43 (3H, s), 2,86-2,94 (9H, m), 4,22 (2H, s), 4,39 (2H, s), 6,83 (1H, d), 6,89-6,94 (2H, m), 7,26 (1H, d), 7,40 (1H, d), 7,54 (1H, s), MS *m/z* ($ES^-$) 393 ($M-H^+$) |
| 98 | Ejemplo 74 |  |  | Sal de HCl. $\delta_H$ ($CD_3OD$, 300 MHz) 2,36 (3H, s), 2,47 (3H, s), 2,98 (6H, s), 4,43 (2H, s), 4,63 (2H, s), 6,89 (1H, d), 6,91-7,00 (2H, m), 7,30 (1H, d), 7,43 (1H, d), 7,55 (1H, s), MS *m/z* ($ES^+$) 318 ($MH^+$) |
| 99 | Ejemplo 76 |  |  | Sal de HCl $\delta_H$ ($CD_3OD$, 300 MHz) 2,39 (3H, s), 2,47 (3H, s), 2,85 (6H, s), 4,32 (2H, s), 4,44 (2H, s), 6,80-6,86 (3H, m), 7,21 (1H, d), 7,35 (1H, d), 8,08 (1H, s); MS *m/z* ($ES^+$) 449 ($MH^+$), ($ES^-$) 447 ($M-H^+$) |
| 100 | Ejemplo 102 |  |  | $\delta_H$ ($CD_3OD$, 400 MHz) 2,26 (6H, s), 3,58 (2H, s), 6,97 (1H, d), 7,35 (1H, d), 7,46 (1H, dd), 7,54 (1H, d), 7,80 (1H, d), 8,03 (2H, m), 8,20 (1H, d), 8,74 (1H, d); MS *m/z* ($TS^+$) 322 ($MH^+$) |

El Ejemplo 94 se preparó también como sigue.

Se añadió una solución del producto de la Preparación 30 (200 g, 0,78 mmol) en DCM (1, 4 l) a THF (1,4 l) A esta mezcla se añadieron sucesivamente hidrocloruro de dimetilamina (69,5 g, 0,85 mol) y trietilamina (235 g, 2,33 mol) La temperatura

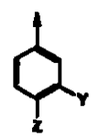
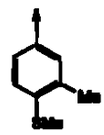
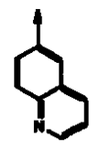
se ajustó a 20°C y después de 3 h se añadió triacetoxiborohidruro de sodio (246 g, 1,16 mol) (después de 20 h, si la reacción se ha completado, se continúa con el tratamiento posterior, en caso contrario, véase nota más adelante) Se añadió diclorometano (2 l) y se añadió una solución de bicarbonato de sodio al 8% (0,9 l) a lo largo de 0,5 h Se separaron las capas y la capa orgánica se lavó con agua (1 l) Las capas se separaron de nuevo y la capa orgánica se concentró Se añadió acetato de etilo (0,27 l) y el disolvente se separó reponiéndolo con acetato de etilo de nueva aportación (800 ml) Luego la solución se enfrió por debajo de 5°C y se añadió HCl/IPA 7,02 M (0,117 l, 0,82 mol) mientras que la temperatura se mantenía por debajo de 10°C Después de agitar durante 1 h a temperatura inferior a 5°C, la suspensión se filtró, se lavó con acetato de etilo (3 x 0,2 l) y se secó en una estufa a vacío a 50°C durante una noche para dar el producto deseado como un sólido pulverulento (141,5 g, 56%) [Nota si la reacción no se ha completado después de 20 h, se añade sucesivamente otra porción de hidrocloruro de dimetilamina (13 g, 0,16 mol) y trietilamina (43,4 g, 0,43 mol) Después de 2 h a temperatura ambiente, se añade triacetoxiborohidruro de sodio (46 g, 0,22 mol) Se deja estar durante 20 h más y luego se trata como antes]

Los compuestos de fórmula II, es decir los compuestos de fórmula general I en la que $R^2$ es metilo, $R^4$ es hidrógeno y $R^5$ es $-C(=O)NH_2$, mostrados en la Tabla 11, se prepararon de acuerdo con el Ejemplo 79 a partir de los precursores indicados



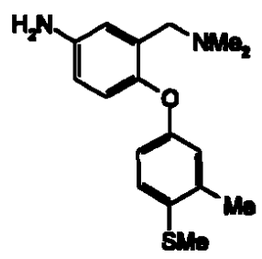

(II)

Tabla 11

| Ejemplo | Precursor | $R^1$ |  | Datos |
|---|---|---|---|---|
| 101 | Ejemplo 92 | Me |  | $\delta_H$ ($CDCl_3$, 300 MHz) 2,30 (6H, s), 2,35 (3H, s), 2,46 (3H, s), 3,58 (2H, s), 5,60-5,80 (1H, brs), 6 00-6,20 (1H, brs), 6,32 (3H, m), 7,19 (1H, m), 7,71 (1H, d), 7,90 (1H, s); MS *m/z* ($TS^+$) 331 ($MH^+$) |
| 102 | Ejemplo 49 | H |  | $\delta_H$ ($CDCl_3$, 400 MHz) 2,43 (3H, s), 3,84 (2H, s), 6,94 (1H, d), 7,20 (1H, d), 7,34-7,39 (1H, m), 7,43 (1H, dd), 7,70 (1H, d), 7,91 (1H, s), 7,99 (1H, d), 8,09 (1H, d), 8,82 (1H, d), MS *m/z* ($ES^+$) 309 ($MH^+$) |

**EJEMPLO 103**

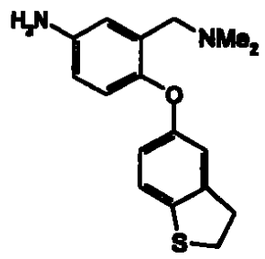
***N*-{5-Amino-2-[3-metil-4-(metilsulfanil)fenoxi]bencil}-*N*,*N*-dimetilamina**



Una mezcla del nitrocompuesto del Ejemplo 27 (2,0 g, 6 mmol), polvo de hierro (2,51 g, 44,9 mmol) y $CaCl_2$ (300 mg, 2,7 mmol) en EtOH (20 ml) y agua (4 ml) se calentó a reflujo durante 20 h Después de enfriar a temperatura ambiente, el disolvente se separó a vacío y el residuo se repartió entre salmuera (100 ml) y éter (100 ml) La capa acuosa se extrajo con éter (50 ml) y las capas orgánicas combinadas se secaron ($MgSO_4$) y se evaporaron para dar el producto (1,47 g, 81%) como un aceite de color naranja, $\delta_H$ ($CDCl_3$, 300 MHz) 2,22 (6H, s), 2,32 (3H, s), 2,40 (3H, s), 3,33 (2H, s), 6,59 (1H, dd), 6,60-6,75 (2H, m), 6,78 (1H, dd), 6,94 (1H, s), 7,10-7,20 (3H, m), MS *m/z* ($ES^+$) 303 ($MH^+$)

**EJEMPLO 104**

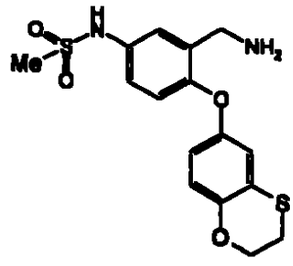
***N*-[5-Amino-2-(2,3-dihidro-1-benzotien-5-iloxi)bencil]-*N,N*-dimetilamina**



El compuesto del título se preparó a partir del nitrocompuesto del Ejemplo 28 por el método del Ejemplo 103, $\delta_H$ ($CDCl_3$, 400 MHz) 2,20 (6H, s), 3,16 (2H, t), 3,30 (4H, m), 3,54 (2H, br), 6,53 (1H, dd), 6,60 (1H, d), 6,71 (2H, m), 6,79 (1H, d), 7,01 (1H, d); MS *m/z* ($ES^+$) 301 ($MH^+$)

**EJEMPLO 105**

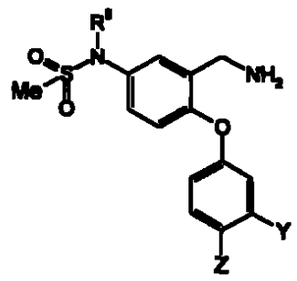
***N*-[3-(Aminometil)-4-(2,3-dihidro-1,4-benzoxatiin-6-iloxi)fenil]metanosulfonamida**



El nitrilo de la Preparación 95 (720 mg, 1,99 mmol) se disolvió en una solución 1 M de $BH_3$ THF en THF (10 ml, 10 mmol) y la mezcla se calentó a reflujo durante 3 h Después de enfriar a temperatura ambiente, la reacción se inactivó por adición cuidadosa de MeOH (10 ml) El disolvente se evaporó, el residuo se trató con HCl 6 M (10 ml) y se calentó a reflujo durante 1 h. Después de enfriar, la mezcla se alcalinizó con NaOH 2 M y el pH se ajustó a 7 con $NH_4Cl$ acuoso saturado La mezcla se extrajo con EtOAc (3 x 50 ml) y DCM (2 x 50 ml) y las capas orgánicas combinadas se secaron ($MgSO_4$) y se evaporaron para dar una espuma beige (685 mg, 94%) que se utilizó sin más purificación, $\delta_H$ ($CDCl_3$, 400 MHz) 3,00 (3H, s), 3,13 (2H, m),

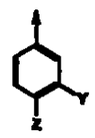
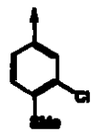
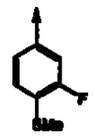
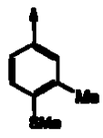
3,87 (2H, s), 4,40 (2H, m), 6,62 (1H, d), 6,67 (1H, s), 6,79 (2H, d), 7,08 (1H, d), 7,25 (1H, d), MS *m/z* ($TS^+$) 367 ($MH^+$)

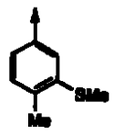
Los compuestos de fórmula Ij, es decir los compuestos de fórmula general I en la que $R^1$, $R^2$ y $R^4$ son hidrógeno y $R^5$ es $-NR^8-SO_2Me$, mostrados en la Tabla 12, se prepararon de acuerdo con el Ejemplo 105 a partir de los precursores indicados



(Ij)

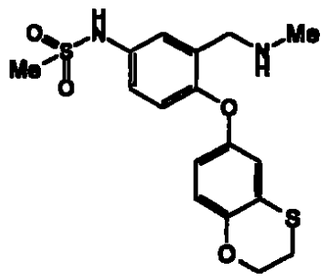
Tabla 12

| Ejemplo | Precursor |  | $R^8$ | Datos |
|---|---|---|---|---|
| 106 | Prep 96 |  | H | $\delta_H$ ($CDCl_3$, 300 MHz) 2,47 (3H, s), 3,02 (3H, s), 3,08 (3H, br), 3,85 (2H, s), 6,87 (2H, m), 6,99 (1H, d),7,15 (1H, dd), 7,20 (1H, d), 7,30 (1H, d), MS *m/z* ($ES^-$) 371 ($M-H^+$) |
| 107 | Prep 97 |  | H | Utilizado en bruto en una etapa subsiguiente $\delta_H$ ($CD_3OD$, 400 MHz) 2,37 (3H, s), 2,95 (3H, s), 3,75 (2H, s), 6,58 (1H, d), 6,71 (2H, m), 6,89 (1H, d), 7,15 (1H, dd), 7,28 (1H, obs) |
| 108 | Prep 100 |  | Me | Utilizado en bruto en una etapa subsiguiente $\delta_H$ ($CDCl_3$, 300 MHz) 2,36 (3H, s), 2,46 (3H, s), 2,90 (3H, s), 3,36 (3H, s), 3,93 (2H, s), 6,83 (3H, m), 7,20 (2H, m), 7,42 (1H, d) |

| Ejemplo | Precursor | | $R^8$ | Datos |
|---|---|---|---|---|
| 109 | Prep 99 |  | H | $\delta_H$ ($CD_3OD$, 400 MHz) 2,24 (3H, s), 2,40 (3H, s), 2,97 (3H, s), 3,80 (2H, s), 6,60 (1H, d), 6,81-6,87 (2H, m), 7,08-7,17 (2H, m), 7,29 (1H, d), MS *m/z* ($ES^+$) 353 ($MH^+$), ($ES^-$) 351 ($M-H^+$) |

**EJEMPLO 110**

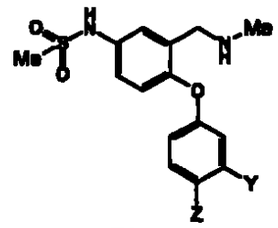
***N*-{4-(2,3-Dihidro-1,4-benzoxatiin-6-iloxi)-3-[(metilamino)metil]fenil}metanosulfonamida**



Se añadió diciclohexilcarbodiimida (460 mg, 2,23 mmol) a una solución de pentafluorofenol (413 mg, 2,24 mmol) en éter (10 ml) seguido por ácido fórmico (95 µl, 2,5 mmol) La mezcla se agitó durante 2 h y luego se filtró, lavando el residuo con éter El filtrado se concentró a ~5 ml y se añadió una solución de la amina primaria del Ejemplo 105 (411 mg, 1,1 mmol) en DCM (10 ml). La mezcla se agitó durante 16 h y luego se concentró para dar un residuo oleoso Este aceite bruto se recogió en una solución de $BH_3$ THF en THF (1 M, 20 ml, 20 mmol) y se calentó a reflujo durante 1,5 h en atmósfera de nitrógeno Después de enfriar a temperatura ambiente, la reacción se inactivó por adición cuidadosa de MeOH (10 ml) y luego se concentró a vacío. El residuo oleoso se trató con HCl 6 M y se calentó a reflujo durante 30 min Después de enfriar a temperatura ambiente, la mezcla se alcalinizó con $K_2CO_3$ acuoso y se extrajo con DCM (3 x) Los extractos orgánicos combinados se secaron ($MgSO_4$) y se evaporaron. El residuo se purificó por cromatografía en columna [$SiO_2$, (DCM/MeOH/$NH_3$ 880) 90 10 1] para dar un aceite incoloro que se recogió en EtOAc

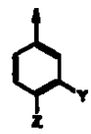
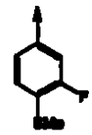
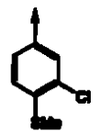
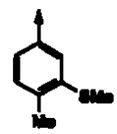
(20 ml) y se trató con HCl etéreo 1 M (2 ml) Después de agitar durante 1,5 h, el sólido se recogió por filtración para dar el producto (282 mg, 60%) como un sólido blanco; $\delta_H$ ($CD_3OD$, 400 MHz) 2,78 (3H, s), 2,98 (3H, s), 3,18 (2H, m), 4,29 (2H, s), 4,39 (2H, m), 6,74 (1H, d), 6,80-6,90 (3H, m), 7,22 (1H, d), 7,44 (1H, s), MS *m/z* ($TS^+$) 381 ($MH^+$)

Los compuestos de fórmula Ik, es decir los compuestos de fórmula general I en la que $R^1$ y $R^4$ son hidrógeno, $R^2$ es metilo y $R^5$ es -$NHSO_2Me$, mostrados en la Tabla 13, se prepararon de acuerdo con el Ejemplo 110 a partir de los precursores indicados

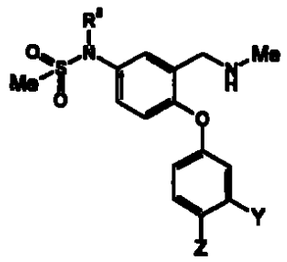


(Ik)

Tabla 13

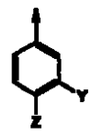
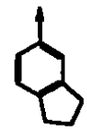
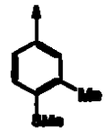
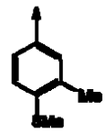
| Ejemplo | Precursor |  | Datos |
|---|---|---|---|
| 111 | Ejemplo 107 |  | $\delta_H$ ($CDCl_3$, 400 MHz) 2,40 (6H, s), 2,99 (3H, s), 3,70 (2H, s), 6,64 (2H, t), 6,88 (1H, d), 7,15 (1H, d), 7,25 (2H, s), MS *m/z* ($TS^+$) 371 ($MH^+$) |
| 112 | Ejemplo 106 |  | Sal de HCl $\delta_H$ ($CD_3OD$, 400 MHz) 2,55 (3H, s), 3,82 (3H, s), 3,04 (3H, s), 4,32 (2H, s), 6,97 (1H, d), 7,11 (1H, d), 7,23 (1H, s), 7,30 (1H, d), 7,39 (1H, d), 7,56 (1H, s), MS *m/z* ($TS^+$) 387 ($MH^+$) |
| 113 | Ejemplo 109 |  | Sal de HCl. $\delta_H$ ($CD_3OD$, 400 MHz) 2,24 (3H, s), 2,39 (3H, s), 2,76 (3H, s), 2,93 (3H, s), 4,25 (2H, s), 6,69 (1H, d), 6,82 (1H, d), 6,93 (1H, s), 7,17 (1H, d), 7,21 (1H, d), 7,43 (1H, s), MS *m/z* ($ES^+$) 367 ($MH^+$), ($ES^-$) 365 ($M-H^+$) |

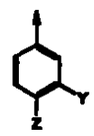
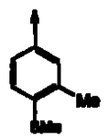
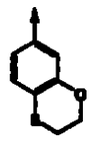
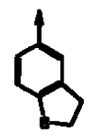
Los compuestos de fórmula Im, es decir los compuestos de fórmula general I en la que $R^1$ y $R^4$ son hidrógeno, $R^2$ es metilo y $R^5$ es $-NR^8SO_2Me$, mostrados en la Tabla 14, se prepararon de acuerdo con el Ejemplo 110 a partir de los precursores indicados



(Im)

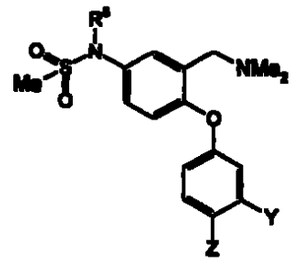
Tabla 14

| Ejemplo | Precursor | $R^8$ |  | Datos |
|---|---|---|---|---|
| 114 | Prep 85 | H |  | Sal de HCl $\delta_H$ ($CDCl_3$, 400 MHz) 2,09 (2H, m), 2,73 (3H, s), 2,88 (4H, t), 3,00 (3H, s), 4,21 (2H, s), 6,80 (2H, m), 6,88 (1H, s), 7,19 (1H, d), 7,34 (1H, d), 7,75 (1H, s); MS *m/z* ($TS^+$) 347 ($MH^+$) |
| 115 | Prep 84 | H |  | Sal de HCl. $\delta_H$ ($d_6$-DMSO, 400 MHz) 2,20 (3H, s), 2,40 (3H, s), 2,55 (3H, s), 2,97 (3H, s), 4,08 (2H, s), 6,80 (1H, d), 6,87 (1H, d), 6,91 (1H, s), 7,14 (1H, d), 7,20 (1H, d), 7,39 (1H, s), MS *m/z* ($TS^+$) 367 ($MH^+$) |
| 116[a] | Prep 88 | Me |  | $\delta_H$ ($CDCl_3$, 300 MHz) 2,17 (3H, s), 2,37 (3H, s), 2,48 (3H, s), 2,62 (3H, s) 2,97 (3H, s), 3,34 (3H, s), 4,23 (2H, s), 6,79 (1H, d), 6,94 (2H, s), 7,35 (2H, m), 7,81 (1H, s), MS *m/z* ($TS^+$) 381 ($MH^+$) |

| Ejemplo | Precursor | $R^8$ |  | Datos |
|---|---|---|---|---|
| 117 | Prep 89 |  |  | Sal de HCl. $\delta_H$ ($CDCl_3$, 400 MHz) 2,29 (3H, s), 2,39 (3H, s), 2,42 (3H, s), 2,94 (3H, s), 3,60 (2H, t), 3,74 (2H, t), 3,79 (2H, s), 6,78 (3H, m), 7,14 (2H, m), 7,41 (1H, s), MS *m/z* ($TS^+$) 410 ($MH^+$) |
| 118 | Prep 87 | H |  | $\delta_H$ ($CDCl_3$, 400 MHz) 2,42 (3H, s), 2,58-2,79 (2H, br), 2,94 (3H, s), 3,08 (2H, m), 3,71 (2H, s), 4,38 (2H, m), 6,39 (1H, s), 6,47 (1H, d), 6,82 (1H, d), 6,94 (1H, d), 7,07 (1H, d), 7,18 (1H, s), MS *m/z* ($TS^+$) 381 ($MH^+$) |
| 119 | Prep 86 | H |  | $\delta_H$ ($CD_3OD$, 400 MHz) 2,80 (3H, s), 3,00 (3H, s), 3,27 (2H, m), 3,40 (2H,m), 4,28 (2H, m), 6,85 (2H, m), 7,00 (1H, s), 7,20 (1H, d), 7,24 (1H, dd), 7,47 (1H, d), MS *m/z* ($TS^+$) 365 ($MH^+$) |

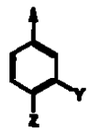
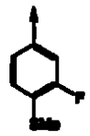
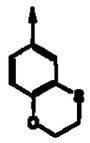
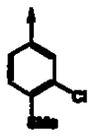
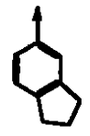
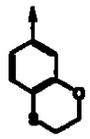
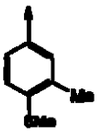
[a] Preparado también a partir del Ejemplo 108 por el método del Ejemplo 110

Los compuestos de fórmula In, es decir los compuestos de fórmula general I en la que $R^1$ y $R^2$ son metilo, $R^4$ es hidrógeno y $R^5$ es $-NR^8SO_2Me$, mostrados en la Tabla 15, se prepararon de acuerdo con el Ejemplo 12 a partir de los precursores indicados



(In)

Tabla 15

| Ejemplo | Precursor | $R^8$ |  | Datos |
|---|---|---|---|---|
| 120 | Ejemplo 111 | H |  | Sal de HCl: $\delta_H$ ($CD_3OD$, 400 MHz) 2,42 (3H, s), 2,89 (6H, s), 2,98 (3H, s), 4,37 (2H, s), 6,88 (2H, m), 6,97 (1H, d), 7,28 (1H, d), 7,39 (1H, t), 7,48 (1H, s), MS *m/z* (TS+) 385 ($MH^+$) |
| 121 (de la amina primaria) | Ejemplo 105 | H |  | $\delta_H$ ($CDCl_3$, 400 MHz) 3,00 (3H, s), 3,13 (2H, m), 3,87 (2H, s), 4,40 (2H, m), 6,62 (1H, d), 6,67 (1H, s), 6,79 (2H, d), 7,08 (1H, d), 7,25 (1H, d), MS *m/z* ($TS^+$) 367 ($MH^+$) |
| 122 (de la amina primaria) | Ejemplo 106 | H |  | Sal de HCl $\delta_H$ ($CD_3OD$, 400 MHz) 2,49 (3H, s), 2,93 (6H, s), 3,00 (3H, s), 4,41 (2H, s), 6,95 (1H, d), 7,07 (1H, d), 7,21 (1H, s), 7,33 (2H, m), 7,54 (1H, s), MS *m/z* ($TS^+$) 395 ($MH^+$) |
| 123 | Ejemplo 114 | H |  | Sal de HCl· $\delta_H$ ($CDCl_3$, 400 MHz) 2,12 (2H, m), 2,81 (6H, s), 2,91 (4H, t), 3,13 (3H, s), 4,25 (2H, s), 6,73 (1H, d), 6,83 (2H, m), 7,10 (1H, d), 7,39 (1H, d), 7,90 (1H, s); MS *m/z* ($TS^+$) 360 ($MH^+$) |
| 124 | Ejemplo 118 | H |  | $\delta_H$ ($CDCl_3$, 400 MHz) 2,22 (6H, s), 2,98 (3H, s), 3,07 (2H, m), 3,41 (2H, s), 4,38 (2H, m), 6,36 (1H, s), 6,45 (1H, d), 6,86 (1H, d), 6,92 (1H, d), 7,12 (1H, d), 7,27 (1H, s), MS *m/z* ($TS^+$) 395 ($MH^+$) |
| 125 | Ejemplo 117 |  |  | Sal de HCl $\delta_H$ ($CDCl_3$, 300 MHz) 2,38 (3H, s), 2,48 (3H, s), 2,86 (6H, brs), 3,15 (3H, s), 3,73 (2H, brs), 3,87 (2H, brs), 4,35 (2H, brs), 6,82 (3H, brs), 7,20 (2H, m), 7,41 (1H, d), MS *m/z* ($TS^+$) 425 ($MH^+$) |

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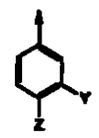
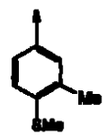
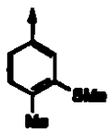
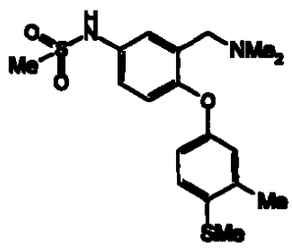
| Ejemplo | Precursor | $R^8$ |  | Datos |
|---|---|---|---|---|
| 126 (de la amina primaria) | Ejemplo 108 | Me |  | Sal de HCl $\delta_H$ ($CD_3OD$, 400 MHz) 2,29 (3H, s), 2,43 (3H, s), 2,89 (3H, s), 2,91 (6H, s), 3,26 (3H, s), 4,42 (2H, s), 6,84 (1H, d), 6,97 (2H, m), 7,27 (1H, d), 7,47 (1H, dd), 7,60 (1H, d), MS *m/z* ($TS^+$) 395 ($MH^+$) |
| 127 (de la amina primaria) | Ejemplo 109 | H |  | Sal de HCl $\delta_H$ ($CD_3OD$, 400 MHz) 2,27 (3H, s), 2,42 (3H, s), 2,94 (6H, s), 2,99 (3H, s), 4,42 (2H, s), 6,77 (1H, d), 6,89 (1H, d), 6,99 (1H, s), 7,19 (1H, d), 7,28 (1H, dd), 7,50 (1H, s); MS *m/z* ($TS^+$) 381 ($MH^+$), ($ES^+$) 381 ($MH^+$), ($ES^-$) 379 ($M-H^+$) |

**EJEMPLO 128**

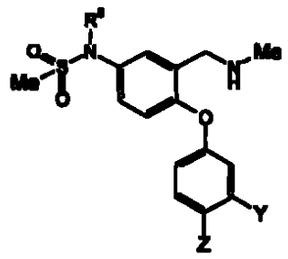
***N*-(3-{(Dimetilamino)metil}-4-[3-metil-4-(metilsulfanil)fenoxi]fenil}metanosulfonamida**



Se añadió cloruro de metanosulfonilo (371 µl, 4,79 mmol) a una solución de la anilina del Ejemplo 103 (725 mg, 2,4 mmol) y $Et_3N$ (1 ml, 7,17 mmol) en DCM (10 ml) a 0°C. Después de agitar a 0°C durante 1 h, la reacción se dejó calentar a temperatura ambiente antes de separar el disolvente a vacío Se añadió NaOH 2 M (10 ml) al residuo y la mezcla se agitó durante una noche La solución clara resultante se neutralizó por la adición de $NH_4Cl$ acuoso saturado y se extrajo con DCM (2 x 30 ml) Las capas orgánicas combinadas se secaron ($MgSO_4$) y se evaporaron para dar un aceite Éste se recogió en EtOAc (10 ml), la sal de HCl se precipitó por la adición de HCl etéreo 1 M y el producto (669 mg, 67%) se recogió por filtración, $\delta_H$ ($d_6$-DMSO,

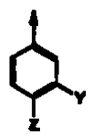
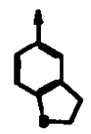
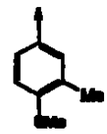
400 MHz) 2,23 (3H, s), 2,42 (3H, s), 2,75 (6H, s), 3,04 (3H, s), 4,38 (2H, s), 6,84 (1H, d), 6,93 (1H, d), 6,98 (1H, s), 7,17-7,25 (2H, m), 7,50 (1H, s), MS *m/z* ($ES^+$) 381 ($MH^+$)

Los compuestos de fórmula Ip, es decir los compuestos de fórmula general I en la que $R^1$ y $R^2$ son metilo, $R^4$ es hidrógeno y $R^5$ es $-NHSO_2R^9$, mostrados en la Tabla 16, se prepararon de acuerdo con el Ejemplo 128 a partir de los precursores indicados



(Ip)

Tabla 16

| Ejemplo | Precursor | $R^9$ |  | Datos |
|---|---|---|---|---|
| 129 | Ejemplo 104 | Me |  | Sal de HCl $\delta_H$ ($CD_3OD$, 400 MHz) 2,92 (6H, s), 2,99 (3H, s), 3,26 (2H, t), 3,40 (2H, t), 4,41 (2H, s), 6,88 (2H, d), 7,00 (1H, s), 7,10 (1H, d), 7,27 (1H, d), 7,50 (1H, s), MS *m/z* ($TS^+$) 381 ($MH^+$) |
| 130 | Ejemplo 103 | Et |  | Sal de HCl $\delta_H$ ($d_6$-DMSO, 400 MHz) 1,21 (3H, t), 2,23 (3H, s), 2,42 (3H, s), 2,74 (6H, s), 3,16 (2H, q), 4,26 (2H, s), 6,92 (1H, d), 6,92 (1H, d), 6,98 (1H, s), 7,18-7,25 (2H, m), 7,51 (1H, s), MS *m/z* ($ES^+$) 395 ($MH^+$) |

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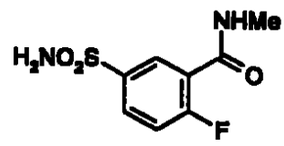
**PREPARACIONES**

**PREPARACIÓN 1**

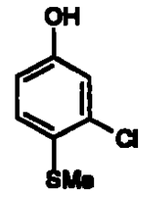
**5-(Aminosulfonil)-2-fluoro-N-metilbenzamida**




A una solución del ácido 5-(aminosulfonil)-2-fluorobenzoico [preparado de acuerdo con *Chem Pharm Bull* 1995, 43, 582-7] (22,98 g, 105 mmol) en THF (500 ml) a temperatura ambiente bajo nitrógeno, se añadió carbonildiimidazol (17 g, 105 mmol) Después de agitar durante 2,25 h, se añadió gota a gota una solución de metilamina en THF (2 M, 70 ml, 140 mmol) y la reacción se mantuvo con agitación durante 18 h La mezcla de reacción bruta se concentró a un bajo volumen y se añadió EtOAc (150 ml) al aceite denso resultante Esta mezcla se agitó y se formó un precipitado granular que se recogió por filtración Este producto bruto, contaminado con imidazol, se suspendió en DCM (300 ml) y se calentó a reflujo durante 5 h Después de enfriar a temperatura ambiente, la mezcla se filtró para dar el producto deseado (19,8 g, 81%) que contenía <2% en peso de imidazol; $^1$H NMR $\delta_H$ (300 MHz, $d_6$-MeOH) 2,97 (3H, s), 7,40 (1H, t), 8,05 (1H, m), 8,29 (1H, d), MS *m/z* ($TS^+$) 250 ($MNH_4^+$)

**PREPARACIÓN 2**

**3-Cloro-4-(metilsulfanil)fenol**




(i) Preparación de 2-cloro-1-(metilsulfanil)-4-nitrobenceno

A una solución de 4-fluoro-3-cloronitrobenceno (27 g, 156 mmol) en DMF

(150 ml) a temperatura ambiente se añadió sulfuro de 5-terc-butil-4-hidroxi-2-metil-fenilo (100 mg) seguido por tiometóxido de sodio (NaSMe) (10 g, 143 mmol) y la reacción se agitó durante 6 h La DMF se separó a vacío y el residuo se repartió entre éter (1 l) y agua (1 l) La capa etérea se lavó con agua (1 l) y salmuera (1 l), se secó ($MgSO_4$) y el disolvente se separó a presión reducida El residuo se purificó por cromatografía en columna ($SiO_2$, DCM pentano 1 5 polaridad creciente hasta 3 7) para dar el compuesto del título (15,22 g, 49%) como un sólido amarillo, $\delta_H$ (400 MHz, $CDCl_3$) 2,53 (3H, s), 7,20 (1H, d), 8,09 (1H, dd), 8,20 (1H, d)

(ii) Preparación de 3-cloro-4-(metilsulfanil)anilina

A una mezcla del compuesto anterior (14,08 g, 69 mmol) en ácido acético (300 ml) y agua (60 ml) se añadió polvo de hierro (23 g, 412 mmol) y la mezcla de reacción se agitó hasta que se hubo disuelto todo el material de partida La mezcla se dejó estar durante 1,5 h y luego el ácido acético se separó a presión reducida. El residuo se recogió en $NaHCO_3$ saturado (acuoso) (500 ml) y EtOAc (500 ml) y se filtró a través de Arbacel® Las capas se separaron, la fase acuosa se extrajo con EtOAc (300 ml) y los extractos orgánicos combinados se lavaron con salmuera, se secaron ($MgSO_4$) y el disolvente se separó a vacío para dar el compuesto del título (11,52 g, 96%) como un sólido beige, $\delta_H$ (400 MHz, $CDCl_3$) 2,38 (3H, s), 3,66 (2H, br), 6,53 (1H, dd), 6,70 (1H, d), 7,12 (1H, d), MS *m/z* ($ES^+$) 174 ($MH^+$)

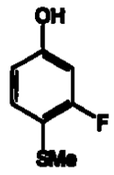
(iii) Preparación de 3-cloro-4-(metilsulfanil)fenol

La anilina anterior (11,5 g, 66,2 mmol) se disolvió en la mínima cantidad de THF (~15 ml) y se añadió agua (500 ml) con agitación vigorosa, seguida por $H_2SO_4$ concentrado (25 ml) La mezcla se enfrió en un baño de hielo y agua y se añadió con una pipeta una solución de $NaNO_2$ (5,0 g, 72,5 mmol) en agua helada (10 ml) introduciéndola por debajo la superficie de la mezcla de reacción La reacción se agitó a 0°C durante 1,5 h y la solución amarilla/parda resultante se decantó para separarla del sólido restante empleando un embudo de goteo que contenía hielo (~200 g). Esta solución se añadió a velocidad constante durante 7 min a una mezcla agitada vigorosamente de $Cu(NO_3)_2$ (230 g, 0,99 mol) y $Cu_2O$ (8,52 g, 67,4 mmol) en agua (1 l) a temperatura ambiente Una vez completada la adición, la mezcla se agitó durante 15 min más antes de ser extraída con éter (500 ml) El sólido rojo/pardo residual del matraz de reacción se recogió en MeOH (100 ml) y se diluyó con éter

(300 ml) antes de ser vertido en la capa acuosa de antes La capa etérea se separó y las capas orgánicas combinadas se extrajeron con NaOH 1 M (3 x 100 ml) Los extractos acuosos se acidularon con HCl concentrado y luego se extrajeron con éter (2 x 150 ml) Luego las capas etéreas se lavaron con salmuera, se secaron ($MgSO_4$) y el disolvente se separó a vacío para dar el fenol (5,465 g, 47%) como un sólido cristalino pardo, $\delta_H$ (400 MHz, $CDCl_3$) 2,44 (3H, s), 5,08 (1H, br), 6,77 (1H, d), 6,93 (1H, d), 7,18 (1H, d), MS *m/z* ($ES^-$) 173 $(M-H)^+$)

**PREPARACIÓN 3**

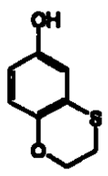
**3-Fluoro-4-(metilsulfanil)fenol**




Este compuesto se preparó utilizando un método similar al descrito anteriormente para la Preparación 2 partiendo de 3,4-difluoronitrobenceno comercialmente disponible, $\delta_H$ ($CDCl_3$, 300 MHz) 2,40 (3H, s), 5,03 (1H, br), 6,60 (2H, m), 7,27 (1H, m oscuro), MS *m/z* ($ES^-$) 157 $(M-H^+)$

**PREPARACIÓN 4**

**2,3-Dihidro-1,4-benzoxatiin-6-ol**

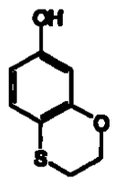



Se suspendieron 1,2-dibromoetano (2,3 ml, 26,7 mmol) y $K_2CO_3$ (8,21 g, 59,4 mmol) en acetona (250 ml) y se añadió una solución de 2-sulfanil-1,4-bencenodiol (preparado de acuerdo con *J Org Chem* 1990, 55, 2736) (4,22 g, 29,7 mmol) en acetona (50 ml) a lo largo de 4 h a la mezcla agitada Una vez terminada la adición, la agitación se continuó durante 10 h más antes de separar el disolvente a

vacío El residuo se repartió entre agua (50 ml) y EtOAc (50 ml), la capa acuosa se extrajo con EtOAc (50 ml) y las capas orgánicas combinadas se secaron ($MgSO_4$) y se evaporaron La purificación del residuo por cromatografía en columna [$SiO_2$, (pentano/EtOAc) 9 1] dio el compuesto del título (2,48 g, 55%) como aceite naranja pálido, $\delta_H$ ($CDCl_3$, 400 MHz) 3,08 (2H, m), 4,31 (2H, m), 4,44 (1H, s), 6,42 (1H, d), 6,49 (1H, s), 6,66 (1H, d); MS *m/z* ($ES^-$) 167 ($M-H^+$)

**PREPARACIÓN 5**

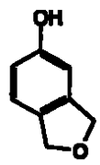
**2,3-Dihidro-1,4-benzoxatiin-7-ol**




El compuesto del título se preparó de una manera similar al compuesto de la Preparación 4 partiendo de 4-sulfanil-1,3-bencenodiol (preparado de acuerdo con *J Org Chem* 1979, 26, 4971-4973), $\delta_H$ ($CDCl_3$, 400 MHz) 3,05 (2H, t), 4,37 (2H, t), 6,32 (1H, s), 6,35 (1H, d), 6,84 (1H, d), MS *m/z* ($TS^+$) 169 ($MH^+$)

**PREPARACIÓN 6**

**1,3-Dihidro-2-benzofuran-5-ol**

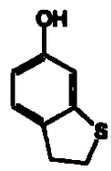



Se disolvió 1,3-dihidro-2-benzofuran-5-amina (preparada de acuerdo con el documento US 4000286) (2,7 g, 20 mmol) en una mezcla de agua (300 ml) y $H_2SO_4$ concentrado (21 ml), se enfrió a 0°C y se añadió $NaNO_2$ (1,43 g, 20,7 mmol) en agua (10 ml) a lo largo de 15 min Después de agitar a 0°C durante 1 h, la mezcla se mantuvo con agitación a 0°C durante 30 min y se añadió urea hasta que se observó una prueba negativa con almidón/papel KI. Luego la solución se vertió a lo largo de 2

min en una mezcla de agua (180 ml) y $H_2SO_4$ concentrado (12, 6 ml) a 90°C y se agitó a esta temperatura durante 1,5 h Luego la mezcla caliente se filtró y se dejó enfriar a temperatura ambiente La mezcla acuosa se extrajo con EtOAc (2 x 100 ml) y las capas orgánicas combinadas se secaron ($MgSO_4$) y se evaporaron para dar el fenol del título (974 mg, 36%) como un sólido cremoso, $\delta_H$ ($CDCl_3$, 400 MHz) 5,03 (4H, s), 6,71 (2H, m), 7,08 (1H, d)

**PREPARACIÓN 7**

**2,3-Dihidro-1-benzotiofen-6-ol**




(i) Preparación de 1,1-dióxido de 2,3-dihidro-1-benzotiofen-6-ol

Una suspensión de 1,1-dióxido de 2,3-dihidro-1-benzotiofen-6-amina [preparada de acuerdo con *J Am Chem Soc* 1955, 77, 5939] (15,73 g, 85,8 mmol) en agua (500 ml) y $H_2SO_4$ concentrado (35 ml) se calentó hasta alcanzar una solución La mezcla se enfrió a 0°C y luego se añadió una solución de $NaNO_2$ (6,22 g, 90 mmol) en agua (15 ml) a lo largo de 5 min La reacción se agitó a 0°C durante 1 h y luego se añadió urea, para separar el exceso de nitrito, hasta que se obtuvo un ensayo negativo con almidón/papel KI La mezcla se dejó calentar a temperatura ambiente, luego se añadió con agitación a una mezcla de $H_2SO_4$ concentrado (55 ml) y agua (750 ml) a 90°C La reacción se calentó de nuevo a 90°C y se agitó a esta temperatura durante 30 min La mezcla de reacción caliente se filtró a través de Arbocel® y luego se agitó a temperatura ambiente durante una noche. La mezcla acuosa se extrajo con éter (2,5 l) y luego con EtOAc (5 x 500 ml) y las capas orgánicas combinadas se secaron ($MgSO_4$) y se evaporaron para dar el fenol deseado (12,7 g, 80%) que se utilizó sin más purificación; $\delta_H$ ($CDCl_3$, 400 MHz) 3,30 (2H, m), 3,50 (2H, m), 7,05 (1H, m), 7,14 (1H, s), 7,23 (1H, m); MS *m/z* ($ES^-$) 183 ($M\text{-}H^+$)

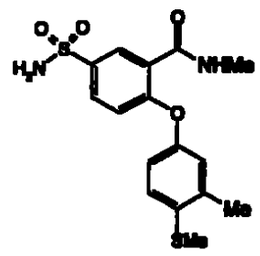
(ii) Preparación de 2,3-dihidro-1-benzotiofen-6-ol

Se añadió una solución de la sulfona de la etapa (i) (4,84 g, 26,3 mmol) en

tolueno (100 ml) y THF (70 ml) a una solución de DIBAL en tolueno (1 M, 100 ml, 100 mmol) y luego la mezcla se calentó a reflujo durante 16 h Después de enfriar a temperatura ambiente, se añadió cuidadosamente EtOH (75 ml) seguido por agua (100 ml) con agitación Se añadió HCl 6 M a la suspensión densa resultante y se separó la capa orgánica La capa acuosa se extrajo con EtOAc (3 x 150 ml) y las capas orgánicas combinadas se secaron ($MgSO_4$) y se evaporaron para dar un sólido beige. La purificación por cromatografía en columna [$SiO_2$, DCM/MeOH/$NH_3$ 880 (97 3 0,25) aumentando la polaridad a (95·5·0,5) proporcionó el fenol del título deseado como un sólido beige (1,85 g, 53%), $\delta_H$ ($CD_3OD$, 400 MHz) 3,13 (2H, t), 3,30 (2H, m), 6,41 (1H, d), 6,60 (1H, s), 6,98 (1H, d); MS *m/z* ($ES^-$) 151 ($M-H^+$)

**PREPARACIÓN 8**

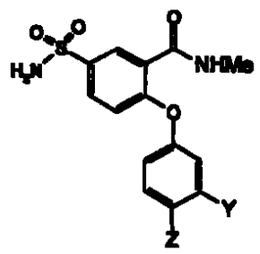
**5-(Aminosulfonil)-2-[3-metil-4-(metilsulfanil)fenoxi]-*N*-metilbenzamida**



La fluoroamida de la Preparación 1 (732 mg, 3,15 mmol) se trató con 4-(metiltio)-*m*-cresol (comercialmente disponible) (535 mg, 3,47 mmol) y carbonato de potasio (457 mg, 3,31 mmol) en DMF (10 ml). La mezcla se calentó a 100°C durante 5 horas El disolvente se separó por evaporación a presión reducida y el residuo se trató con HCl 2 M (10 ml) La suspensión resultante se extrajo varias veces con diclorometano. Las capas combinadas de diclorometano contenían una suspensión y se evaporaron para dar un residuo sólido El residuo se trituró con éter (5 ml) y el sólido restante se lavó con éter (3 x 10 ml) para dar un sólido blanquecino (765 mg, 66%), $\delta_H$ (300 MHz, $d_6$-DMSO) 2,28 (3H, s), 2,48 (3H, s), 2,70 (3H, d), 6,90 (1H, d), 7,02 (1H, d), 7,03 (1H, s), 7,30 (1H, d), 7,35 (2H, s), 7,79 (1H, d), 8,10 (1H, d), 8,30 (1H, m), MS *m/z* ($TS^+$) 367 ($MH^+$), 385 ($MNH_4^+$)

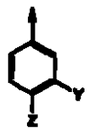
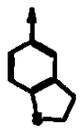
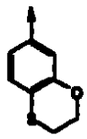
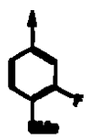
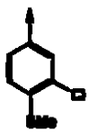
**PREPARACIONES 9-18**

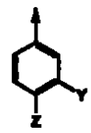
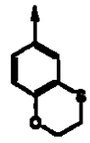
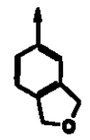
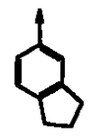
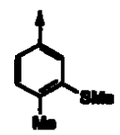
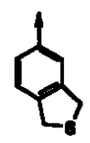
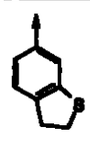
Los compuestos de fórmula Va, es decir los compuestos de fórmula general V en la que T es -C(=O)NHMe, $R^4$ es hidrógeno y $R^5$ es $-SO_2NH_2$, mostrados en la Tabla 17, se prepararon de acuerdo con la Preparación 8 utilizando la sulfonamida de la Preparación 1 y el fenol indicado



(Va)

Tabla 17

| Preparación | Fenol precursor |  | Datos |
|---|---|---|---|
| 9 | *Synth Commun* 1991, 21, 959-964 |  | $\delta_H$ ($d_6$-DMSO, 400 MHz) 2,80 (3H, d), 3,20 (2H, t), 3,40 (2H, t), 6,90 (1H, m), 7,05 (1H, s), 7,25 (1H, d), 7,35 (1H, s), 7,80 (1H, m), 8,10 (1H, s), 8,30 (1H, brs); MS *m/z* ($TS^+$) 365 ($MH^+$) |
| 10 | Prep 5 |  | $\delta_H$ ($CD_3OD$, 400 MHz) 2,92 (3H, s), 3,17 (2H, m), 4,41 (2H, m), 6,60-6,70 (2H, m), 6,97 (1H, d), 7,18 (1H, d), 7,90 (1H, d), 8,31 (1H, s); MS *m/z* ($TS^+$) 381 ($MH^+$) |
| 11 | Prep. 3 |  | $\delta_H$ ($CD_3OD$, 400 MHz) 2,43 (3H, s), 2,97 (1H, s), 6,89 (2H, m), 7,00 (1H, d), 7,39 (1H, br), 7,88 (1H, brd), 8,23 (1H, s), MS *m/z* ($ES^+$) 371 ($MH^+$) |
| 12 | Prep 2 |  | $\delta_H$ ($CD_3OD$, 400 MHz) 2,85 (3H, s), 2,99 (3H, s), 6,99 (1H, d), 7,09 (1H, d), 7,22 (1H, s), 7,37 (1H, d), 7,92 (1H, d), 8,28 (1H, s), MS *m/z* ($ES^+$) 387 ($MH^+$) |

| Preparación | Fenol precursor |  | Datos |
|---|---|---|---|
| 13 | Prep 4 |  | $\delta_H$ ($CD_3OD$, 400 MHz) 2,87 (3H, brs), 3,13 (2H, brs), 4,37 (2H, brs), 6,73 (1H, brs), 6,82 (3H, m), 7,82 (1H, s), 8,28 (1H, brs), MS *m/z* ($ES^+$) 381 ($MH^+$) |
| 14 | Prep 6 |  | $\delta_H$ ($d_6$-DMSO, 400 MHz) 2,79 (3H, s), 4,98 (4H, brs), 6,92 (1H, d), 7,04 (1H, d), 7,09 (1H, s), 7,37 (3H, m), 7,79 (1H, m), 8,10 (1H, s), 8,30 (1H, s); MS *m/z* ($TS^+$) 349 ($MH^+$) |
| 15 | Comercial |  | $\delta_H$ ($CD_3OD$, 400 MHz) 2,08 (2H, m), 2,90 (7H, m), 6,84 (2H, m), 6,97 (1H, s), 7,23 (1H, d), 7,81 (1H, d), 8,31 (1H, s), MS *m/z* ($TS^+$) 347 ($MH^+$) |
| 16 | *Tetrahedron* 1982, 38, 2721 y *Synthesis* 1982, 475 |  | Producto utilizado sin purificación |
| 17 | Prep 101 |  | $\delta_H$ ($CD_3OD$, 400 MHz) 2,88 (3H, s), 4,20 (4H, s), 6,89 (1H, d), 6,97 (1H, d), 7,01 (1H, s), 7,30 (1H, d), 7,84 (1H, d), 8,28 (1H, s), MS *m/z* ($TS^+$) 382 ($MNH_4^+$) |
| 18 | Prep 7 |  | $\delta_H$ (DMSO-$d_6$, 400 MHz) 2,78 (3H, d), 3,23 (2H, m), 3,40 (2H, m), 6,75 (1H, dd), 6,90 (1H, d), 7,02 (1H, s), 7,27 (1H, d), 7,34 (1H, d), 7,80 (1H, d), 8,10 (1H, s), 8,26 (1H, br, d); MS *m/z* ($ES^-$) 363 ($M\text{-}H^+$) |

157

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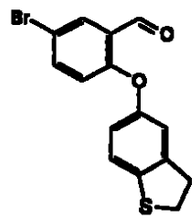
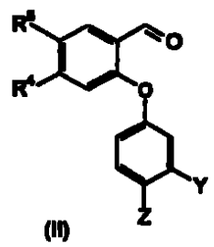
**PREPARACIÓN 19**

**5-Bromo-2-(2,3-dihidro-1-benzotien-5-iloxi)benzaldehído**



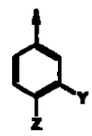
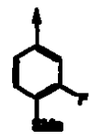
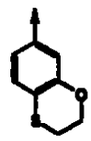
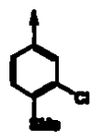
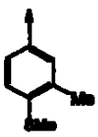
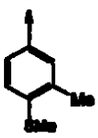
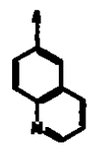
Una mezcla de 5-bromo-2-fluorobenzaldehído (1,08 g, 5,32 mmol), 5-hidroxi-2,3-dihidrobenzotiofeno (preparado como se describe en *Synth Commun.* 1991, 21, 959-964) (808 mg, 5,31 mmol) y $K_2CO_3$ (1,47 g, 10,6 mmol) en DMF (5 ml) se calentó a 90°C durante 16 h Después de enfriar a temperatura ambiente, la mezcla se repartió entre agua (50 ml) y éter (50 ml), extrayéndose la capa acuosa con éter (50 ml) Los extractos orgánicos combinados se lavaron con agua (50 ml), se secaron ($MgSO_4$) y se evaporaron El residuo se purificó por cromatografía en columna [$SiO_2$, (pentano/EtOAc) 9 1], y luego se trituró con éter, para dar el producto (1,1 g, 62%) como un sólido amarillo pálido, $\delta_H$ ($CDCl_3$, 400 MHz) 3,28 (2H, t), 3,41 (2H, t), 6,78 (1H, d), 6,84 (1H, d), 6,92 (1H, s), 7,20 (1H, d), 7,58 (1H, d), 8,00 (1H, s), 10,43 (1H, s)

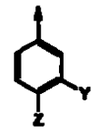
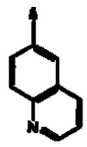
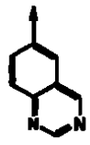
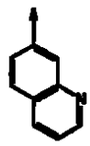
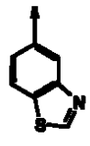
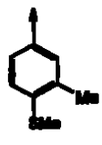
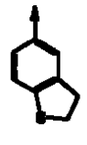
Los compuestos de la fórmula general II, mostrados en la Tabla 18, se prepararon de acuerdo con la Preparación 19 haciendo reaccionar el fenol indicado con el 2-fluorobenzaldehído requerido En la mayoría de los casos, el producto de reacción bruto después del tratamiento acuoso se utilizó directamente en las etapas subsiguientes sin más purificación

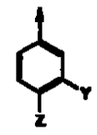
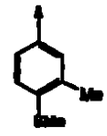
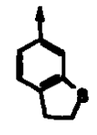
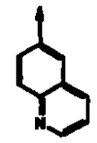


(II)

Tabla 18

| Preparación | Fenol precursor | $R^4$ | $R^5$ |  | Datos |
|---|---|---|---|---|---|
| 20 | Prep 3 | H | Br |  | $\delta_H$ ($CDCl_3$, 300 MHz) 2,48 (3H, s), 6,81 (3H, m), 7,37 (1H, t), 7,64 (1H, d), 8,06 (1H, s), 10,39 (1H, s), MS *m/z* ($TS^+$) 358, 360 ($MNH_4^+$) |
| 21 | Prep 5 | H | Br |  | $\delta_H$ ($CDCl_3$, 400 MHz) 3,13 (2H,m), 4,42 (2H, m), 6,55 (1H, s), 6,59 (1H, d), 6,81 (1H, d), 7,04 (1H, d), 7,59 (1H, d), 8,01 (1H, s), 10,40 (1H, s) |
| 22 | Prep 2 | H | Br |  | $\delta_H$ ($CDCl_3$, 400 MHz) 2,43 (3H, s), 6,78 (1H, d), 6,94 (1H, d), 7,08 (1H, s), 7,19 (1H, d), 7,59 (1H, d), 8,00 (1H, s) |
| 23 | Comercial | H | Br |  | $\delta_H$ ($CDCl_3$, 300 MHz) 2,35 (3H, s), 2,49 (3H, s), 6,78 (1H, d), 6,90 (2H, s), 7,22 (1H, d), 7,59 (1H, d), 8,05 (1H, s), 10,45 (1H, s); MS *m/z* ($TS^+$) 356, 354 ($MNH_4^+$) |
| 24 | Comercial | H | MeO |  | $\delta_H$ ($CDCl_3$, 300 MHz) 2,35 (3H, s), 2,45 (3H, s), 3,87 (3H, s), 6,82 (1H, d), 6,83 (1H, s), 6,92 (1H, d), 7,13 (1H, dd), 7,19 (1H, d), 7,40 (1H, d), 10,40 (1H, s); MS *m/z* ($TS^+$) 389 ($MH^+$) |
| 25 | Comercial | H | F |  | $\delta_H$ ($CDCl_3$, 300 MHz) 7,02 (1H, dd), 7,21 (1H, s), 7,30 (1H, m), 7,40 (1H, m), 7,54 (1H, d), 7,66 (1H, dd), 8,01 (1H, d), 8,18 (1H, d), 8,88 (1H, d), 10,43 (1H, s), MS *m/z* ($ES^+$) 268 ($MH^+$) |

| Preparación | Fenol precursor | $R^4$ | $R^5$ |  | Datos |
|---|---|---|---|---|---|
| 26 | Comercial | H | H |  | $\delta_H$ ($CDCl_3$, 400 MHz) 6,97 (1H, d), 7,21-7,27 (2H, m), 7,92-8,01 (2H, m), 8,11 (1H, d), 8,83 (1H, d), 10,50 (1H, s), MS *m/z* ($ES^+$) 272 ($MNa^+$), ($ES^-$) 248 ($M-H^+$) |
| 27 | *J Chem Soc* 1952, 4985-4993 | H | H |  | $\delta_H$ ($CDCl_3$, 300 MHz) 7,08 (1H, d), 7,36 (2H, m), 7,65 (1H, m), 7,79 (1H, dd), 8,01 (1H, d), 8,13 (1H, d), 9,29 (1H, d), 10,45 (1H, s), MS *m/z* ($TS^+$) 251 ($MH^+$) |
| 28 | Comercial | H | H |  | $\delta_H$ ($CDCl_3$, 400 MHz) 7,09 (1H, d), 7,28 (1H, m), 7,35 (1H, m), 7,40 (1H, m), 7,50 (1H, br), 7,59 (1H, m), 7,86 (1H, dd), 7,99 (1H, dt), 8,15 (1H, d), 8,86 (1H, m), 10,46 (1H, s); MS *m/z* 250 ($MH^+$) |
| 29 | *Chem Pharm Bull* ,1978, 26, 1443 | H | H |  | $\delta_H$ ($CDCl_3$, 400 MHz) 6,91 (1H, d), 7,25 (2H, m), 7,55 (2H, m), 7,96 (1H, m), 8,12 (1H, d), 8,95 (1H, s), 10,5 (1H, s), MS *m/z* 256 ($MH^+$) |
| 30 | Comercial | H | H |  | $\delta_H$ ($CDCl_3$, 300 MHz) 2,35 (3H, s), 3,44 (3H, s), 6,87 (3H, m), 7,17 (2H, m), 7,50 (1H, t), 7,92 (1H, dd), 10,52 (1H, s); MS *m/z* ($TS^+$) 259 ($MH^+$) |
| 31 | *Synth Commun* 1991, 21, 959-964 | H | H |  | $\delta_H$ ($CDCl_3$, 400 MHz) 3,26 (2H, t), 3,39 (2H, m), 6,85 (2H, t), 6,92 (1H, s), 7,18 (2H, m), 7,48 (1H, t), 7,92 (1H, d), 10,51 (1H, s), MS *m/z* ($TS^+$) 257 ($MH^+$) |

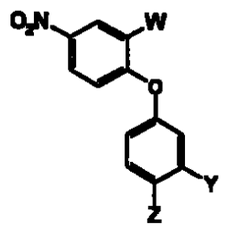
| Preparación | Fenol precursor | $R^4$ | $R^5$ |  | Datos |
|---|---|---|---|---|---|
| 32 | Comercial | Br | H |  | $\delta_H$ ($CDCl_3$, 400 MHz) 2,36 (3H, s), 2,44 (3H, s), 6,88 (2H, m), 6,96 (1H, s), 7,18-7,25 (2H, obs), 7,77 (1H, d), 10,43 (1H, s) |
| 33 | Prep 7 | H | Br |  | $\delta_H$ ($CDCl_3$, 400 MHz) 3,27 (2H, m), 3,42 (2H, m), 6,67 (1H, d), 6,80 (1H, d), 6,90 (1H, s), 7,16 (1H, d), 7,58 (1H, d), 8,01 (1H, s), 10,41 (1H, s), MS *m/z* ($TS^+$) 354 ($MNH_4^+$) |
| 34[a] | Comercial | H | CN |  | $\delta_H$ (DMSO-$d_6$, 300 MHz) 6,26 (1H, d), 6,43 (1H, d), 7,49 (1H, d), 7,65-7,71 (2H, m), 7,88 (1H, d), 8,07 (1H, d), 8,17 (1H, s), 8,73 (1H, d), 8,89 (1H, s), MS *m/z* (ES-) 273 (M-H), ($ES^+$) 275 ($MH^+$) |

[a] El 4-fluoro-3-formilbenzonitrilo se sintetizó de acuerdo con *Synth Commun* 1997, 27(7), 1199 y *J Org Chem* 1961, 26, 2522.

El producto de la Preparación 30 también se preparó como sigue.

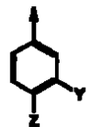
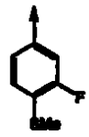
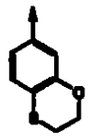
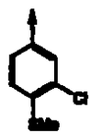
Se añadieron sucesivamente carbonato de potasio (334,1 g, 2,42 mmol) y 4-(metiltio)-m-cresol (273,4 g, 1,77 mmol) a DMF (2 l). Luego se añadió 2-fluorobenzaldehído (200 g, 1,61 mol) a la suspensión y la mezcla se calentó en el intervalo de 100-110°C Después de 48 h, la mezcla de reacción se dejó enfriar a temperatura ambiente y se añadió agua (1,2 l) La solución se enfrió por debajo de 10°C y el pH se ajustó a 5 con HCl concentrado (0,37 l), manteniendo la temperatura por debajo de 10°C. Se añadieron agua (0,15 l) y diclorometano (0,9 l) y se agitó la mezcla Se separaron las capas y la capa orgánica se lavó con agua (4 x 0,75 l) El disolvente se destiló para separar azeotrópicamente el agua Se añadió diclorometano de nueva aportación, en caso necesario Luego la solución en diclorometano, seca, se concentró a vacío para dar el producto bruto como un aceite (422 g, 100%).

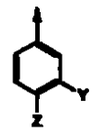
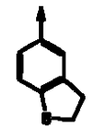
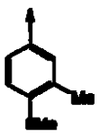
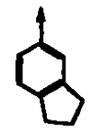
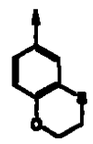
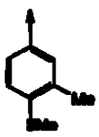
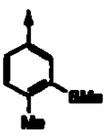
Los compuestos de fórmula IX, mostrados en la Tabla 19, se prepararon de acuerdo con la Preparación 19, utilizando o bien 2-cloro-5-nitrobenzaldehído o 2-cloro-5-nitrobenzonitrilo con el fenol indicado Para estas reacciones, habitualmente era suficiente un tiempo de reacción más corto (aproximadamente 2-3 h) para conseguir una buena conversión En la mayoría de los casos, el producto bruto de reacción después del tratamiento acuoso se utilizó directamente en las etapas subsiguientes sin más purificación.



(IX)

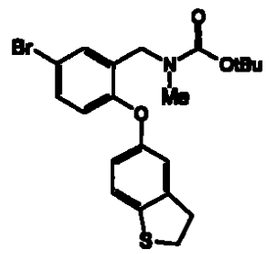
Tabla 19

| Preparación | Precursor | W |  | Datos |
|---|---|---|---|---|
| 35 | Prep 3 | -C≡N |  | $\delta_H$ ($CDCl_3$, 400 MHz) 2,48 (3H, s), 6,85-6,95 (3H, m), 7,28 (1H, t), 8,30 (1H, d), 8,52 (1H, s) |
| 36 | Prep 5 |  |  | $\delta_H$ ($CDCl_3$, 400 MHz) 3,14 (2H, d), 4,43 (2H, d), 6,62 (2H, m), 6,92 (1H, d), 7,08 (1H, d), 8,27 (1H, d), 8,72 (1H, s), 10,51 (1H, s), MS *m/z* ($TS^+$) 318 ($MH^+$) |
| 37 | Prep 2 | -C≡N |  | $\delta_H$ ($CDCl_3$, 300 MHz) 2,55 (3H, s), 6,94 (1H, d), 7,09 (1H, dd), 7,22 (1H, d), 7,27 (1H, d), 8,36 (1H, dd), 8,60 (1H, d), MS *m/z* ($TS^+$) 338 ($MNH_4^+$) |

| Preparación | Precursor | W |  | Datos |
|---|---|---|---|---|
| 38 | *Synth Commun*, 1991, 21, 959-964 |  |  | $\delta_H$ ($CDCl_3$, 400 MHz) 3,29 (2H, m), 3,42 (2H, m), 6,88 (2H, m), 6,96 (1H, s), 7,23 (1H, d), 8,26 (1H, d), 8,75 (1H, s), 10,54 (1H, s) |
| 39 | Comercial |  |  | $\delta_H$ ($CDCl_3$, 400 MHz) 2,38 (3H, s), 2,50 (3H, s), 6,92 (1H, d), 6,99 (2H, m), 7,24 (1H, d), 8,28 (1H, dd), 8,78 (1H, d), 10,57 (1H, s) |
| 40 | Comercial |  |  | $\delta_H$ ($CDCl_3$, 400 MHz) 2,18 (2H, m), 2,95 (4H, t), 6,90 (2H, m), 7,29 (1H, d), 8,27 (1H, d), 8,79 (1H, s), 10,59 (1H, s), MS *m/z* ($TS^+$) 301 ($MNH_4^+$) |
| 41 | Prep 4 | -C≡N |  | $\delta_H$ ($CDCl_3$, 400 MHz) 3,18 (2H, t), 4,44 (2H, t), 6,76 (1H, d), 6,86 (1H, s), 6,92 (2H, d), 8,32 (1H, d), 8,57 (1H, s); MS *m/z* ($TS^+$) 332 ($MNH_4^+$) |
| 42 | Comercial | -C≡N |  | $\delta_H$ ($CDCl_3$, 400 MHz) 2,32 (3H, s), 2,47 (3H, s), 6,87 (1H, d), 6,94 (2H, m), 7,21 (1H, d), 8,26 (1H, dd), 8,51 (1H, d), MS *m/z* ($TS^+$) 318 ($MNH_4^+$) |
| 43 | *Tetrahedron* 1982, 38, 2721 y *Synthesis* 1982, 475 | -C≡N |  | $\delta_H$ ($CDCl_3$, 400 MHz) 2,31 (3H, s), 2,41 (3H, s), 6,76 (1H, dd), 6,85 (2H, m), 7,19 (1H, d), 8,24 (1H, dd), 8,53 (1H, d); MS *m/z* ($TS^+$) 318 ($MNH_4^+$) |

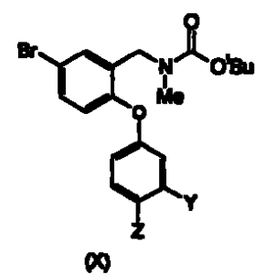
**PREPARACIÓN 44**

**5-Bromo-2-(2,3-dihidro-1-benzotien-5-iloxi)bencil(metil)carbamato de terc-butilo**



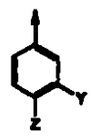
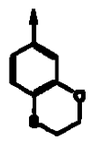
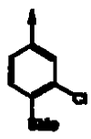
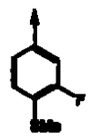
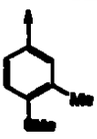
La sal de hidrocloruro del Ejemplo 36 (1,04 g, 2,7 mmol) se suspendió en DCM (12 ml) y se añadió $Et_3N$ (750 µl, 5,38 mmol), seguida por dicarbonato de di-terc-butilo (766 mg, 351 mmol) Después de agitar a temperatura ambiente durante 20 min, la reacción se inactivó por la adición de HCl 0,2 M (20 ml) La mezcla bien agitada se separó y la capa acuosa se extrajo con DCM (10 ml) Las capas orgánicas combinadas se secaron ($MgSO_4$) y se evaporaron para dar el producto (se presume rendimiento cuantitativo) como un aceite incoloro que se utilizó sin más purificación, $\delta_H$ ($CDCl_3$, 400 MHz) 1,56 (9H, s), 2,82-2,98 (3H, brd), 3,23 (2H, t), 3,40 (2H, t), 4,44 (2H, brd), 6,71 (2H, d), 6,79 (1H, s), 7,12 (1H, d), 7,29 (1H, d), 7,39 (1H, s).

Los compuestos de fórmula X, mostrados en la Tabla 20, se prepararon de acuerdo con la Preparación 44 partiendo de los precursores indicados



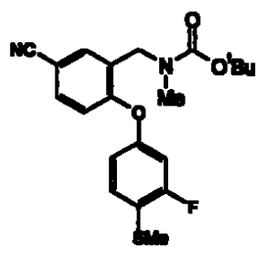
(X)

Tabla 20

| Preparación | Precursor |  | Datos |
|---|---|---|---|
| 45 | Ejemplo 38 |  | $\delta_H$ ($CDCl_3$, 400 MHz) 1,41 (9H, brs), 2,81 (3H, m), 3,07 (2H, m), 4,36 (4H, m), 6,38 (1H, s), 6,43 (1H, d), 6,71 (1H, d), 6,92 (1H, d), 7,26 (1H, d), 7,34 (1H, s), MS *m/z* ($ES^+$) 468 ($MH^+$) |
| 46 | Ejemplo 39 |  | $\delta_H$ ($CDCl_3$, 400 MHz) 1,48 (9H, s), 2,41 (3H, s), 2,82 (3H, brd), 4,39 (2H, brd), 6,73 (1H, d), 6,80 (1H, d), 6,93 (1H, s), 7,04 (1H, d), 7,32 (1H, d), 7,39 (1H, s), MS *m/z* ($TS^+$) 474 ($MH^+$) |
| 47 | Ejemplo 37 |  | $\delta_H$ ($CDCl_3$, 300 MHz) 1,46 (9H, brs), 2,46 (3H, s), 2,89 (3H, brs), 4,41 (2H, brs), 6,68 (2H, m), 6,82 (1H, d), 7,27 (1H, obs), 7,40 (1H, d), 7,43 (1H, s), MS *m/z* ($TS^+$) 458 ($MH^+$) |
| 48 | Ejemplo 44 |  | $\delta_H$ ($CDCl_3$, 300 MHz) 1,45 (9H, br), 2,38 (3H, s), 2,44 (3H, s), 2,90 (3H, br), 4,47 (2H, br), 6,70-6,81 (3H, m), 7,20 (1H, d), 7,24-7,58 (2H, m) |

**PREPARACIÓN 49**

**5-Ciano-2-[3-fluoro-4-(metilsulfanil)fenoxi]bencil(metil)carbamato de terc-butilo**

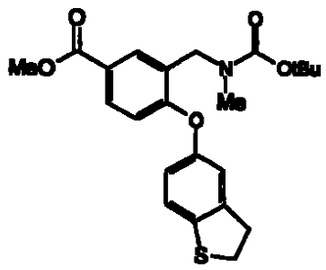


El compuesto del título se preparó a partir del bromuro de la Preparación 47 por el método del Ejemplo 78; $\delta_H$ ($CDCl_3$, 300 MHz) 1,48 (9H, brs), 2,50 (3H, s), 2,93 (3H, brs), 4,55 (2H, brs), 6,79 (2H, m), 6,88 (1H, d), 7,35 (1H, t), 7,53 (1H, d),

7,59 (1H, s), MS *m/z* ($TS^+$) 403 ($MH^+$)

**PREPARACIÓN 50**

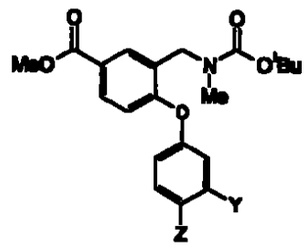
**3-{[(terc-Butoxicarbonil)(metil)amino]metil}-4-(2,3-dihidro-1-benzotien-5-iloxi)benzoato de metilo**



Una mezcla del bromuro de la Preparación 44 (1,22 g, 2,7 mmol), $Et_3N$ (1,13 ml, 8,11 mmol) y diclorobis(trifenilfosfina)paladio (II) (190 mg, 0,27 mmol) en MeOH (14 ml) se calentó a 80°C a una presión de CO de 7 kg/cm$^2$ durante 18 h El análisis por tlc indicó que la reacción no era completa, por lo que se añadió una porción adicional de catalizador (190 mg, 0,27 mmol) y la mezcla se calentó a 100°C a una presión de 7 kg/cm$^2$ de CO durante 24 h La mezcla se diluyó con EtOAc (20 ml) y se filtró a través de un tapón de gel de sílice, eluyendo con EtOAc en exceso El disolvente se separó a vacío y el residuo se repartió entre EtOAc (50 ml) y una mezcla 2 1 de agua $NH_3$ 880 (50 ml) La capa acuosa se extrajo con EtOAc (25 ml) y las capas orgánicas combinadas se secaron ($MgSO_4$) y se evaporaron. La purificación por cromatografía en columna [$SiO_2$, (pentano/EtOAc) 4·1] dio el producto (970 mg, 84%) como un aceite, $\delta_H$ ($CDCl_3$, 400 MHz) 1,42 (9H, s), 2,90 (3H, brs), 3,22 (2H, t), 3,38 (2H, t), 3,84 (3H, s), 4,50 (2H, brd), 6,74 (2H, d), 6,82 (1H, s), 7,13 (1H, d), 7,82 (1H, d), 7,93 (1H, brd), MS *m/z* ($ES^+$) 430 ($MH^+$)

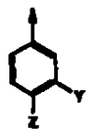
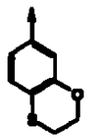
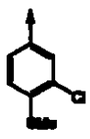
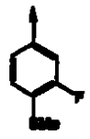
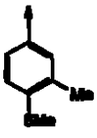
Los compuestos de fórmula XI, mostrados en la Tabla 21, se prepararon de acuerdo con la Preparación 50 partiendo de los precursores indicados.

166



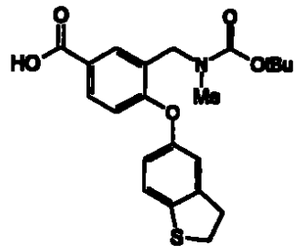
(XI)

Tabla 21

| Preparación | Precursor |  | Datos |
|---|---|---|---|
| 51 | Prep 45 |  | $\delta_H$ ($CDCl_3$, 400 MHz) 1,42 (9H, s), 2,86 (2H, m), 3,07 (2H, m), 3,85 (3H, s), 4,37 (2H, m), 4,48 (2H, m), 6,48 (2H, m), 6,79 (1H, d), 6,97 (1H, d), 7,83 (1H, d), 7,95 (1H, s); MS *m/z* ($ES^+$) 446 ($MH^+$) |
| 52 | Prep 46 |  | $\delta_H$ ($CDCl_3$, 400 MHz) 1,43 (9H, brs), 2,47 (3H, s), 2,88 (3H, brd), 3,90 (3H, s), 4,51 (2H, brd), 6,81 (1H, d), 6,91 (1H, d), 7,06 (1H, s), 7,20 (1H, d),7,89 (1H, d), 7,98 (1H, brd), MS *m/z* ($TS^+$) 469 ($MNH_4^+$) |
| 53 | Prep 47 |  | $\delta_H$ ($CDCl_3$, 300 MHz) 1,47 (9H, brs), 2,46 (3H, s), 2,91 (3H, brs), 3,94 (3H, s), 4,52 (2H, brs), 6,78 (2H, m), 6,91 (1H, d), 7,35 (1H, m), 7,92 (1H, d), 8,02 (1H, brs), MS *m/z* ($TS^+$) 453 ($MNH_4^+$) |
| 54 | Prep 48 |  | $\delta_H$ ($CDCl_3$, 300 MHz) 1,44 (9H, s), 2,37 (3H, s), 2,47 (3H, s), 2,94 (3H, br), 3,90 (3H, s), 4,73 (2H, br), 6,79-6,87 (3H, m), 7,20 (1H, d), 7,86 (1H, d), 8,00 (1H, br), MS *m/z* ($ES^+$) 454 ($MNa^+$) |

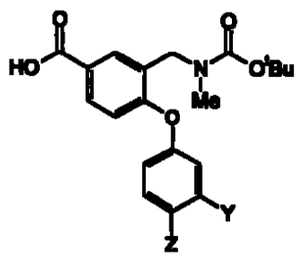
**PREPARACIÓN 55**

**Ácido 3-{[(terc-butoxicarbonil)(metil)amino]metil}-4-(2,3-dihidro-1-benzotien-5-iloxi)-benzoico**



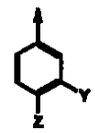
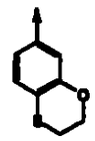
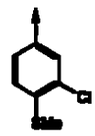
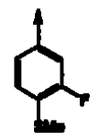
Una solución del éster de la Preparación 50 (970 mg, 2,26 mmol) en THF (20 ml) y LiOH 1 M (20 ml) se calentó a reflujo durante 16 h Después de enfriar a temperatura ambiente, el THF se separó a vacío, el residuo se neutralizó con $NH_4Cl$ acuoso saturado y la mezcla se extrajo con DCM (100 ml) y luego con éter (100 ml) Las capas orgánicas combinadas se secaron ($MgSO_4$) y se evaporaron para dar una espuma blanca (960 mg) que se utilizó sin más purificación, $\delta_H$ ($CDCl_3$, 400 MHz) 1,30 (9H, s), 2,78 (3H, brs), 3,20 (2H, brs), 3,38 (2H, t), 4,41 (2H, m), 6,62 (2H, m), 6,78 (1H, m), 7,10 (1H, m), 7,84 (1H, m), 7,99 (1H, m), MS *m/z* ($ES^-$) 414 (M-H)

Los compuestos de fórmula XII, mostrados en la Tabla 22, se prepararon de acuerdo con la Preparación 55 a partir de los precursores indicados



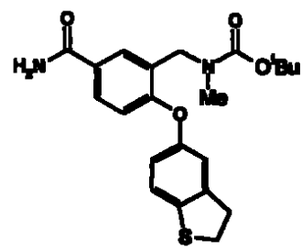
(XII)

Tabla 22

| Preparación | Precursor |  | Datos |
|---|---|---|---|
| 56 | Prep 51 |  | $\delta_H$ ($CDCl_3$, 400 MHz) 1,26 (9H, s), 2,74 (3H, s), 3,02 (2H, m), 4,31 (4H, m), 6,38 (2H, m), 6,64 (1H, d), 6,87 (1H, d), 7,68 (1H, brs), 7,78 (1H, brs), MS *m/z* ($ES^-$) 430 ($M-H^+$) |
| 57 | Prep 52 |  | $\delta_H$ ($CDCl_3$, 400 MHz) 1,44 (9H, brs), 2,49 (3H, s), 2,92 (3H, brd), 4,57 (2H, brd), 6,82 (1H, d), 6,94 (1H, d), 7,08 (1H, s), 7,21 (1H, d), 7,97 (1H, d), 8,04 (1H, brd), MS *m/z* ($ES^-$) 436 ($M-H^+$) |
| 58 | Prep 53 |  | $\delta_H$ ($CDCl_3$, 300 MHz) 1,46 (9H, brs), 2,49 (3H, s), 2,93 (3H, brs), 4,57 (2H, brs), 6,77 (2H, m), 6,92 (1H, d), 7,32 (1H, t), 7,99 (1H, d), 8,08 (1H, brs), MS *m/z* ($ES^-$) 420 ($M-H^+$) |

**PREPARACIÓN 59**

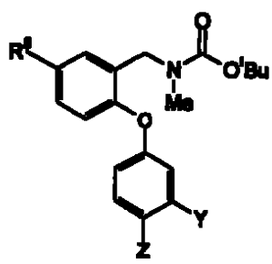
**5-(Aminocarbonil)-2-(2,3-dihidro-1-benzotien-5-iloxi)bencil(metil)carbamato de terc-butilo**



Se añadieron $Et_3N$ (267 µl, 1,92 mmol), $HOBt.H_2O$ (129 mg, 0,84 mmol) y WSCDI (191 mg, 1,0 mmol) a una solución del ácido de la Preparación 55 (318 mg, 0,77 mmol) en DCM (10 ml) y la mezcla se agitó durante 1 h antes de la adición de una solución saturada de $NH_3$ en THF (2 ml). Después de agitar durante 16 h más, la reacción se diluyó con agua (50 ml), HCl 0,2 M (20 ml) y DCM (25 ml) La capa

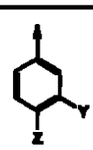
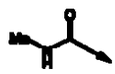
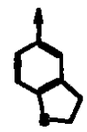
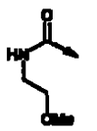
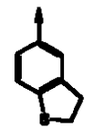
orgánica se separó y la capa acuosa se extrajo con DCM (25 ml) Las capas orgánicas combinadas se secaron ($MgSO_4$) y se evaporaron para dar una espuma blanca (se presume rendimiento cuantitativo) que se utilizó sin más purificación, $\delta_H$ ($CDCl_3$, 400 MHz) 1,44 (9H, s), 2,91 (3H, br), 3,27 (2H, t), 3,40 (2H, t), 4,54 (2H, br), 6,75-6,88 (3H, m), 7,18 (1H, d), 7,68 (1H, d), 7,74 (1H, s)

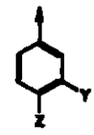
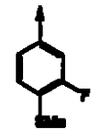
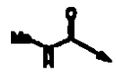
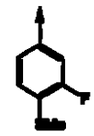
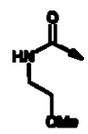
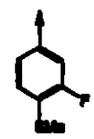
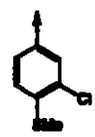
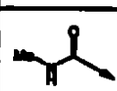
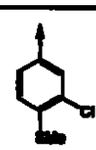
Los compuestos de fórmula XIII, mostrados en la Tabla 23, se prepararon de acuerdo con la Preparación 59 a partir de los precursores indicados

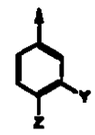
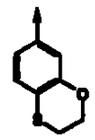
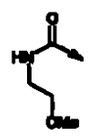
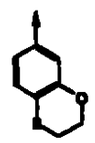


(XIII)

Tabla 23

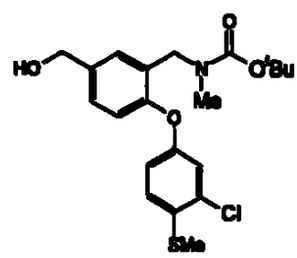
| Preparación | Precursor | $R^5$ |  | Datos |
|---|---|---|---|---|
| 60 | Prep 55 |  |  | $\delta_H$ ($CDCl_3$, 400 MHz) 1,43 (9H, s), 2,83-3,00 (6H, m), 3,24 (2H, t), 3,39 (2H, t), 4,61 (2H, brs), 6,70-6,85 (3H, m), 7,15 (1H, d), 7,62 (1H, d),7,68 (1H, s) |
| 61 | Prep 55 |  |  | $\delta_H$ ($CDCl_3$, 400 MHz) 1,46 (9H, s), 2,89 (3H, br), 3,24 (2H, t), 3,37-3,43 (5H,m), 3,56 (2H, t), 3,63 (2H, m), 4,54 (2H, br), 6,46 (1H, br), 6,75-6,86 (3H, m), 7,16 (1H, d), 7,62 (1H, d), 7,69 (1H, s) |

| Preparación | Precursor | $R^5$ |  | Datos |
|---|---|---|---|---|
| 62 | Prep 58 |  |  | $\delta_H$ ($d_6$-DMSO, 400 MHz) 1,29 (9H, br), 2,40 (3H, s), 2,75 (3H, s), 4,39 (2H, s), 6,78 (1H, d), 6,91 (2H, m), 7,23 (1H, br), 7,36 (1H t), 7,78 (2H, m),7,90 (1H, br); MS *m/z* ($TS^+$) 438 ($MNH_4^+$) |
| 63 | Prep. 58 |  |  | $\delta_H$ ($CDCl_3$, 400 MHz) 1,41 (9H, s), 2,40 (3H, s), 2,92 (3H, brs), 2,98 (3H, d), 4,45 (2H, brs), 6,10 (1H, brs), 6,67 (2H, m), 6,88 (1H, d), 7,27 (1H, obs), 7,63 (2H, m), MS *m/z* ($TS^+$) 452 ($MNH_4^+$) |
| 64 | Prep 58 |  |  | $\delta_H$ ($CDCl_3$, 400 MHz) 1,40 (9H, s), 2,40 (3H, s), 2,81 (3H, brs), 3,35 (3H, s), 3,53 (2H, m), 3,61 (2H, m), 4,44 (2H, brs), 6,45 (1H, brs), 6,66 (2H, m), 6,87 (1H, d), 7,29 (1H, d), 7,64 (1H, d), 7,72 (1H, s), MS *m/z* ($TS^+$) 479 ($MH^+$) |
| 65 | Prep 57 |  |  | $\delta_H$ ($CDCl_3$, 400 MHz) 1,43 (9H, brs), 2,47 (3H, s), 2,90 (3H, brd), 4,52 (2H, brs), 6,87 (1H, d), 6,91 (1H, d), 7,03 (1H, s), 7,10 (1H, d), 7,72 (1H, d), 7,78 (1H, s); MS *m/z* ($ES^-$) 435 ($M-H^+$) |
| 66 | Prep 57 |  |  | $\delta_H$ ($CDCl_3$, 400 MHz) 1,42 (9H, brs), 2,47 (3H, s), 2,88 (3H, brd), 3,00 (3H, d), 4,48 (2H, brs), 6,16 (1H, brd), 6,85 (2H,m), 7,01 (1H, s), 7,19 (1H, d), 7,67 (2H, m); MS *m/z* ($ES^-$) 449 ($M-H^+$) |

| Preparación | Precursor | $R^5$ |  | Datos |
|---|---|---|---|---|
| 67 | Prep 56 |  |  | $\delta_H$ ($CDCl_3$, 400 MHz) 1,42 (9H, s), 2,86 (3H, m), 3,08 (2H, m), 3,97 (2H, m), 4,48 (2H, brs), 5,86-6,27 (2H brs), 6,45 (1H, s), 6,49 (1H, d), 6,82 (1H, d), 6,96 (1H, d), 7,64 (1H, d), 7,71 (1H, s); MS *m/z* ($TS^+$) 331 ($MH^+$-Boc) |
| 68 | Prep 56 |  |  | $\delta_H$ ($CDCl_3$, 400 MHz) 1,26 (9H, s), 2,74 (3H, s), 3,02 (2H, m), 4,31 (4H, m), 6,38 (2H, m), 6,64 (1H, d), 6,87 (1H, d), 7,68 (1H, brs), 7,78 (1H, brs), MS *m/z* ($ES^-$) 430 ($M-H^+$) |

**PREPARACIÓN 69**

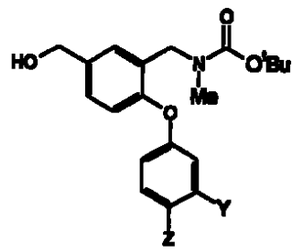
**2-[3-Cloro-4-(metilsulfanil)fenoxi]-5-(hidroximetil)bencil(metil)carbamato de terc-butilo**



Se añadió gota a gota una solución de $LiAlH_4$ en THF (1 M, 2 ml, 2 mmol) a una solución del éster de la Preparación 52 (452 mg, 1 mmol) en THF (10 ml) en atmósfera de nitrógeno Una vez que se juzgó completa la reacción por análisis tlc, se añadió éter (10 ml) y el exceso de $LiAlH_4$ se inactivó por adición cuidadosa de NaOH 2 M. La capa orgánica se separó, se lavó con salmuera, se secó ($MgSO_4$) y se evaporó La purificación del residuo por cromatografía en columna [$SiO_2$, (DCM/MeOH) 39 1] dio el alcohol deseado (200 mg, 47%) como un sólido blanco gomoso, $\delta_H$ ($CDCl_3$, 400 MHz) 1,41 (9H, brs), 1,80 (1H, brs), 2,43 (3H, s), 2,81 (3H, brd), 4,42 (2H, brd), 4,66 (2H, s), 6,82 (1H, d), 6,88 (1H, d), 6,96 (1H, s), 7,16 (1H,

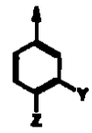
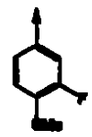
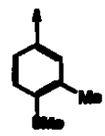
d), 7,27 (2H, obs), MS *m/z* ($ES^+$) 446 ($MNa^+$)

Los compuestos de fórmula XIV, mostrados en la Tabla 24, se prepararon de acuerdo con la Preparación 69 partiendo de los precursores indicados



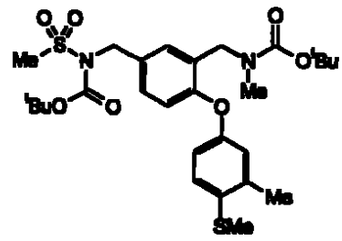

(XIV)

Tabla 24

| Preparación | Precursor |  | Datos |
|---|---|---|---|
| 70 | Prep 53 |  | $\delta_H$ ($CDCl_3$, 400 MHz) 1,39 (9H, brs), 1,99 (1H, brs),2,39 (3H, s), 2,78 (3H, brd), 4,39 (2H, brs), 4,62 (2H, d), 6,61 (2H, t), 6,88 (1H, d), 7,20-7,30 (3H, m+$CHCl_3$), MS *m/z* ($TS^+$) 408 ($MH^+$) |
| 71 | Prep 54 |  | $\delta_H$ ($CDCl_3$, 300 MHz) 1,45 (9H, s), 2,34 (3H, s), 2,46 (3H, s), 2,90 (3H, br), 4,49 (2H, s), 4,67 (2H, s), 6,72-6,81 (2H, m), 6,85 (1H, d), 7,18 (1H, d), 7,21-7,30 (2H, obs), MS *m/z* ($TS^+$) 404 ($MH^+$) |

**PREPARACIÓN 72**

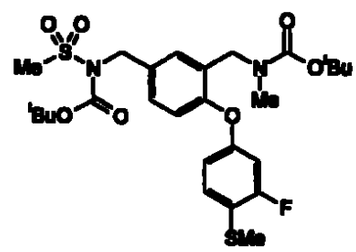
**3-{[(terc-Butoxicarbonil)(metil)amino]metil}-4-[3-metil-4-(metilsulfanil)fenoxi]bencil-(metilsulfonil)carbamato de terc-butilo**



Se añadió gota a gota una solución de azodicarboxilato de dietilo (505 µl, 3,21 mmol) en THF (5 ml) a una solución de metilsulfonilcarbamato de terc-butilo (sintetizado de acuerdo con *Tetrahedron Lett.* 1994, 35, 379-380) (655 mg, 3,36 mmol), el alcohol de la Preparación 71 (1,226 g, 3,04 mmol) y trifenilfosfina (880 mg, 3,36 mmol) en THF (15 ml) a 0°C La reacción se agitó a 0°C durante 2 h, luego se diluyó con EtOAc (80 ml) y se lavó con $K_2CO_3$ acuoso al 10% (100 ml) La capa orgánica se lavó con salmuera, se secó ($MgSO_4$) y se evaporó El residuo se purificó por cromatografía en columna [$SiO_2$, EtOAc pentano 1 4] para dar el compuesto del título (1,406 g, 80%) como un aceite incoloro; $\delta_H$ ($CDCl_3$, 300 MHz) 1,45 (9H, s), 1,52 (9H, s), 2,38 (3H, s), 2,44 (3H, s), 2,83 (3H, s), 3,22 (3H, s), 4,49 (2H, s), 4,85 (2H, s), 6,74-6,83 (3H, m), 7,18-7,29 (3H, obs), MS *m/z* ($TS^+$) 481 ($MH^+$-BOC)

**PREPARACIÓN 73**

**3-{[(terc-Butoxicarbonil)(metil)amino]metil}-4-[3-fluoro-4-(metilsulfanil)fenoxi]bencil-(metilsulfonil)carbamato de terc-butilo**

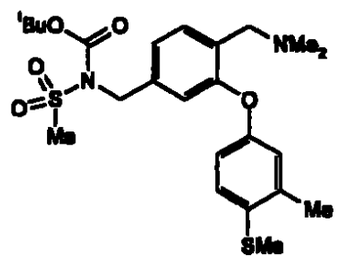


El compuesto se preparó a partir del alcohol de la Preparación 70 por el método de la preparación 72, $\delta_H$ ($CDCl_3$, 300 MHz) 1,44 (9H, s), 1,52 (9H, s), 2,44

(3H, s), 2,82 (3H, s), 3,23 (3H, s), 4,45 (2H, s), 4,87 (2H, s), 6,61-6,70 (2H, m), 6,90 (1H, d), 7,25-7,33 (3H, m), MS *m/z* ($ES^+$) 607 ($MNa^+$)

**PREPARACIÓN 74**

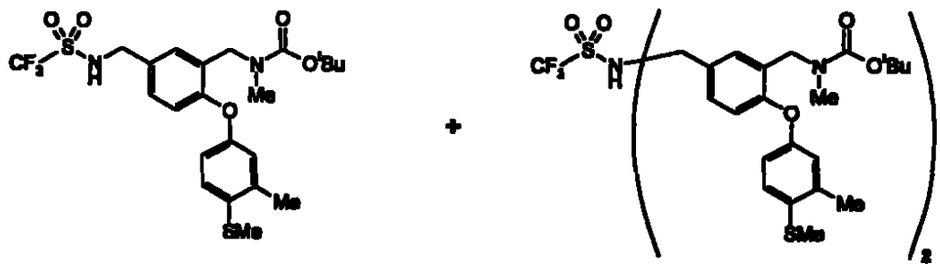
**4-[(Dimetilamino)metil]-3-[3-metil-4-(metilsulfanil)fenoxi]bencil(metilsulfonil)carbamato de terc-butilo**



El compuesto del título se preparó a partir del alcohol del Ejemplo 59 por el método de la Preparación 72 El producto bruto no se purificó por cromatografía en columna, sino que se recogió directamente en la etapa siguiente, $\delta_H$ ($CDCl_3$, 400 MHz) 1,39 (9H, s), 2,22 (6H, s), 2,28 (3H, s), 2,38 (3H, s), 3,07 (3H, s), 3,42 (2H, s), 4,76 (2H, s), 6,72 (2H, m), 6,79 (1H, s), 7,07 (1H, d), 7,12 (1H, d), 7,40 (1H, obs)

**PREPARACIÓN 75**

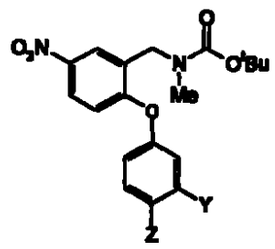
**Metil-[2-[3-metil-4-(metilsulfanil)fenoxi]-5-({[trifluorometil)sulfonil]amino}metil)bencil]-carbamato de terc-butilo**



El compuesto del título se preparó a partir del alcohol de la Preparación 71 por el método de la Preparación 72 utilizando trifluorometanosulfonamida en lugar de

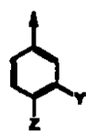
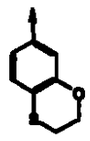
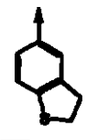
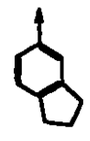
metilsulfonilcarbamato de terc-butilo El producto deseado estaba contaminado con 5-({{3-{[(terc-butoxicarbonil)(metil)amino]metil}-4-[3-metil-4-(metilsulfanil)fenoxi]-bencil}[trifluorometil)sulfonil]amino}metil)-2-[3-metil-4-(metilsulfanil)fenoxi]bencil-(metil)carbamato de terc-butilo y se recogió como una mezcla, MS *m/z* ($ES^-$) 533 ($M-H^+$)

Los compuestos de fórmula XV mostrados en la Tabla 25 se prepararon de acuerdo con la Preparación 44 utilizando los precursores indicados



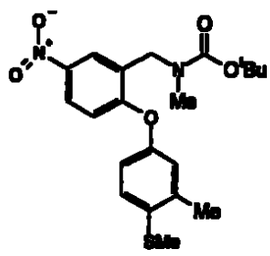
(XV)

Tabla 25

| Preparación | Precursor |  | Datos |
|---|---|---|---|
| 76 | Ejemplo 41 |  | $\delta_H$ ($CDCl_3$, 400 MHz) (rotámero principal) 1,51 (9H, s), 2,92 (3H, s), 3,10 (2H, m), 4,40 (2H, m), 4,52 (2H, br), 6,53 (2H, m), 6,81 (1H, m), 7,03 (1H, d), 7,97-8,21 (2H, m), MS *m/z* ($TS^+$) 433 ($MH^+$) |
| 77 | Ejemplo 40 |  | $\delta_H$ ($CDCl_3$, 300 MHz) 1,50 (9H, br), 2,99 (3H, s), 3,29 (2H, m), 3,43 (2H, m), 4,60 (2H, br), 6,81 (2H, m), 6,91 (1H, s), 7,22 (1H, d), 8,04 (1H, d), 8,21 (1H, br) |
| 78 | Ejemplo 42 |  | $\delta_H$ ($CDCl_3$, 400 MHz) 1,56 (9H, s), 2,15 (2H, m), 2,85-3,00 (7H, m), 4,60 (2H, brd), 6,78 (2H, m), 6,87 (1H, s), 7,12 (1H, d), 8,03 (1H, d), 8,10 (1H, s), MS *m/z* ($TS^+$) 399 ($MH^+$) |

**PREPARACIÓN 79**

**Metil-{2-[3-metil-4-(metilsulfanil)fenoxi]-5-nitrobencil}carbamato de terc-butilo**



*N*-Metil-*N*-{2-[3-metil-4-(metilsulfanil)fenoxi]-5-nitrobencil}amina y {2-[3-metil-4-(metilsulfanil)fenoxi]-5-nitrofenil}metanol

A una suspensión del aldehído de la Preparación 39 (21,0 g, 69,2 mmol) en EtOH (100 ml) se añadió metilamina 8 M en EtOH (86,5 ml, 692 mmol) Se administró una solución y después de agitar durante un corto período de tiempo se observó un precipitado Éste se re-disolvió por adición de THF (100 ml), la solución se enfrió a 0°C y luego se añadió $NaBH_4$ (7,85 g, 208 mmol) La reacción se dejó calentar lentamente a temperatura ambiente y se agitó durante una noche antes de separar el disolvente a vacío El residuo se recogió en agua (150 ml) y éter (150 ml), y se añadió cuidadosamente HCl 2 M hasta pH 1 Las capas se separaron y la capa acuosa se lavó con éter (2 x 100 ml). Los extractos orgánicos combinados se secaron y se evaporaron para dar {2-[3-metil-4-(metilsulfanil)fenoxi]-5-nitrofenil}metanol (18,9 g, 89%) como un sólido amarillo, $\delta_H$ ($CDCl_3$, 400 MHz) 2,35 (3H, s), 2,48 (3H, s), 4,90 (2H, s), 6,79 (1H, d), 6,89 (1H, s), 6,91 (1H, d), 7,22 (1H, d), 8,07 (1H, dd), 8,41 (1H, d)

La capa acuosa anterior se neutralizó vertiéndola en $K_2CO_3$ sólido en exceso La solución básica se extrajo con éter (2 x 100 ml) y estos extractos etéreos se secaron ($MgSO_4$) y se evaporaron para dar *N*-metil-*N*-{2-[3-metil-4-(metilsulfanil)-fenoxi]-5-nitrobencil}amina (1,65 g, 7,5%) como un aceite naranja, MS *m/z* ($ES^+$) 319 ($MH^+$)

*N*-Metil-*N*-{2-[3-metil-4-(metilsulfanil)fenoxi]-5-nitrobencil}amina a partir de {2-[3-metil-4-(metilsulfanil)fenoxi]-5-nitrofenil}metanol

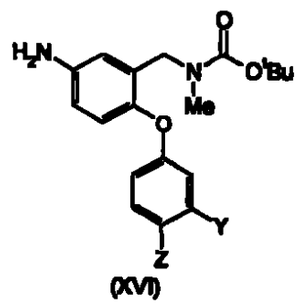
Se añadió lentamente cloruro de metanosulfonilo (4,81 ml, 61,9 mmol) a una

solución de {2-[3-metil-4-(metilsulfanil)fenoxi]-5-nitrofenil}metanol (18,9 g, 61,9 mmol) y $Et_3N$ (9,5 ml, 68,2 mmol) en DCM (60 ml) La mezcla se agitó a temperatura ambiente durante 3 h y luego se vertió en agua y se extrajo con DCM (3 veces). Los extractos orgánicos combinados se secaron ($MgSO_4$) y se evaporaron para dar un aceite viscoso oscuro Este aceite se recogió en DCM (50 ml) y se añadió metilamina 8 M en EtOH (200 ml, 1,6 mol) seguida por $Et_3N$ (10 ml, 71,7 mmol). Después de agitar durante 18 h, la mezcla se concentró a vacío para dar la amina bruta que se utilizó sin más purificación

Metil-{2-[3-metil-4-(metilsulfanil)fenoxi]-5-nitrobencil}carbamato de terc-butilo

La amina bruta de antes se disolvió en DCM (100 ml) a 0°C y se añadió $Et_3N$ (11,4 ml, 81,8 mmol), seguida por dicarbonato de di-terc-butilo (15,0 g, 68,7 mmol) La reacción se dejó calentar a temperatura ambiente y se agitó durante 16 h antes de ser concentrada a vacío El residuo se repartió entre EtOAc y agua y la capa acuosa se extrajo con EtOAc (2 veces) Las capas orgánicas combinadas se secaron ($MgSO_4$) y se evaporaron. El residuo se purificó por cromatografía en columna ($SiO_2$, 1ª columna, 3% de MeOH en DCM; 2ª columna, EtOAc·pentano 1·3) para dar el compuesto del título (14,2 g, 54%) como un aceite amarillo; $\delta_H$ ($CDCl_3$, 400 MHz) 1,44 (9H, s), 2,32 (3H, s), 2,44 (3H, s), 2,95 (3H, s), 4,56 (2H, br), 6,75 (1H; d), 6,84 (2H, m), 7,17 (1H, d), 8,00 (1H, d), 8,18 (1H, br), MS *m/z* ($TS^+$) 419 ($MH^+$)

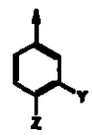
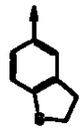
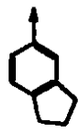
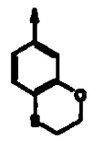
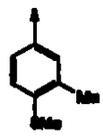
Los compuestos de fórmula XVI mostrados en la Tabla 26 se prepararon de acuerdo con el Ejemplo 103 a partir de los precursores indicados.




(XVI)

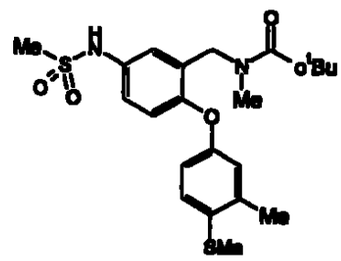
~~180~~ 178

Tabla 26

| Preparación | Precursor |  | Datos |
|---|---|---|---|
| 80 | Prep 77 |  | $\delta_H$ ($CDCl_3$, 300 MHz) 1,50 (9H, br), 2,80 (3H, br), 3,20 (2H, m), 2,37 (2H, m), 3,60 (2H, br), 4,40 (2H, s), 6,50-6,80 (5H, m), 7,05 (1H, d), MS *m/z* ($ES^+$) 387 ($MH^+$) |
| 81 | Prep 78 |  | $\delta_H$ ($CDCl_3$, 400 MHz) 1,42 (9H, s), 2,05 (2H, m), 2,80 (7H, m), 4,37 (2H, s), 6,50-6,65 (3H, m), 6,69 )1H, s), 6,78 (1H, d), 7,08 (1H, d), MS *m/z* ($TS^+$) 369 ($MH^+$) |
| 82 | Prep 76 |  | $\delta_H$ ($CDCl_3$, 400 MHz) 1,43 (9H, s), 2,88 (3H, br), 3,07 (2H, m), 3,59 (2H, br), 4,30 (2H, s), 4,36 (2H, m), 6,32 (1H, s), 6,40 (1H, d), 6,49-6,65 (2H, m), 6,75 (1H, d), 6,88 (1H, d), MS *m/z* ($TS^+$) 403 ($MH^+$) |
| 83 | Prep 79 |  | $\delta_H$ ($CDCl_3$, 300 MHz) 1,47 (9H, s), 2,33 (3H, s), 2,40 (3H, s), 2,82 (3H, br), 3,60 (2H, s), 4,35 (2H, s), 6,50-6,77 (4H, m), 6,80 (1H, d), 7,16 (1H, d), MS *m/z* ($TS^+$) 389 ($MH^+$) |

**PREPARACIÓN 84**

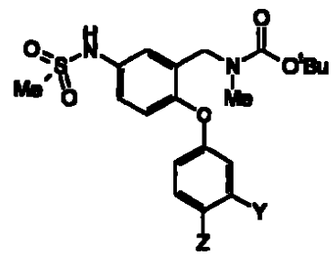
**Metil-{2-[3-metil-4-(metilsulfanil)fenoxi]-5-[(metilsulfonil)amino]bencil}carbamato de terc-butilo**



Se añadió gota a gota cloruro de metanosulfonilo (4,16 ml, 53,7 mmol) a una

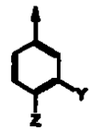
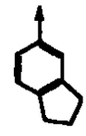
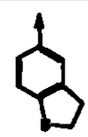
solución de la anilina de la Preparación 83 (9,5 g, 24,5 mmol) y $Et_3N$ (7,5 ml, 53,8 mmol) en DCM (50 ml) a 0°C. Después de agitar a 0°C durante 30 min, la reacción se dejó calentar a temperatura ambiente antes de separar el disolvente a vacío Se añadió NaOH 2 M (50 ml) al residuo y la mezcla se agitó durante 30 min. La mezcla se extrajo con EtOAc y la capa orgánica se lavó con salmuera, se secó ($MgSO_4$) y se evaporó para dar un aceite La purificación por cromatografía en columna [$SiO_2$, (DCM/MeOH/$NH_3$ 880) 97,5 2,5 0,25] dio el producto (9,0 g, 79%) como una espuma de color pardo, $\delta_H$ ($CDCl_3$, 300 MHz) 1,43 (9H, brs), 2,35 (3H, s), 2,42 (3H, s), 2,88 (3H, brs), 3,01 (3H, s), 4,46 (2H, brs), 6,76 (2H, d+s), 6,83 (1H, d), 7,16 (1H, s), 7,20 (2H, brs); MS *m/z* ($ES^+$) 467 ($MH^+$)

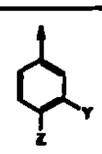
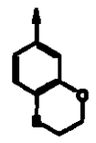
Los compuestos de fórmula XVII mostrados en la Tabla 27 se prepararon de acuerdo con la Preparación 84 a partir de los precursores indicados



(XVII)

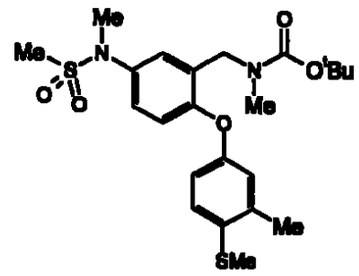
Tabla 27

| Preparación | Precursor |  | Datos |
|---|---|---|---|
| 85 | Prep 81 |  | $\delta_H$ ($CDCl_3$, 400 MHz) (rotámeros) 1,44 y 1,48 (9H, 2xs), 2,10 (2H, quintete), 2,88 (7H, m), 3,00 (3H, s), 4,49 (2H, br), 6,23 (1H, br), 6,72 (1H, d), 6,81 (1H, s), 6,83 (1H, d), 7,13 (3H, m), MS *m/z* ($TS^+$) 347 ($MH^+$-Boc) |
| 86 | Prep 80 |  | Producto utilizado sin purificación |

| Preparación | Precursor |  | Datos |
|---|---|---|---|
| 87 | Prep 82 |  | $\delta_H$ ($CDCl_3$, 400 MHz) (rotámeros) 1,40 y 1,44 (9H, 2xs), 2,80 y 2,85 (3H, 2xs), 2,95 (3H, s), 3,07 (2H, m), 4,38 (2H, m), 6,36 (1H, s), 6,44 (1H, d), 6,84 (1H, d), 6,92 (1H, d), 7,12 (2H, m), MS *m/z* ($TS^+$) 498 ($MNH_4^+$) |

**PREPARACIÓN 88**

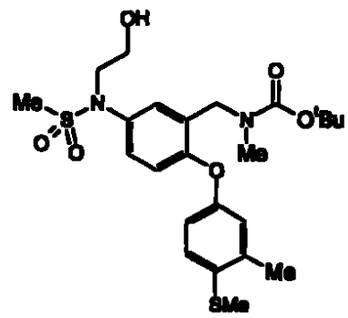
**Metil-{2-[3-metil-4-(metilsulfanil)fenoxi]-5-[metil(metilsulfonil)amino]bencil}carbamato de terc-butilo**



Se añadió gota a gota MeI (1,07 ml, 17,2 mmol) a una mezcla de la sulfonamida de la Preparación 84 (2,0 g, 4,3 mmol) y $K_2CO_3$ (592 mg, 4,3 mmol) en $CH_3CN$ (10 ml) en atmósfera de nitrógeno. La mezcla se agitó durante 16 h y luego se repartió entre EtOAc (50 ml) y NaOH 2 M (50 ml) La capa orgánica se lavó con salmuera, se secó ($MgSO_4$) y se evaporó El residuo se purificó por cromatografía en columna [$SiO_2$, (DCM/MeOH/$NH_3$ 880) 590 10.1] para dar el producto (1,23 g, 60%) como un aceite amarillo, $\delta_H$ ($CDCl_3$, 300 MHz) 1,45 (9H, s), 2,34 (3H, s), 2,42 (3H, s), 2,86 (3H, s), 2,90 (3H, s), 3,28 (3H, s), 4,49 (2H, s), 6,30 (3H, br), 7,18 (3H, m), MS *m/z* ($TS^+$) 498 ($MNH_4^+$)

**PREPARACIÓN 89**

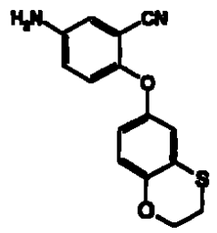
**5-[(2-Hidroxietil)(metilsulfonil)amino]-2-[3-metil-4-(metilsulfanil)fenoxi]bencil(metil)-carbamato de terc-butilo**



Se añadió 2-bromoetanol (1,34 ml, 18,9 mmol) a una mezcla de la sulfonamida de la Preparación 84 (2,0 g, 4,3 mmol) y $K_2CO_3$ (2,605 g, 18,8 mmol) en $CH_3CN$ (10 ml) en atmósfera de nitrógeno La mezcla se calentó a reflujo durante 16 h, se enfrió y luego se repartió entre EtOAc (50 ml) y NaOH 2 M (50 ml). La capa orgánica se lavó con salmuera, se secó ($MgSO_4$) y se evaporó El residuo se purificó por cromatografía en columna [$SiO_2$, (DCM/MeOH/$NH_3$ 880) 390 10 1] para dar el producto (524 mg, 24%) como una espuma rosa, $\delta_H$ ($CDCl_3$, 300 MHz) 1,42 (9H, s), 2,37 (3H, s), 2,43 (3H, s), 2,91 (3H, s), 2,98 (3H, s), 3,68 (2H, brs), 3,79 (2H, d), 4,49 (2H, s), 6,81 (3H, m), 7,19 (3H, m), MS *m/z* ($TS^+$) 528 ($MNH_4^+$)

**PREPARACIÓN 90**

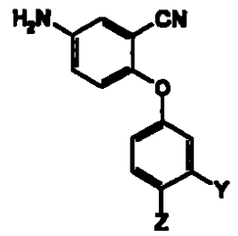
**5-Amino-2-(2,3-dihidro-1,4-benzoxatiin-6-iloxi)benzonitrilo**



Se añadió polvo de hierro (930 mg, 16,7 mmol) al nitrocompuesto de la Preparación 41 (740 mg, 2,38 mmol) en AcOH (5 ml) y agua (1 ml) y la mezcla se agitó a temperatura ambiente durante 16 h El disolvente se separó a vacío, el residuo

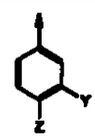
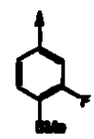
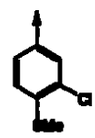
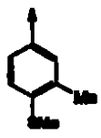
se recogió en EtOAc (50 ml) y $K_2CO_3$ acuoso al 10% (50 ml) y se filtró a través de Arbacel® La capa orgánica se separó y la capa acuosa se extrajo con EtOAc (50 ml) Los extractos orgánicos combinados se secaron ($MgSO_4$) y se evaporaron para dar una espuma de color pardo (670 mg, 99%) que se utilizó sin más purificación, $\delta_H$ ($CDCl_3$, 400 MHz) 3,18 (2H, m), 4,36 (2H, m), 6,60-6,70 (2H, m), 6,70-6,80 (3H, m), 6,85 (1H, s), MS *m/z* ($TS^+$) 302 ($MNH_4^+$)

Los compuestos de fórmula Vb, es decir los compuestos de fórmula V en la que T es ciano, $R^4$ es hidrógeno y $R^5$ es amino, mostrados en la Tabla 28, se prepararon de acuerdo con la Preparación 90 a partir de los precursores indicados



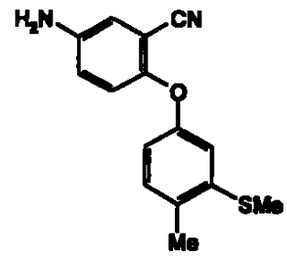

(Vb)

Tabla 28

| Preparación | Precursor |  | Datos |
|---|---|---|---|
| 91 | Prep 35 |  | $\delta_H$ ($CDCl_3$, 400 MHz) 2,40 (3H, s), 6,62-6,72 (2H, m), 6,80-6,90 (3H, m), 7,28 (1H, d) |
| 92 | Prep 37 |  | $\delta_H$ ($CDCl_3$, 300 MHz) 2,47 (3H, s), 3,83 (2H, br), 6,83-6,94 (4H, m), 7,01 (1H, s), 7,19 (1H, d); MS *m/z* ($TS^+$) 308 ($MNH_4^+$) |
| 93 | Prep 42 |  | $\delta_H$ ($CDCl_3$, 400 MHz) 2,30 (3H, s), 2,40 (3H, s), 3,84 (2H, br), 6,77 (4H, m), 6,85 (1H, s), 7,13 (3H, d), MS *m/z* ($TS^+$) 288 ($MNH_4^+$) |

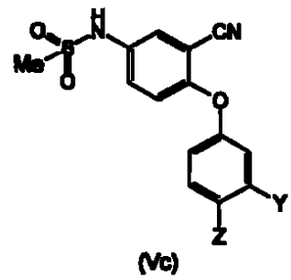
**PREPARACIÓN 94**

**5-Amino-2-[4-metil-3-(metilsulfanil)fenoxi]benzonitrilo**



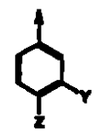
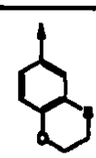
El compuesto del título se preparó a partir del nitro compuesto de la Preparación 43 por el método del Ejemplo 103, $\delta_H$ ($CDCl_3$, 400 MHz) 2,27 (3H, s), 2,41 (3H, s), 3,66 (2H, br), 6,62 (1H, d), 6,79 (2H, s), 6,82 (1H, s), 6,89 (1H, s), 7,08 (1H, d), MS *m/z* ($ES^+$) 293 ($MNa^+$), ($ES^-$) 269 ($M-H^+$)

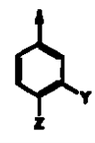
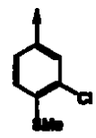
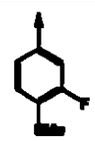
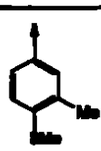
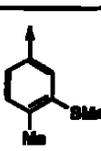
Los compuestos de fórmula Vc, es decir los compuestos de fórmula V en la que T es ciano, $R^4$ es hidrógeno y $R^5$ es $-NHSO_2Me$, mostrados en la Tabla 29, se prepararon de acuerdo con la Preparación 84 a partir de los precursores indicados



(Vc)

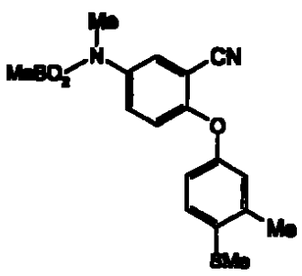
Tabla 29

| Preparación | Precursor |  | Datos |
|---|---|---|---|
| 95 | Prep. 90 |  | $\delta_H$ ($CDCl_3$, 400 MHz) 2,98 (3H, s), 3,10 (2H, m), 4,39 (2H, m), 6,67 (1H, dd), 6,76 (1H, s), 6,81 (1H, d), 7,33 (1H, dd), 7,49 (1H, s), MS *m/z* ($TS^+$) 380 ($MNH_4^+$) |

| Preparación | Precursor |  | Datos |
|---|---|---|---|
| 96 | Prep 92 |  | $\delta_H$ ($CDCl_3$, 300 MHz) 2,51 (3H, s), 3,06 (3H, s), 6,52 (1H, br), 6,92 (1H, d), 7,02 (1H, dd), 7,14 (1H, d), 7,24 (1H, d), 7,41 (1H, dd), 7,57 (1H, d), MS *m/z* ($ES^+$) 391 ($MNa^+$) |
| 97 | Prep 91 |  | $\delta_H$ ($CDCl_3$, 400 MHz) 2,43 (3H, s), 3,02 (3H, s), 6,41 (1H, brs), 6,72-6,85 (2H, m), 6,92 (1H, d), 7,28 (1H, t), 7,38 (1H, d), 7,51 (1H, s), MS *m/z* ($ES^+$) 351 ($MH^+$) |
| 98 | Prep 93 |  | $\delta_H$ ($CDCl_3$, 400 MHz) 2,19 (3H, s), 2,42 (3H, s), 2,99 (3H, s), 6,81 (1H, d), 6,86 (2H, m), 7,15 (1H, d), 7,33 (1H, d), 7,51 (1H, s), MS *m/z* ($TS^+$) 366 ($MNH_4^+$) |
| 99 | Prep 94 |  | $\delta_H$ ($CDCl_3$, 400 MHz) 2,31 (3H, s), 2,43 (3H, s), 3,02 (3H, s), 6,61 (1H, s), 6,72 (1H, dd), 6,83 (1H, d), 6,88 (1H, s), 7,17 (1H, d), 7,37 (1H, dd), 7,55 (1H, s), MS *m/z* ($TS^+$) 366 ($MNH_4^+$) |

**PREPARACIÓN 100**

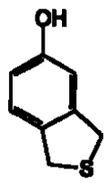
***N*-{3-Ciano-4-[3-metil-4-(metilsulfanil)fenoxi]fenil}-*N*-metilmetanosulfonamida**



El compuesto del título se preparó a partir de la sulfonamida de la Preparación 98 por el método de la Preparación 88, $\delta_H$ ($CDCl_3$, 400 MHz) 2,31 (3H, s), 2,44 (3H, s), 2,83 (3H, s), 3,27 (3H, s), 6,79 (1H, d), 6,88 (2H, m), 7,17 (1H, d), 7,44 (1H, dd), 7,58 (1H, d), MS *m/z* ($ES^+$) 385 ($MNa^+$)

**PREPARACIÓN 101**

**1,3-Dihidro-2-benzotiofen-5-ol**




(i) Preparación de [4-(aliloxi)-2-(hidroximetil)fenil]metanol

Se disolvió 4-(aliloxi)ftalato de dimetilo [preparado de acuerdo con Inouye, M , Tsuchiya, K , Kitao, T *Angew Chem* 1992, 104, 198-200 (véase también *Angew Chem Int Ed Engl* , 1992, 204-205)] (9,9 g, 38 mmol) en THF (40 ml) y se enfrió a 0°C antes de la adición gota a gota de hidruro de litio y aluminio (1 M en THF, 77 ml, 77 mmol) a lo largo de 10 min. Luego la mezcla se mantuvo con agitación a temperatura ambiente durante 3 h antes de inactivarla cuidadosamente por adición de agua (1,4 ml) seguida por NaOH 2 M (1,4 ml) Luego se añadió exceso de $MgSO_4$ seguido por agua hasta que se formó un precipitado granular (aproximadamente 5 ml). Luego la mezcla se filtró y se evaporó para dar un aceite pardo (7,1 g, aproximadamente 95%) La $^1H$ NMR mostró que el material era de una pureza del 85% aproximadamente Se utilizó directamente en la etapa siguiente sin más purificación, $\delta_H$ ($CDCl_3$, 400 MHz) 2,63 (1H, brs), 2,91 (1H, brs), 4,52 (2H, m), 4,67 (4H, m), 5,26 (1H, dd), 5,38 (1H, dd), 5,97-6,09 (1H, m), 6,80 (1H, dd), 6,92 (1H, d), 7,22 (1H, d)

(ii) Preparación de 5-(aliloxi)-1,3-dihidro-2-benzotiofeno

Se disolvió el diol bruto de la etapa (i) (3,5 g, 18 mmol) en DCM (60 ml) y se trató con $Et_3N$ (10 ml, 72 mmol) y la solución se enfrió a 0°C. Se añadió gota a gota cloruro de metanosulfonilo (4,2 ml, 54 mmol) y la solución se agitó durante 1 h dejando que se alcanzara la temperatura ambiente. Luego la reacción se inactivó por adición de agua seguida por HCl 2 M (50 ml) La capa de DCM se separó y la capa acuosa se extrajo de nuevo con DCM (50 ml) Las fracciones orgánicas combinadas se lavaron con agua (50 ml), se secaron ($MgSO_4$) y se concentraron a un volumen de aproximadamente 30 ml Se añadió cloruro de benciltrietilamonio (1 g) seguido por una solución de sulfuro de sodio (5 g, 91 mmol) en agua (50 ml) La mezcla se agitó

rápidamente en atmósfera de nitrógeno durante 15 h Se separó la capa orgánica y la capa acuosa se extrajo de nuevo con DCM (50 ml). Las capas orgánicas combinadas se secaron ($MgSO_4$) y se evaporaron para dar un aceite amarillo. La cromatografía instantánea proporcionó dos fracciones, la primera fue producto puro y la segunda producto contaminado con material dímero La trituración de la segunda fracción produjo cristalización del material dímero que se separó por filtración El filtrado se combinó con la primera fracción cromatográfica para proporcionar el producto deseado (800 mg, 23%), $\delta_H$ ($CDCl_3$, 400 MHz) 4,16 (2H, s), 4,19 (2H, s), 4,48 (2H, m), 5,26 (1H, d), 5,37 (1H, d), 5,95-6,06 (1H, m), 6,74 (2H, m), 7,09 (1H, d)

(iii) Preparación de 1,3-dihidro-2-benzotiofen-5-ol

Se disolvió el éter de alilo de la etapa (ii) (800 mg, 4,16 mmol) en THF (10 ml) y se trató con tetraquis(trifenilfosfina)paladio (481 mg, 0,42 mmol) seguido por borohidruro de sodio (944 mg, 25 mmol) Luego la mezcla se calentó a 45°C y se agitó a esta temperatura durante 15 h Después de enfriar a temperatura ambiente, se evaporó el THF y el residuo se repartió entre una solución de NaOH 2 M (25 ml) y éter dietílico (25 ml) La capa acuosa se separó y la capa orgánica se extrajo de nuevo con una solución de NaOH 2 M (25 ml) Las capas acuosas combinadas se neutralizaron a pH 7-8 con ácido clorhídrico concentrado y se extrajeron con EtOAc (2 x 25 ml) Los extractos orgánicos combinados se secaron ($MgSO_4$) y se evaporaron para dar un aceite claro del fenol del título que solidificó al dejar estar (540 mg, 85%), 4,14 (2H, s), 4,17 (2H, s), 6,63-6,68 (2H, m), 7,04 (1H, d)

**Actividad biológica**

Se ensayaron cierto número de compuestos para determinar su actividad biológica mediante su capacidad para inhibir la absorción de serotonina por los transportadores de serotonina humana como sigue.

(I) **Cultivo celular**

Bajo condiciones clásicas de cultivo celular (cultivo de células a 37°C con 5% de $CO_2$ en medio de cultivo DMEM (enriquecido con 10% de suero vacuno fetal (FCS) dializado, l-glutamina 2 mM y geneticina en una proporción de 250 µg/ml)) se cultivaron células de riñón embrónico humano (HEK-293) establemente transfectadas con, o bien el transportador de

serotonina humana (hSERT), el transportador de noradrenalina (hNET) o el transportador de dopamina (hDAT) Se recogieron las células para el análisis obteniéndose una suspensión de células a razón de 750 000 células/ml

(ii) <u>Determinación de la potencia del inhibidor</u>

Todos los compuestos de ensayo se disolvieron en DMSO al 100% y se diluyeron en tampón de análisis para dar las concentraciones apropiadas de ensayo Los análisis se llevaron a cabo en placas de fondo filtrante de 96 pocillos Las células (7 500 células/pocillo de análisis) se pre-incubaron en un tampón clásico para análisis, que contenía o bien el compuesto de ensayo, el inhibidor clásico o el vehículo para el compuesto (DMSO al 1%) durante 5 minutos Las reacciones empezaron por la adición de substratos $^3$H-Serotonina, $^3$H-Noradrenalina o $^3$H-Dopamina Todas las reacciones se llevaron a cabo a temperatura ambiente en una incubadora con agitación orbital Los tiempos de incubación fueron 5 minutos para los análisis de hSERT y hDAT y de 15 minutos para el análisis de hNET Las reacciones se terminaron por separación de la mezcla de reacción utilizando un múltiple de vacío, seguido por lavado rápido con tampón de análisis enfriado en hielo. Después se cuantificó la cantidad de $^3$H-substrato incorporada en las células Las placas analíticas se secaron en un horno microondas, se añadió fluido de centelleo y se midió la radiactividad La potencia de los compuestos de ensayo fue cuantificada como valores de $CI_{50}$ (concentración del compuesto de ensayo que se necesita para inhibir la absorción específica de substrato radiomarcado en las células en un 50%).

(iii) <u>Composición del tampón de análisis clásico:</u>

Hidrocloruro Trizma (26 mM)
NaCl (124 mM)
KCl (4,5 mM)
$KH_2PO_4$ (1,2 mM)
$MgCl_2$ $6H_2O$ (1,3 mM)
Ácido ascórbico (1,136 mM)
Glucosa (5,55 mM)
pH 7,40

$CaCl_2$ (2,8 mM)
Pargilina (100 µM)

Nota el pH del tampón se ajustó a 7,40 con NaOH 1 M antes de la adición de $CaCl_2$ y pargilina

(iv) **Resumen de los parámetros del análisis**

| | Análisis de hSERT | Análisis de hDAT | Análisis de hNET |
|---|---|---|---|
| Concentración celular por pocillo de análisis | 75 000 | 75 000 | 75 000 |
| Concentración del substrato | $^3$H-5HT (50 nM) | $^3$H-Dopamina (200 nM) | $^3$H-Noradrenalina (200 nM) |
| Tiempo de incubación (minutos) | 5 | 5 | 15 |

Los compuestos que tienen un valor $CI_{50}$ para la inhibición de la reabsorción de serotonina (SRI) menor o igual que 100 nM incluyen los compuestos del título de los Ejemplos 1-6, 8-23, 25, 26, 29-32, 34-36, 43, 45-49, 51, 56-102, 109-130

Los compuestos que tienen un valor $CI_{50}$ para la inhibición de la reabsorción de serotonina (SRI) menor o igual que 100 nM y que son más de 10 veces más potentes en la inhibición de la reabsorción de serotonina que en la inhibición de la reabsorción de dopamina o reabsorción de noradrenalina incluyen los compuestos del título de los Ejemplos 1-6, 9-13, 16-19, 21, 22, 25, 26, 29-32, 34-36, 43, 45, 47-49, 51, 57-88, 90-102, 109-121, 123, 124, 127, 129

Los compuestos que tienen un valor $CI_{50}$ para la inhibición de la reabsorción de serotonina (SRI) menor o igual que 100 nM y que son más de 100 veces más potentes en la inhibición de la reabsorción de serotonina que en la inhibición de la reabsorción de dopamina o reabsorción de noradrenalina incluyen los compuestos del título de los Ejemplos 1, 2, 4, 5, 9, 12, 13, 16-19, 21, 22, 25, 26, 29-32, 34-36, 43, 45, 48, 49, 58-80, 83-88, 90, 92-97, 99-102, 111-113, 115-118, 120, 123, 124, 127

Los compuestos que tienen un valor $CI_{50}$ para la inhibición de la reabsorción de serotonina (SRI) menor o igual que 50 nM y que son más de 100 veces más potentes en la inhibición de la reabsorción de serotonina que en la inhibición de la reabsorción de dopamina y reabsorción de noradrenalina incluyen los compuestos del título de los Ejemplos 1, 2, 4, 9, 12, 17, 18, 26, 29, 30, 36, 43, 45, 48, 49, 60-66, 68-75, 78, 79, 90, 92-94, 100, 102, 116, 118, 124

En particular, el compuesto del título del Ejemplo 16 tenía un valor $CI_{50}$ para la inhibición de la reabsorción de serotonina (SRI) de 4,7 nM, el compuesto del título del Ejemplo 29 tenía un valor $CI_{50}$ para la inhibición de la reabsorción de serotonina (SRI) de 2,0 nM, y el compuesto del título del Ejemplo 62 tenía un valor $CI_{50}$ para la inhibición de la reabsorción de serotonina (SRI) de 3,7 nM.

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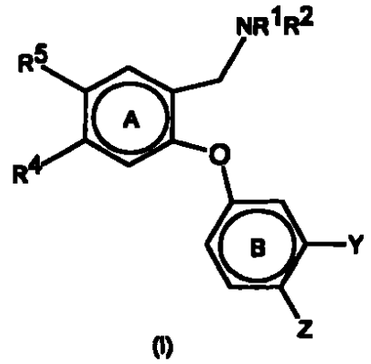
## REIVINDICACIONES

1 Un compuesto de fórmula general (I), sus sales, solvatos o polimorfos farmacéuticamente aceptables




(I)

en la que.

$R^1$ y $R^2$, que pueden ser iguales o diferentes, son H, alquilo $C_1$-$C_6$ o $(CH_2)_d$-(cicloalquilo $C_3$-$C_6$), donde d es 0, 1, 2 ó 3, o $R^1$ y $R^2$ junto con el nitrógeno al que están unidos forman un anillo de azetidina;

uno de Z o Y es $-SR^3$ y el otro de Z o Y es halógeno o $-R^3$, donde $R^3$ es independientemente alquilo $C_1$-$C_4$ opcionalmente sustituido con flúor, excepto que $R^3$ no es $CF_3$,

o Z e Y están unidos de manera que, junto con los átomos de interconexión, Z e Y forman un anillo carbocíclico o heterocíclico de 5 a 7 miembros, condensado, que puede ser saturado, insaturado o aromático, y donde, cuando Z e Y forman un anillo heterocíclico, además de átomos de carbono, el enlace contiene uno o dos heteroátomos seleccionados independientemente entre oxígeno, azufre y nitrógeno, con la condición de que cuando $R^5$ es flúor y $R^2$ es metilo, entonces el anillo condensado no es 1,3-dioxolano, y Z e Y juntos no forman un anillo de fenilo condensado,

$R^4$ y $R^5$, que pueden ser iguales o diferentes, son:

A-X, donde A es $-CH=CH-$ o $-(CH_2)_p-$, donde p es 0, 1 ó 2, X es hidrógeno, F, Cl, Br, I, $CONR^6R^7$, $SO_2NR^6R^7$, $SO_2NHC(=O)R^8$, OH, alcoxi $C_{1-4}$, $NR^8SO_2R^9$, $NO_2$, $NR^6R^{11}$, CN, $CO_2R^{10}$, CHO, $SR^{10}$,

$S(O)R^9$ ó $SO_2R^{10}$, $R^6$, $R^7$, $R^8$ y $R^{10}$, que pueden ser iguales o diferentes, son hidrógeno o alquilo $C_{1-6}$ opcionalmente sustituido independientemente con uno o más $R^{12}$, $R^9$ es alquilo $C_{1-6}$ opcionalmente sustituido independientemente con uno o más $R^{12}$, $R^{11}$ es hidrógeno, alquilo $C_{1-6}$ opcionalmente sustituido independientemente con uno o más $R^{12}$, $C(O)R^6$, $CO_2R^9$, $C(O)NHR^6$ ó $SO_2NR^6R^7$, $R^{12}$ es F, OH, $CO_2H$, cicloalquilo $C_{3-6}$, $NH_2$, $CONH_2$, alcoxi $C_{1-6}$, alcoxi $C_{1-6}$-carbonilo o un anillo heterocíclico de 5 ó 6 miembros que contiene 1, 2 ó 3 heteroátomos seleccionados entre N, S y O, opcionalmente sustituido independientemente con uno o más $R^{13}$, o $R^6$ y $R^7$, junto con el nitrógeno al que están unidos, forman un anillo heterocíclico de 4, 5 ó 6 miembros opcionalmente sustituido independientemente con uno o más $R^{13}$, o

un anillo heterocíclico de 5 ó 6 miembros que contiene 1, 2 ó 3 heteroátomos seleccionados entre N, S y O, opcionalmente sustituido independientemente con uno o más $R^{13}$,

donde $R^{13}$ es hidroxi, alcoxi $C_1$-$C_4$, F, alquilo $C_1$-$C_6$, haloalquilo, haloalcoxi, $-NH_2$, -NH(alquilo $C_1$-$C_6$) o -N(alquilo $C_1$-$C_6$)$_2$

2 Un compuesto según la reivindicación 1, o sus sales, solvatos o polimorfos farmacéuticamente aceptables, en el que $R^1$ y $R^2$, que pueden ser iguales o diferentes, son hidrógeno o alquilo $C_1$-$C_6$.

3 Un compuesto según las reivindicaciones 1 ó 2, o sus sales, solvatos o polimorfos farmacéuticamente aceptables, en el que cuando Z o Y es $-SR^3$, $R^3$ es metilo o etilo

4 Un compuesto según las reivindicaciones 1 ó 2, o sus sales, solvatos o polimorfos farmacéuticamente aceptables, en el que cuando Z e Y están unidos para formar un anillo condensado, el anillo es un anillo heterocíclico

5 Un compuesto según la reivindicación 4, o sus sales, solvatos o polimorfos farmacéuticamente aceptables, en que además de átomos de carbono, el

grupo enlazador contiene uno o dos átomos de azufre

6 Un compuesto segun cualquiera de las reivindicaciones precedentes, o sus sales, solvatos o polimorfos farmacéuticamente aceptables, en el que $R^6$ y $R^7$, que pueden ser iguales o diferentes, son hidrógeno, alquilo $C_1$-$C_3$ opcionalmente sustituido con hidroxi, $-CONH_2$ o alcoxi $C_1$-$C_3$

7 Un compuesto según cualquiera de las reivindicaciones precedentes, o sus sales, solvatos o polimorfos farmacéuticamente aceptables, en el que $R^8$ es hidrógeno, hidroxietilo o metilo

8 Un compuesto según cualquiera de las reivindicaciones precedentes, o sus sales, solvatos o polimorfos farmacéuticamente aceptables, en el que $R^9$ es metilo, etilo, isopropilo, trifluorometilo o metoxietilo

9 Un compuesto según cualquiera de las reivindicaciones precedentes, o sus sales, solvatos o polimorfos farmacéuticamente aceptables, en el que p es 1 ó 0

10 Un compuesto según cualquiera de las reivindicaciones precedentes, o sus sales, solvatos o polimorfos farmacéuticamente aceptables, en el que $R^4$ y $R^5$, que pueden ser iguales o diferentes, son

$-(CH_2)_p$-X, donde p es 0, 1 ó 2, X es hidrógeno, hidroxi, $CONR^6R^7$, $SO_2NR^6R^7$, $NR^8SO_2R^9$, $SR^{10}$, $SOR^9$ ó $SO_2R^{10}$, donde $R^6$, $R^7$, $R^8$, $R^9$ y $R^{10}$ son como se han definido en la reivindicación 1, o

un anillo heterocíclico de 5 ó 6 miembros que contiene 1, 2 ó 3 heteroátomos seleccionados entre N, S y O

11 Un compuesto según cualquiera de las reivindicaciones precedentes, o sus sales, solvatos o polimorfos farmacéuticamente aceptables, en el que $R^4$ y $R^5$, que pueden ser iguales o diferentes, son

$-(CH_2)_p$-X, donde p es 0 ó 1, X es hidrógeno, hidroxi, $CONR^6R^7$, $SO_2NR^6R^7$ ó $NR^8SO_2R^9$, donde $R^6$ y $R^7$, que pueden ser iguales o diferentes, son hidrógeno o alquilo $C_1$-$C_3$ opcionalmente sustituido con hidroxi, $-CONH_2$ o

alcoxi $C_1$-$C_3$ (preferiblemente metoxi), $R^8$ es hidrógeno, hidroxietilo o metilo, o $R^9$ es metilo, etilo, isopropilo, trifluorometilo o metoxietilo; o triazolilo, imidazolilo o pirazolilo.

12 Un compuesto segun cualquiera de las reivindicaciones precedentes, o sus sales, solvatos o polimorfos farmacéuticamente aceptables, en el que $R^4$ y $R^5$ no son ambos hidrógeno

13 Un compuesto según cualquiera de las reivindicaciones precedentes, o sus sales, solvatos o polimorfos farmacéuticamente aceptables, en el que $R^4$ es hidrógeno

14 Un compuesto según la reivindicación 1, o sus sales, solvatos o polimorfos farmacéuticamente aceptables, seleccionados del grupo

4-(2,3-dihidro-1-benzotien-5-iloxi)-3-[(metilamino)metil]bencenosulfonamida (Ejemplo 2),

3-[(dimetilamino)metil]-4-[3-metil-4-(metilsulfanil)fenoxi]bencenosulfonamida (Ejemplo 12),

4-(2,3-dihidro-1-benzotien-5-iloxi)-3-[(dimetilamino)metil]bencenosulfonamida (Ejemplo 16),

4-[3-cloro-4-(metilsulfanil)fenoxi]-3-[(dimetilamino)metil]bencenosulfonamida (Ejemplo 17),

3-[(dimetilamino)metil]-4-[3-fluoro-4-(metilsulfanil)fenoxi]bencenosulfonamida (Ejemplo 18),

*N,N*-dimetil-*N*-[2-(6-quinoliniloxi)bencil]amina (Ejemplo 29)

3-[(metilamino)metil]-4-(6-quinoliniloxi)bencenosulfonamida (Ejemplo 35),

4-(2,3-dihidro-1-benzotien-5-iloxi)-3-[(metilamino)metil]benzamida (Ejemplo 60),

4-(2,3-dihidro-1-benzotien-5-iloxi)-*N*-metil-3-[(metilamino)metil]benzamida (Ejemplo 62),

*N*-{3-[(metilamino)metil]-4-[3-metil-4-(metilsulfanil)fenoxi]bencil}metanosulfonamida (Ejemplo 75),

3-[(metilamino)metil]-4-[3-metil-4-(metilsulfanil)fenoxi]benzamida (Ejemplo 79),

4-(2,3-dihidro-1,4-benzoxatiin-7-iloxi)-3-[(dimetilamino)metil]benzamida (Ejemplo 88),

{3-[(dimetilamino)metil]-4-[3-fluoro-4-(metilsulfanil)fenoxi]fenil}metanol (Ejemplo 90),

3-[(dimetilamino)metil]-4-(6-quinoliniloxi)benzamida (Ejemplo 100),

3-[(metilamino)metil]-4-(6-quinoliniloxi)benzamida (Ejemplo 102),

*N*-metil-*N*-{3-[(metilamino)metil]-4-[3-metil-4-(metilsulfanil)fenoxi]fenil}-metanosulfonamida (Ejemplo 116), y

*N*-{4-(2,3-dihidro-1,4-benzoxatiin-7-iloxi)-3-[(dimetilamino)metil]fenil}metanosulfonamida (Ejemplo 124)

15 Un compuesto según cualquiera de las reivindicaciones precedentes, o sus sales, solvatos o polifomorfos farmacéuticamente aceptables, para uso como un fármaco

16 Una formulación farmacéutica que contiene un compuesto según cualquiera de las reivindicaciones 1 a 14, o sus sales, solvatos o polifomorfos farmacéuticamente aceptables, y un coadyuvante, diluyente o vehículo farmacéuticamente aceptable

17 El uso de un compuesto según una cualquiera de las reivindicaciones 1 a 14, o sus sales, solvatos o polifomorfos farmacéuticamente aceptables, en la fabricación de un medicamento para el tratamiento o prevención de un trastorno en el que está implicada la regulación de la función de los transportadores de monoaminas

18 El uso segun la reivindicación 17, en el que el trastorno es depresión, trastorno de hiperactividad con déficit de atención, trastorno obsesivo compulsivo, trastorno de estrés post-traumático, trastornos de abuso de sustancias o disfunción sexual

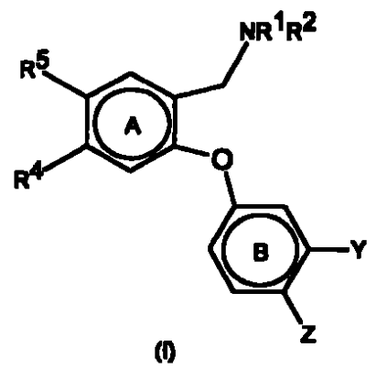
19 El uso según la reivindicación 18, en la fabricación de un medicamento para el tratamiento o prevención de eyaculación precoz.

20 Un método de tratamiento o prevención de un trastorno en el que está implicada la regulación de la función de los transportadores de monoaminas, que comprende la administración de una cantidad eficaz de un compuesto según una cualquiera de las reivindicaciones 1 a 14, o sus sales, solvatos o polimorfos farmacéuticamente aceptables, a un paciente que necesita dicho tratamiento o prevención

21 Un método de tratamiento o prevención de eyaculación precoz, que comprende la administración de una cantidad eficaz de este compuesto según una cualquiera de las reivindicaciones 1 a 14, o sus sales, solvatos o polimorfos farmacéuticamente aceptables, a un paciente con necesidad de dicho tratamiento o prevención,

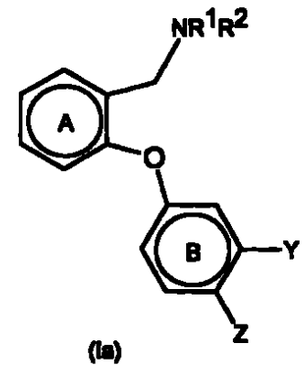
22. Un método para incrementar la latencia eyaculatoria, que comprende la administración de una cantidad eficaz de un compuesto según una cualquiera de las reivindicaciones 1 a 14, o sus sales, solvatos o polimorfos farmacéuticamente aceptables, a un varón que desea latencia eyaculatoria incrementada

23 Un procedimiento para la preparación de un compuesto de fórmula general (I):




(I)

en la que $R^1$, $R^2$, $R^4$, $R^5$, X y Z son como se han definido en una cualquiera de las reivindicaciones 1 a 14, que comprende hacer reaccionar un compuesto de fórmula general Ia




(Ia)

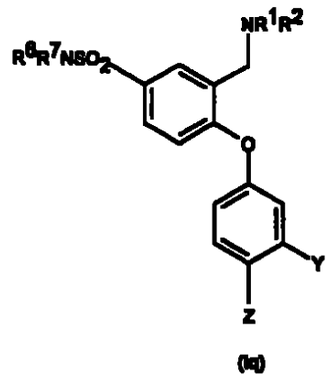
en condiciones de reacción adecuadas para formar el compuesto de fórmula I, en la que las condiciones de reacción adecuadas son.

i) Cuando $R^4/R^5$ son halógeno, por reacción de (Ia) con un agente halogenante adecuado en un disolvente inerte que no afecte adversamente a la reacción,

ii) Cuando $R^4/R^5$ son $-NO_2$, por reacción de (Ia) con un agente nitrante adecuado en un disolvente inerte que no afecte adversamente a la reacción a temperatura ambiente o más baja,

ii) Cuando $R^4/R^5$ es $-SO_2NR^6R^7$, por reacción de un cloruro de sulfonilo intermedio con la amina requerida de fórmula $HNR^6R^7$ en un disolvente adecuado

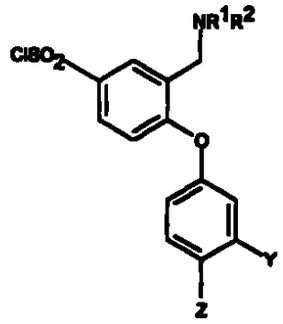
24 Un procedimiento según la reivindicación 23, para preparar un compuesto de fórmula (Iq), es decir un compuesto de fórmula I en la que $R^5$ es $-SO_2NR^6R^7$ y $R^4$ es hidrógeno,




(Iq)

que comprende

a) hacer reaccionar un compuesto de fórmula Ia, opcionalmente en un disolvente adecuado, con ácido clorosulfónico para dar un compuesto de fórmula XVIII



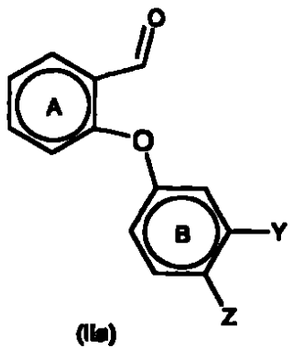
(XVIII)

seguido por

b) hacer reaccionar con $HNR^6R^7$ para dar el compuesto de fórmula (Iq)

25 Un procedimiento según la reivindicación 24, en donde el compuesto de fórmula XVIII se genera *in situ* y se hace reaccionar con $HNR^6R^7$ sin aislamiento

26 Un procedimiento según una cualquiera de las reivindicaciones 23 a 25, que comprende además la etapa de preparar compuestos de fórmula (Ia), haciendo reaccionar compuestos de fórmula (IIa)



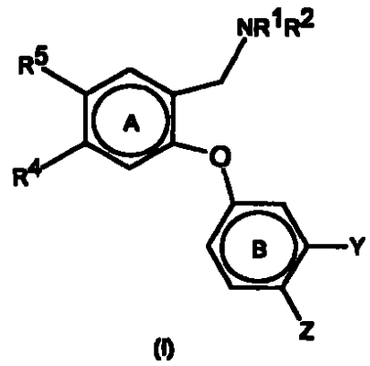
(IIa)

con un compuesto de fórmula $HNR^1R^2$, o con una forma de sal adecuada de la misma, junto con un agente reductor de tipo hidruro en un disolvente adecuado, para

formar el compuesto de fórmula (Ia)

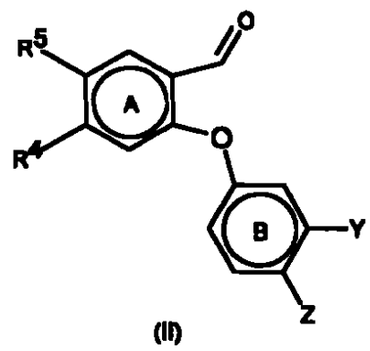
27 Un compuesto intermedio de fórmula (IIa) o (XVIII) según las reivindicaciones 23 a 26

28 Un procedimiento para preparar un compuesto de fórmula I




(I)

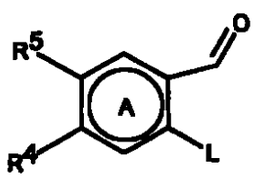
en la que $R^1$, $R^2$, $R^4$, $R^5$, X y Z son como se han definido en una cualquiera de las reivindicaciones 1 a 14, que comprende hacer reaccionar compuestos de fórmula II




(II)

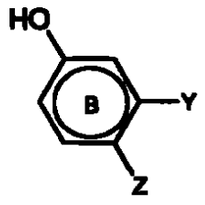
con un compuesto de fórmula $HNR^1R^2$, o con una forma de sal adecuada de la misma, junto con un agente reductor de tipo hidruro en un disolvente adecuado

29 Un procedimiento según la reivindicación 28, que comprende además acoplar en condiciones de reacción adecuadas un compuesto de fórmula III,



(III)

en la que L es un grupo fácilmente eliminable adecuado tal como halógeno o un éster sulfonato tal como trifluorometanosulfonato o metanosulfonato, con un compuesto de fórmula IV



(IV)

para dar el compuesto de fórmula II

30 Un compuesto intermedio de fórmula II según la reivindicación 28

31. Un compuesto de fórmula general (I), o sus sales, solvatos o polimorfos farmacéuticamente aceptables, en la que $R^1$, $R^2$, Y y Z son como se han definido en la reivindicación 1, y $R^4$ y $R^5$, que pueden ser iguales o diferentes, son $-(CH_2)_p$-A', donde p es 0, 1 ó 2 y A' es un grupo polar .

32 Un compuesto segun la reivindicación 23, en el que el grupo polar tiene un valor δ más negativo que -0,1

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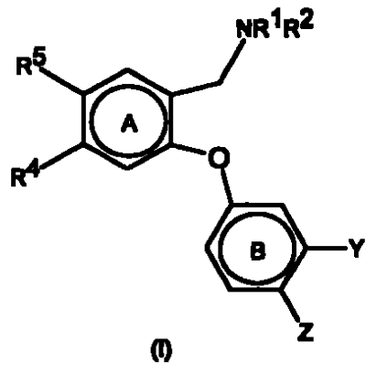
200

## RESUMEN

Un compuesto de fórmula general (I) en la que $R^1$ y $R^2$ son H, alquilo $C_1$-$C_6$ o $(CH_2)_d$-(cicloalquilo $C_3$-$C_6$), donde d es 0, 1, 2 ó 3, o $R^1$ y $R^2$ junto con el nitrógeno al que están unidos forman un anillo de azetidina, uno de Z o Y es $-SR^3$ y el otro de Z o Y es halógeno o $-R^3$, donde $R^3$ es independientemente alquilo $C_1$-$C_4$ opcionalmente sustituido con flúor, excepto que $R^3$ no es $CF_3$, o Z e Y están unidos de manera que, junto con los átomos de interconexión, Z e Y forman un anillo carbocíclico o heterocíclico de 5 a 7 miembros, condensado, y donde, cuando Z e Y forman un anillo heterocíclico, además de átomos de carbono, el enlace contiene uno o dos heteroátomos seleccionados independientemente entre oxígeno, azufre y nitrógeno, $R^4$ y $R^5$, que pueden ser iguales o diferentes, son A-X, donde A es $-CH=CH-$ o $-(CH_2)_p-$, donde p es 0, 1 ó 2, X es hidrógeno, F, Cl, Br, I, $CONR^6R^7$, $SO_2NR^6R^7$, $SO_2NHC(=O)R^6$, OH, alcoxi $C_{1-4}$, $NR^8SO_2R^9$, $NO_2$, $NR^6R^{11}$, CN, $CO_2R^{10}$, CHO, $SR^{10}$, $S(O)R^9$ ó $SO_2R^{10}$, o un anillo heterocíclico de 5 ó 6 miembros que contiene 1, 2 ó 3 heteroátomos seleccionados entre N, S y O, opcionalmente sustituido independientemente con uno o más $R^{13}$, donde $R^{13}$ es hidroxi, alcoxi $C_1$-$C_4$, F, alquilo $C_1$-$C_6$, haloalquilo, haloalcoxi, $-NH_2$, -NH(alquilo $C_1$-$C_6$) o -N(alquilo $C_1$-$C_6$)$_2$




(I)

13

204

201

# PATENT COOPERATION TREATY

# PCT

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

| Applicant's or agent's file reference | FOR FURTHER ACTION | See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) |
|---|---|---|
| PCS10945ARCS | | |
| International application No. | International filing date *(day/month/year)* | Priority date *(day/month/year)* |
| PCT/IB01/01521 | 22/08/2001 | 31/08/2000 |
| International Patent Classification (IPC) or national classification and IPC | | |
| C07C323/20 | | |
| Applicant | | |
| PFIZER LIMITED et al | | |

1 This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36

2 This REPORT consists of a total of 8 sheets, including this cover sheet.

☒ This report is also accompanied by ANNEXES, i e sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70 16 and Section 607 of the Administrative Instructions under the PCT)

These annexes consist of a total of 2 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

| Date of submission of the demand | Date of completion of this report |
|---|---|
| 22/11/2001 | 20.12.2002 |
| Name and mailing address of the international preliminary examining authority: | Authorized officer |
| European Patent Office<br>D-80298 Munich<br>Tel +49 89 2399 - 0 Tx 523656 epmu d<br>Fax +49 89 2399 - 4465 | Seufert, G<br>Telephone No. +49 89 2399 8330 |

Form PCT/IPEA/409 (cover sheet) (January 1994)

285
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# INTERNATI NAL PRELIMINARY EXAMINATION REP RT

International application No PCT/IB01/01521

## I. Basis of the report

1 With regard to the **elements** of the international application *(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 since they do not contain amendments (Rules 70.16 and 70.17))*:
**Description, pages:**

| | | | | | |
|---|---|---|---|---|---|
| 1-96 | as originally filed | | | | |

**Claims, No..**

| | | | | | |
|---|---|---|---|---|---|
| 1-25,26 (part) | as originally filed | | | | |
| 26 (part),27-32 | as received on | 10/07/2002 | with letter of | 04/07/2002 | |

2 With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item

These elements were available or furnished to this Authority in the following language , which is

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23 1(b))
- ☐ the language of publication of the international application (under Rule 48 3(b))
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3)

3 With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing

- ☐ contained in the international application in written form
- ☐ filed together with the international application in computer readable form
- ☐ furnished subsequently to this Authority in written form
- ☐ furnished subsequently to this Authority in computer readable form
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

4 The amendments have resulted in the cancellation of:

- ☐ the description, pages
- ☐ the claims, Nos
- ☐ the drawings, sheets

**INTERNATIONAL PRELIMINARY EXAMINATI N REPORT**

International application No PCT/IB01/01521

5 ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70 2(c))

*(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6 Additional observations, if necessary

**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. 20-22 for industrial applicability

because

☒ the said international application, or the said claims Nos 20-22 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. are so unclear that no meaningful opinion could be formed (*specify*)

☐ the claims, or said claims Nos are so inadequately supported by the description that no meaningful opinion could be formed

☐ no international search report has been established for the said claims Nos

2 A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions.

☐ the written form has not been furnished or does not comply with the standard

☐ the computer readable form has not been furnished or does not comply with the standard

**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 | 1-32 |
| | No | Claims | |
| Inventive step (IS) | Yes | Claims | 1-32 |

| | | | |
|---|---|---|---|
| | No | Claims | |
| Industrial applicability (IA) | Yes | Claims | 1-19, 23-28 |
| | No | Claims | |

2 Citations and explanations
**see separate sheet**

Reference is made to the following documents

D1 US-A-5691373
D2 WO-A-9947497
D3 WO-A-0050380 (certain documents Rule 70 10)
D4 EP-A-516234
D5 WO-A-9717325

## III. Non establishment of opinion

Claims 20-22 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)
Furthermore, the applicant has already been informed by the International Search Authority that the compounds mentioned on page 7 are not included in the claims Additionally, the applicant has been informed that it is unclear what compounds are encompassed by the vague and undefined terms "prodrugs", "promoieties" or "protected derivatives", which according to the description, but not the claims, are meant to be part of the invention. As a result of these inconsistencies and unclarities, the search has been limited to the compounds defined by the claims (compounds of formula I, their salts, solvates and polymorphs)
Consequently, the examination of the present invention with regard to novelty, inventive step and industrial applicability has only been carried out for the claimed subject-matter

## V. Reasoned statement under Art. 35(2) PCT with regard to novelty, inventive step and industrial applicability

### Novelty

The present application refers to phenoxybenzylamine compounds of the general formula (I) (claim 1), their preparation (claims 23, 28), intermediates of the prepa-

ration processes (claims 27, 30), pharmaceutical compositions comprising compounds of the formula (I) (claim 16) and their use in the treatment or prevention of disorders related to the regulation of monoamine transporter function (claims 17, 20).

None of the available prior art discloses compounds falling within the scope of claim 1 Claim 1 as well as claims 16, 17, 20, 23 and 28 and their dependent claims may therefore be regarded as novel (Art. 33(2) PCT)

Novelty over the disclosure of D1 and D3 has been established with the introduction of a disclaimer into claims 27 and 30 Thus, claims 27 and 30 are considered to meet the requirement of Art 33(2) PCT.
The aforementioned statement has been made under the assumption that the variables Z and Y may not form a fused phenyl ring at all independently from the definition of the variables $R^2$ and $R^5$, because in fact the proviso could be read in two ways: either Z and Y do not form a fused phenyl ring when $R^5$ is fluorine and $R^2$ is methyl or Z and Y in general do not form a fused phenyl ring, e.g all compounds whereby Y and Z form a fused phenyl ring are excluded

**Inventive step**

The compounds of the present invention inhibit the monoamine re-uptake and especially exhibit activity as selective serotonin re-uptake inhibitors (SSRIs).

Documents D4 or D5 may be considered as the most relevant state of the art They refer to compounds which are structurally different from the presently claimed compounds, but having the same activity The compounds of D4 are phenoxybenzylamine compounds, which mainly differ by the substituents in the ring B (one or two halogen atoms). They are monoamine re-uptake inhibitors, but not selective for serotonin (see D4, page 2, lines 7-17) Document D5 describes phenylthiobenzylamine derivatives, which are selective serotonin inhibitors (see D5, page 1, first paragraph).

The problem to be solved by the present invention was therefore to provide further compounds with the desired activity.

The problem was solved by the compounds according to the present invention (see pages 94-96 of the description).

The man skilled in the art gets no indication in the prior art for the modification of the prior art compounds in such a way as to obtain the compounds according to the presently claimed compounds Furthermore, it was not obvious that the so modified compounds would still exhibit the required activity.
Thus, the subject-matter of the claims appears to involve an inventive step (Art. 33(3) PCT)

**Industrial applicability**

For the assessment of the present claims 20-22 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

**Further remarks:**

Claim 1 of the present application does not meet the requirement of Art. 6 PCT (clarity and conciseness) for the following reasons.

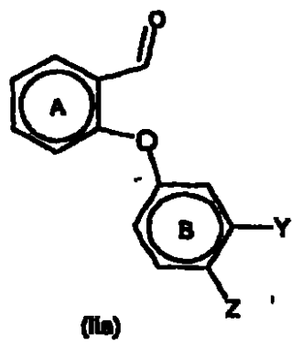
1. There are two ways to read the proviso: either Z and Y do not form a fused ring when $R^5$ is fluorine and $R^2$ is methyl or Z and Y in general, e g. in all compounds of formula (I), do not form a fused ring It is not clear, which compounds are excluded

2 The embodiments of the invention described on page 7, line 6 - page 6, line 15 do not fall within the scope of the claims (different definitions for various substituents, for example Y, Z) This inconsistency between the claims and the description

leads to doubt concerning the matter for which protection is sought, thereby rendering the claims unclear (Article 6 PCT) Furthermore, these compounds are already disclosed in document WO-A-0172687, although this document is not considered to be part of the prior art in the sense of Rule 64.1 for the purpose of Art 33(2) and (3)

3. Claim 31 refers to compounds with two substituents on the ring A ($R^5$ and $R^4$ = $(CH_2)_p$-A', with A' equal to a polar group) Such compounds and their suitability as selective serotonin inhibitors are not sufficiently supported by the application, see all examples, where only one substituent is present, and the biological data on page 95-96 Furthermore, the expression "polar group" is not sufficiently clear With regard to page 8, line 25-32 there appear to exist different ways to define a polar group

4. The embodiments described on pages 11, lines 1-25 do not fall within the scope of the claims This inconsistency between the claims and the description leads to doubt concerning the matter for which protection is sought, thereby rendering the claims unclear (Article 6 PCT)

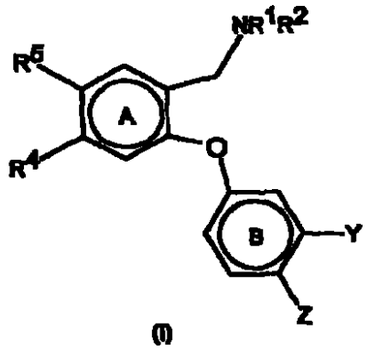


(IIa)

with a compound of formula $HNR^1R^2$, or with a suitable salt form thereof, together with a hydride reducing agent in a suitable solvent, to form the compound of formula (Ia).

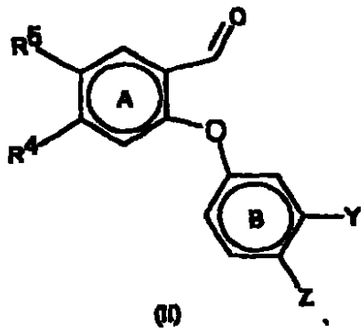
27 An intermediate compound of formula (IIa) or (XVIII) as defined in claims 23 to 26 with the proviso that (IIa) may not be 2 ((3', 4' - Methylenedioxy) phenoxy) benzaldehyde.

28 A process for preparing a compound of formula I



(I)

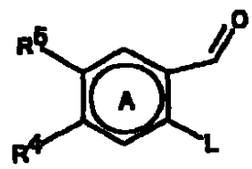
wherein $R^1$, $R^2$, $R^4$, $R^5$, X and Z are as defined in any one of claims 1 to 14, comprising reacting compounds of formula II



(II)

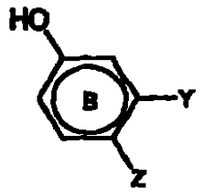
with a compound of formula $HNR^1R^2$ or with a suitable salt form thereof, together with a hydride reducing agent in a suitable solvent.

29 A process according to claim 28 which further comprises coupling under suitable reaction conditions a compound of formula III,



(III)

wherein L is a suitable leaving group such as halogen or a sulfonate ester such as trifluoromethanesulfonate or methanesulfonate, with a compound of formula IV



(IV)

to give the compound of formula II.

30 An intermediate compound of formula II as defined in claim 28 ,with the proviso that (11) may not be 2 -((3',4' - Methylenadioxy) phenoxy) benzaldehyde or 2 ((3',4' - Methylenedioxy) phenoxy) 5-fluorobenzaldehyde.

31 A compound of general formula (I), or pharmaceutically acceptable salts, solvates or polymorphs thereof, wherein $R^1$, $R^2$, Y and Z are as defined in claim 1; and $R^4$ and $R^5$, which may be the same or different, are $-(CH_2)_p-A'$, wherein p is 0, 1 or 2 and A' is a polar group.

32 A compound according to claim 23, wherein the polar group has a δ-value more negative than -0.1

# INTERNATI NAL SEARCH REPORT

Int 'al Application No
PCT/IB 01/01521 211

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C323/20 C07D333/54 C07D327/06 C07D307/87 C07D333/72
C07C311/37 C07D215/18 C07D239/74 C07D277/62 A61K31/18
A61K31/38 A61K31/39 A61K31/34 A61K31/135 A61K31/47 .215

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C C07D

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
BEILSTEIN Data, CHEM ABS Data, EPO-Internal, WPI Data

C DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | US 5 691 373 A (EDMUNDS JEREMY JOHN ET AL) 25 November 1997 (1997-11-25) example 323 | 27,30 |
| X | WO 99 47497 A (MERCK FROSST CANADA INC ,BELLEY MICHEL (CA), GAREAU YVES (CA), JUT) 23 September 1999 (1999-09-23) page 81, line 31 - line 35 | 27,30 |
| P,X | WO 00 50380 A (HOWARD HARRY RALPH JR ,SEEGER THOMAS FRANCIS (US), PFIZER PROD INC) 31 August 2000 (2000-08-31) page 26, preparation 6 | 30 |
| A | EP 0 516 234 A (AKZO NV) 2 December 1992 (1992-12-02) page 2, line 7 - line 17, claims; examples | 1-32 |

-/--

[X] Further documents are listed in the continuation of box C. [X] Patent family members are listed in annex.

* Special categories of cited documents

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

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

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 22 November 2001 | 05/12/2001 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016 | Seufert, G |

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

# INTERNATIONAL SEARCH REP RT

In al Application No
PCT/IB 01/01521

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/495 A61K31/425

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)

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)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | WO 97 17325 A (FARMAK A S ;POLIVKA ZDENEK (CZ); DOBROVSK KAREL (CZ); SILHANKOVA A) 15 May 1997 (1997-05-15) page 1, paragraph 1, claims; examples | 1-32 |
| L | WO 01 72687 A (MIDDLETON DONALD STUART ,STOBIE ALAN (GB), HEPWORTH DAVID (GB); PF) 4 October 2001 (2001-10-04) | |

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

☒ Patent family members are listed in annex.

* Special categories of cited documents

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 22 November 2001 | |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax: (+31-70) 340-3016 | Seufert, G |

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

International Application No. PCT/IB 01 /01521

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

The compounds mentioned on page 7 of the application are not included in the scope of the claims and have not been searched.
Furthermore, it is not clear what compounds are encompassed by the vague and undefined terms "prodrugs", "promoieties" or "protected derivatives", which, according to the description (see page 11) are meant to be part of the invention Therefore, the search has been carried out only for those compounds, which are defined by the claims.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT) The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

# INTERNATI NAL SEARCH REPORT

In al Application No
PCT/IB 01/01521

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| US 5691373 A | 25-11-1997 | US 6017916 A | 25-01-2000 |
| | | AU 693110 B2 | 25-06-1998 |
| | | AU 7561794 A | 14-03-1995 |
| | | CA 2165567 A1 | 23-02-1995 |
| | | CZ 9600409 A3 | 11-09-1996 |
| | | EP 0714391 A1 | 05-06-1996 |
| | | FI 960671 A | 19-04-1996 |
| | | HU 74179 A2 | 28-11-1996 |
| | | JP 9501920 T | 25-02-1997 |
| | | NO 960629 A | 16-02-1996 |
| | | NZ 271833 A | 22-08-1997 |
| | | SK 20396 A3 | 05-03-1997 |
| | | WO 9505376 A1 | 23-02-1995 |
| | | ZA 9406265 A | 19-02-1996 |
| WO 9947497 A | 23-09-1999 | AU 2708699 A | 11-10-1999 |
| | | WO 9947497 A2 | 23-09-1999 |
| | | EP 1071648 A2 | 31-01-2001 |
| | | US 6242493 B1 | 05-06-2001 |
| WO 0050380 A | 31-08-2000 | AU 3070900 A | 14-09-2000 |
| | | EP 1154984 A1 | 21-11-2001 |
| | | WO 0050380 A1 | 31-08-2000 |
| EP 0516234 A | 02-12-1992 | AT 127777 T | 15-09-1995 |
| | | AU 650136 B2 | 09-06-1994 |
| | | AU 1710492 A | 03-12-1992 |
| | | CA 2068373 A1 | 30-11-1992 |
| | | DE 69204743 D1 | 19-10-1995 |
| | | DE 69204743 T2 | 04-04-1996 |
| | | DK 516234 T3 | 29-01-1996 |
| | | EP 0516234 A1 | 02-12-1992 |
| | | ES 2079783 T3 | 16-01-1996 |
| | | FI 922433 A | 30-11-1992 |
| | | GR 3018357 T3 | 31-03-1996 |
| | | IE 921422 A1 | 02-12-1992 |
| | | JP 5148197 A | 15-06-1993 |
| | | NO 178395 B | 11-12-1995 |
| | | US 5430063 A | 04-07-1995 |
| | | US 5190965 A | 02-03-1993 |
| | | ZA 9203283 A | 27-01-1993 |
| WO 9717325 A | 15-05-1997 | CZ 9502935 A3 | 15-12-1999 |
| | | WO 9717325 A1 | 15-05-1997 |
| | | EP 0859757 A1 | 26-08-1998 |
| | | HU 9901136 A2 | 30-08-1999 |
| | | SK 46798 A3 | 09-09-1998 |
| WO 0172687 A | 04-10-2001 | WO 0172687 A1 | 04-10-2001 |

216 213

# REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

| | USUARIO | RADICADOR |
|---|---|---|
| **PATENTE DE INVENCIÓN MODELO DE UTILIDAD** | ( ) | ( ) |
| - Indicación de que se solicita la concesión de una patente. | ( ) | ( ) |
| - Datos de identificación del solicitante o de la persona que se presenta la solicitud. | ( ) | ( ) |
| - Descripción de la invención. | ( ) | ( ) |
| - Dibujos de ser estos pertinentes. | ( ) | ( ) |
| - Comprobante de Pago de las tasas establecidas. | | |
| **COMPLETA ( )** **INCOMPLETA** | ( ) | ( ) |
| **DISEÑO INDUSTRIAL ( )** | | |
| - Indicación de que se solicita el registro de Diseño Industrial | ( ) | ( ) |
| - Datos de identificación del solicitante o de la persona que presenta | ( ) | ( ) |
| - la solicitud. | | |
| - Representación gráfica y fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño. | ( ) | ( ) |
| Comprobante de pago de las tasas establecidas | ( ) | ( ) |
| **COMPLETA ( )** **INCOMPLETA** | ( ) | ( ) |
| **ESQUEMA DE TRAZADO ( )** | | |
| - Indicación de que solicita el registro de un Esquema de trazado. | ( ) | ( ) |
| - Datos de identificación del solicitante o de la persona que presenta La solicitud. | ( ) | ( ) |
| Representación gráfica del esquema de trazado | ( ) | ( ) |
| Comprobante de pago de las tasas establecidas. | ( ) | ( ) |
| **COMPLETA ( )** **INCOMPLETA** | ( ) | ( ) |

**Firma Responsable:**

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Radicacion : 03088184 00000000 Folios: 219

**Fecha:** Fecha (AMD): 2003-02-04 17:13:59
Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia: 2000 DIVISION DE NUEVAS CREACIONES

RC 214

**Industria y Comercio**
**SUPERINTENDENCIA**

2020
Bogotá, D.C.,

217

**Doctor:**
CARLOS R. OLARTE
Apoderado
PFIZER INC.

**Oficio N°** 09134

| **ASUNTO:** | | |
|---|---|---|
| | **Radicación N°** | 03-08184 |
| | **Solicitud Internacional** | PCT/IB01/01521 |
| | **Fecha Inicio fase nacional** | 31/03/2003 |
| | **Trámite** | 011 |
| | **Evento** | 379 |
| | **Actuación** | 430 |
| | **Folios** | 001 |

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

- La solicitud no contiene la traducción de los anexos del reporte de examen preliminar internacional (Art. 36.2.b) del tratado PCT).

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

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

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

El anterior requerimiento fue notificado por fijación en lista de fecha, 24 OCT. 2003.

202047

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