Industria y Comercio

SUPERINTENDENCIA QF

PCT

Delegatura de propiedad Industrial

División de Nuevas Creaciones

SOLICITUD

PATENTE DE INVENCIÓN

21 **EXPEDIENTE No.** 03-79617

54 **TÍTULO** Derivados de Pirrolol

51 **CLASIFICACIÓN INTERNACIONAL**

71 **SOLICITANTE** Pfizer Inc.
235 East 42nd Street, New York

DOMICILIO New York 10017, Estados Unidos de America

74 **APODERADO** Carlos A Olarte.

22 **BOGOTÁ, D. C.,** Septiembre 10- 2003

SS

(FORMA P 10)

1/600 126 1

PETITORIO

Industria y Comercio
SUPERINTENDENCIA

03 079617 00

SUPERINTENDENCIA Y COMERCIO Folios: 600
Radicacion : 03079617 00000000
Fecha (AMD): 2003-09-10 17:14:01
Tramite 011 PCT-PATENT X29 FASE NACI 411 PRESENTACIÓN
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

FORMULARIO UNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL

(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 Eastr 42 nd Street, New York, New York 10017 Estados Unidos de America.

Nacionalidad o Domicilio

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 World Trade Center Torre C, Calle 100 No 8A 55 Piso 10

Teléfono 6386200 Fax 6386201

E-Mail filings@olarterasbeck com

IDENTIFICACION

C C [X] NIT [ ]

C E [ ] Otro [ ]

Cual

Número 79 782 747 Bta TP 74 295

(4) INVENTOR (ES) (72)

Nombre LYN HOWARD JONES CHARLES ERIC MOWBRAY DAVID ANTHONY PRICE, MATTHEW DUNCAN SELBY PAUL ANTHONY STUPPLE

Dirección Ramsgate Road, Sandwich, Kent, CT13 9NJ Reino Unido

Nacionalidad o Domicilio BRITANICA

(5) PCT (86)

Solicitud Internacional No PCT/IB02/01234 Fecha Abril 4 2002

Publicación Internacional No WO 02/085860 Fecha Octubre 31 2002

(6) Titulo (54) DERIVADOS DE PIRAZOL

(7) Clasificación Internacional (51) A61K31/415; C07D231/18

(8) Prioridad

SI [X] NO [ ]

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
GB	Abril 13 2001	0108999 4
GB	Noviembre 15 2001	0127426 5

(9) Comprobante de pago No 61688 **Fecha** 09/01/2003

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
- [ ] Declaraciones
- [X] Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- [X] Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- [ ] Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen preliminar (IPEA)
- [ ] Traducción del examen preliminar internacional efectuado por la IPEA
- [ ] De ser el caso, copia del contrato de acceso
- [ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas
- [ ] De ser el caso, certificado de depósito del material biológico
- [ ] Arte final 12 x 12
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud
- [ ] De ser el caso, modificaciones efectuadas a la solicitud internacional.
- [X] Otros: BUSQUEDA INTERNACIONAL

(11) FIGURA CARATERISTICA

(12) Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTE

FIRMA:

C.C. 74.782.747 de Btá T.P. 74.295

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

3

SUPERINDUSTRIA Y COMERCIO
Radicacion : 03079617 00000000 Folios: 600
Fecha (AMD): 2003-09-10 17:14:01
Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

. NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 03 - 61,688
FECHA : SEPTIEMBRE 1 DE 2003

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
FREDERICK TORRES	CONSIGNACION	BANCO POPULAR	050-00110-6	14578066	29/08/2003	3,870,000.00

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

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	400,000.00
		TOTAL : $	400,000.00

SON: CUATROCIENTOS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

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

APOSTILLA EN PODER DE REPRESENTACIÓN DE

PFIZER INC.

Bilingüe inglés- español otorgado en Nueva York, Estados Unidos el 14 de julio de 2003 y firmado por J. Trevor Lumb, Vicepresidente de Pfizer Products Inc.

CERTIFICACION NOTARIAL

Bilingüe inglés- español, el 14 de julio de 2003 el suscrito notario Kenneth Greenwood certifica que J. Trevor Lumb, domiciliado en Nueva York ejercía funciones de Asistente General Consejero de Patentes la Compañía Pfizer Inc., con sede en Nueva York, Nueva York, Estados Unidos.

Firma del notario: Kenneth Greenwood

Sello notarial: certificado, verificado y autenticado en la Localidad de Egham en Surrey, 14 julio, 2003 por el Notario Kenneth Greenwood-Horne Engall & Freeman

Sello Notario Público en alto relieve rojo.

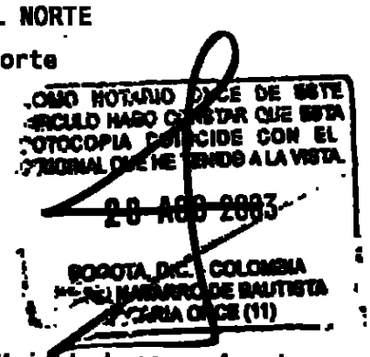
APOSTILLA

REINO UNIDO DE GRAN BRETAÑA E IRLANDA DEL NORTE

1. País :Reino Unido de Gran Bretaña e Irlanda del Norte
   Este documento Público
2. ha sido firmado por K. Greenwood
3. ejerce funciones de Notario Público
4. Lleva el sello de dicho Notario Público

CERTIFICADO

5. En Londres 6. El 17 de julio de 2003
7. Por el Secretario de Estado Principal de su Majestad para Asuntos exteriores y de la mancomunidad
8. No. G210434
9. Sello del Secretario de Estado Principal de su Majestad para Asuntos exteriores y de la mancomunidad
10. Firma de R. Bawden - Por Secretario de Estado



Si el documento se usa en un país que no es parte de la convención de la Haya del 5 de octubre 1961, debe presentarse en sección consular de la misión que representa el país.

Es traducción fiel del inglés, con copia archivo para confrontación. Bogotá 25 de julio-2003. Marlen Neira C

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

OLARTERAISBECK

OLARTE RAISBECK & FRIERI, LTDA.
LEGAL & PROFESSIONAL SERVICES

WORLD TRADE CENTER – TORRE C
CALLE 100 NO. 8A-55 PISO 10
BOGOTA, COLOMBIA
TELEPHONE: +57-1 638-6200
FAX: +57-1 638-6201

www.olarteraisbeck.com

5 3

Power of Attorney

The undersigned,

Pfizer Inc.

domiciled in

235 East 42nd Street, New York, NY 10017 USA

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

Poder

El suscrito,

Pfizer Inc.

domiciliado en

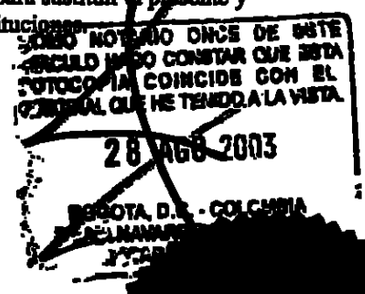
235 East 42nd Street, New York, NY 10017 USA

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

Signature/Firma: _____

Date/Fecha: July 14, 2003

City,Country/Ciudad,País: New York, USA



6 A

OLARTERAISBECK

OLARTE RAISBECK & FRIERI, LTDA.
LEGAL & PROFESSIONAL SERVICES

WORLD TRADE CENTER – TORRE C
CALLE 100 NO. 8A-55 PISO 10
BOGOTA, COLOMBIA
TELEPHONE: +57-1 638-6200
FAX: +57-1 638-6201

www.olarteraisbeck.com

Notarial Certification

On this date,
July 14, 2003
The undersigned Notary Public certifies:

1. That J. Trevor Lumb
of legal age and domiciled in New York, USA
signed the foregoing document.

2. That the grantor has executed the foregoing document as Assistant General Patent Counsel of Pfizer Inc.

3. That Pfizer Inc.,
having its principal place of business located in
New York, New York, U.S.A.
is duly incorporated, is currently in existence, and that the purposes for which the Power of Attorney is granted are within the scope of its corporate purposes.

4. That the grantor has the authority to execute the Power of Attorney and that his/her representation is legal.

5. The foundation for my certifications contained in points 2, 3 and 4 was the exhibition of the following authentic document(s):

Certificación Notarial

En esta fecha,

el Notario Público suscrito certifica:

1. Que
J. Trevor Lumb
mayor de edad y domiciliado
New York
suscribió el documento que antecede.

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

4. Que
con sede principal ubicada en

está legalmente constituida, que tiene existencia legal vigente y que los propósitos para los cuales se otorga el poder se encuentra dentro de los que comprenden su objeto social.

4. Que el otorgante tiene la representación para suscribir el poder, y que ésta es legítima.

5. El fundamento de mis certificaciones contenidas en los puntos 2, 3 y 4 fue la exhibición de los (del) siguiente(s) documento(s) auténtico(s):

NOTARY PUBLIC (Signature):

EXECUTION
Certified Verified and Authenticated
In The Town Of Egham In Surrey
This 14th Day Of July 2003

KENNETH GREENWOOD
NOTARY PUBLIC
HORNE ENGALAND FREEMAN

DESPACHO NOTARIO ONCE DE ESTE CIRCULO HAGO CONSTAR QUE ESTA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA.
28 AGO 2003
BOGOTA, D.C. - COLOMBIA
NOTARIA ONCE (11)

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

UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND

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

   This public document / Le présent acte public

2. Has been signed by / 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

5. at London/à Londres

   Certified/Attesté
6. the/le 17 July 2003

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

8. Number/sous No: **G210434**

9. Stamp: / timbre:

10. Signature: R. Bawden

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

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

Traducción oficial del Inglés por Marlén Neira Castro, resolución 2117 del Ministerio de Justicia de Colombia PCS10958AGML

CESION A PFIZER LIMITED **CO-1**

Por una contraprestación valiosa pagada a nosotros, por PFIZER LIMITED, una compañía organizada bajo las leyes de Inglaterra, cuya dirección postal completa es: Ramsgate Road, Sandwich, Kent, CT13 9NJ Reino Unido, por el presente nosotros vendemos y cedemos a la mencionada PFIZER LIMITED, todos nuestros derechos, título e interés en y referente a nuestra invención para una mejora nueva y útil en DERIVADOS DE PIRAZOL (Pyrazole Derivatives) en cuanto a la República de Colombia, tan totalmente como se describe en la especificación, y por el presente nosotros autorizamos y solicitamos al Comisionado de patentes de Colombia que expida tal patente a la mencionada PFIZER LIMITED, de acuerdo con esta cesión.

En testimonio de lo anterior, firmamos en estas fechas:

Lugar, fecha y Nombre
Sandwich, Kent, Inglaterra, 21 febrero de 2002- Lyn Howard Jones
Sandwich, Kent, Inglaterra, 21 febrero de 2002 Charles Eric Mowbray
Sandwich, Kent, Inglaterra, 21 febrero de 2002- David Anthony Price
Sandwich, Kent, Inglaterra, 21 febrero de 2002- matthey Duncan Selby
Sandwich, Kent, Inglaterra, 21 febrero de 2002- Paul Anthony Stupple

Sello notarial: Certificado, verificado y autenticado en la Localidad de Egham en Surrey, 25 de febrero de 2002 por el Notario Kenneth Greenwood-Horne Engall & Freeman. Sello Notario Público en alto relieve.

En el reverso **APOSTILLA**

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

1. País :Reino Unido de Gran Bretaña e Irlanda del Norte
   Este documento Público 2. ha sido firmado por K. Greenwood
3. ejerce funciones Notario Público 4. Lleva el sello de tal Notario Público
   CERTIFICADO 5. En Londres 6. El 26 de Febrero de 2002
7. Por el Secretario de Estado Principal de su Majestad para Asuntos exteriores y de la mancomunidad. 8. No. G995768
9. Sello del Secretario de Estado Principal de su Majestad para Asuntos exteriores y de la mancomunidad
10. Firma de Y.P.Precieux - Por Secretario de Estado

Es traduccion conforme con copia para traductor, Bogota, 3-9-2003

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

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 **PYRAZOLE DERIVATIVES** 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

Sandwich, Kent, England, 21 February 2002 - Lyn Howard JONES

Sandwich, Kent, England, 21 February 2002 - Charles Eric MOWBRAY

Sandwich, Kent, England, 21 February 2002 - David Anthony PRICE

Sandwich, Kent, England, 21 February 2002 - Matthew Duncan Selby

Sandwich, Kent, England, 21 February 2002 - Paul Anthony STUPPLE

EXECUTION
Certified Verified and Authenticated
In The Town Of Egham In Surrey
This 25th Day Of February 2002

KENNETH GREENWOOD
NOTARY PUBLIC
HORNE ENGALL AND FREEMAN

7916

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 26 February 2002

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 G995768

9. Stamp: / timbre:

10. Signature: Y. P. Precieux

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

Traducción oficial del Inglés por Marlén Neira Castro, resolución 2117 del Ministerio de Justicia de Colombia PCS10958AGML

CESIÓN A PFIZER INC. **CO-1X**

Por una contraprestación valiosa pagada a nosotros, por PFIZER INC., una compañía organizada bajo las leyes del Estado de Delaware, Estados Unidos de América, cuya dirección postal completa es 235 East 42nd Street. Nueva York. Nueva York 10017, Estados Unidos de América, por el presente vendemos y cedemos a la mencionada PFIZER INC., todos nuestros derechos, título e interés en y referente a nuestra invención para una mejora nueva y útil en DERIVADOS DE PYRAZOL (Pyrazole Derivatives) en cuanto a la República de Colombia, tan totalmente como se describe en la especificación, y por el presente nosotros autorizamos y solicitamos al Comisionado de patentes de Colombia que expida tal patente a la mencionada PFIZER INC., de acuerdo con esta cesión.

En testimonio de lo anterior, firmamos en estas fechas:

Sandwich, Kent, Inglaterra, 21 febrero de 2002-

KEITH s. RUDDOCK- Agente autorizado, Reino Unido- Departamento de Patentes

Sello notarial: Certificado, verificado y autenticado en la Localidad de Egham en Surrey, 25 de febrero de 2002 por el Notario Kenneth Greenwood-

Horne Engall & Freeman. Sello Notario Público en alto relieve.

En el reverso

APOSTILLA

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

1. País :Reino Unido de Gran Bretaña e Irlanda del Norte
   Este documento Público
2. *ha sido firmado por K. Greenwood*
3. ejerce funciones Notario Público
4. Lleva el sello de tal Notario Público
   CERTIFICADO 5. En Londres
6. El 26 de Febrero de 2002
7. Por el Secretario de Estado Principal de su Majestad para Asuntos exteriores y de la mancomunidad.
8. No. G995767
9. Sello del Secretario de Estado Principal de su Majestad para Asuntos exteriores y de la mancomunidad
10. Firma de Y.P.Precieux - Por Secretario de Estado

Es traduccion conforme con copia para traductor, Bogota, 3-9-2003

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

Pfizer Limited

12a

PCS10958AGML

CO-1X

10

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

PYRAZOLE DERIVATIVES

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 21 February 2002 - KEITH S RUDDOCK, AUTHORISED ATTORNEY, UK PATENT DEPARTMENT

EXECUTION
Certified Verified and Authenticated
In The Town Of Egham In Surrey
This 25th Day Of February 2002

KENNETH GREENWOOD
NOTARY PUBLIC
HORNE ENGALL AND FREEMAN

11

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 **26 February 2002**

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 **G995767**

9. Stamp:
timbre:

FOREIGN AND COMMONWEALTH OFFICE
LONDON

10. Signature: **Y. P. Precieux**

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

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
31 October 2002 (31.10.2002)

PCT

(10) International Publication Number
WO 02/085860 A1

(51) International Patent Classification[7]: C07D 231/18, 231/20, A61K 31/415, 31/4162, 31/4155, A61P 31/18, C07D 403/06, 413/06, 401/12, 403/12, 405/12, 403/04, 498/04, 401/06, 471/04

(21) International Application Number: PCT/IB02/01234

(22) International Filing Date: 4 April 2002 (04.04.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0108999.4 10 April 2001 (10.04.2001) GB
0127426.5 15 November 2001 (15.11.2001) GB

(71) Applicant *(for GB only)*: PFIZER LIMITED [GB/GB]; Ramsgate Road, Sandwich, Kent CT13 9NJ (GB).

(71) Applicant *(for all designated States except GB)*: PFIZER INC. [US/US]; 235 East 42nd Street, New York, NY 10017 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: JONES, Lyn, Howard [GB/GB]; Pfizer Global Research and Development, Ramsgate Road, Sandwich, Kent CT13 9NJ (GB). MOWBRAY, Charles, Eric [GB/GB]; Pfizer Global Research and Development, Ramsgate Road, Sandwich, Kent CT13 9NJ (GB). PRICE, Davis, Anthony [GB/GB]; Pfizer Global Research and Development, Ramsgate Road, Sandwich, Kent CT13 9NJ (GB). SELBY, Matthew, Duncan [GB/GB]; Pfizer Global Research and Development, Ramsgate Road, Sandwich, Kent CT13 9NJ (GB). STUPPLE, Paul, Anthony [GB/GB]; Pfizer Global Research and Development, Ramsgate Road, Sandwich, Kent CT13 9NJ (GB).

(74) Agents: LANE, Graham, Mark et al.; Pfizer Limited, Ramsgate Road, Sandwich, Kent CT13 9NJ (GB).

(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, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

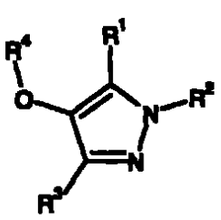
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(54) Title: PYRAZOLE DERIVATIVES FOR TREATING HIV



(I)

(57) Abstract: This invention relates to pyrazole derivatives of the formula, or pharmaceutically acceptable salts, solvates or derivative thereofs, wherein R1 to R4 are defined in the description, and to processes for the preparation thereof, intermediates used in their preparation of, compositions containing them and the uses of such derivatives. The compounds of the present invention bind to the enzyme reverse transcriptase and are modulators, especially inhibitors thereof. As such the compounds of the present invention are useful in the treatment of a variety of disorders including those in which the inhibition of reverse transcriptase is implacated. Disorders of interest include those caused by Human Immunodificiency Virus (HIV) and genetically related retroviruses, such as Aquired Immune Deficiency Syndrome (AIDS).

PYRAZOLE DERIVATIVES FOR TREATING HIV

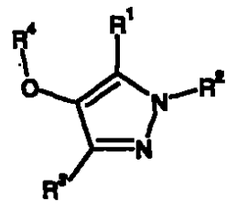
This invention relates to pyrazole derivatives and to processes for the preparation thereof, intermediates used in their preparation of, compositions containing them and the uses of such derivatives.

The compounds of the present invention bind to the enzyme reverse transcriptase and are modulators, especially inhibitors thereof. Reverse transcriptase is implicated in the infectious lifecycle of HIV, and compounds which interfere with the function of this enzyme have shown utility in the treatment of conditions including AIDS. There is a constant need to provide new and better modulators, especially inhibitors, of HIV reverse transcriptase since the virus is able to mutate, becoming resistant to the effects of known modulators.

The compounds of the present invention are useful in the treatment of a variety of disorders including those in which the inhibition of reverse transcriptase is implicated. Disorders of interest include those caused by Human Immunodificiency Virus (HIV) and genetically related retroviruses, such as Acquired Immune Deficiency Syndrome (AIDS).

European patent application EP 0 786 455 A1 discloses a class of imidazole compounds which inhibit the growth of HIV. A class of N-phenylpyrazoles which act as reverse transcriptase inhibitors are disclosed in *J. Med. Chem.*, 2000, 43, 1034. Antiviral activity is ascribed to a class of N-(hydroxyethyl)pyrazole derivatives in US patent number 3,303,200.

According to the present invention there is provided a compound of the formula



(I)

or a pharmaceutically acceptable salt, solvate or derivative thereof, wherein:

either R^1 is H, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, phenyl, benzyl, halo, -CN, -OR^7,

$-CO_2R^{10}$, $-CONR^5R^{10}$, R^8 or R^9, said C_1-C_6 alkyl, C_3-C_7 cycloalkyl, phenyl and benzyl being optionally substituted by halo, -CN, $-OR^{10}$, $S(O)_xR^{10}$, $-CO_2R^{10}$, $-CONR^5R^{10}$, $-OCONR^5R^{10}$, $-NR^5CO_2R^{10}$, $-NR^{10}R^{11}$, $-NR^5COR^{10}$, $-SO_2NR^5R^{10}$, $-NR^5CONR^5R^{10}$, $-NR^5SO_2R^{10}$ or R^{10}; and

R^2 is H, C_1-C_6 alkyl, C_3-C_6 alkenyl, C_3-C_6 alkynyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloalkenyl, phenyl, benzyl, R^8 or R^9, said C_1-C_6 alkyl, C_3-C_7 cycloalkyl, phenyl and benzyl being optionally substituted by halo, $-OR^5$, $-OR^{12}$, -CN, $-CO_2R^7$, $-OCONR^5R^5$, $-CONR^5R^5$, $-C(=NR^5)NR^5OR^5$, $-CONR^5NR^5R^5$, $-NR^6R^6$, $-NR^5R^{12}$, $-NR^5COR^5$, $-NR^5COR^8$, $-NR^5COR^{12}$, $-NR^5CO_2R^5$, $-NR^5CONR^5R^5$, $-SO_2NR^5R^5$, $-NR^5SO_2R^5$, $-NR^5SO_2NR^5R^5$, R^8 or R^9;

or, R^1 and R^2, when taken together, represent unbranched C_3-C_4 alkylene, optionally substituted by oxo, optionally wherein one methylene group of said C_3-C_4 alkylene is replaced by an oxygen atom or a nitrogen atom, said nitrogen atom being optionally substituted by R^{10};

R^3 is H, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, phenyl, benzyl, halo, -CN, $-OR^7$, $-CO_2R^5$, $-CONR^5R^5$, R^8 or R^9, said C_1-C_6 alkyl, C_3-C_7 cycloalkyl, phenyl and benzyl being optionally substituted by halo, -CN, $-OR^5$, $-CO_2R^5$, $-CONR^5R^5$, $-OCONR^5R^5$, $-NR^5CO_2R^5$, $-NR^6R^6$, $-NR^5COR^5$, $-SO_2NR^5R^5$, $-NR^5CONR^5R^5$, $-NR^5SO_2R^5$, R^8 or R^9;

R^4 is phenyl, naphthyl or pyridyl, each being optionally substituted by R^8, halo, -CN, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_7 cycloalkyl, C_1-C_6 alkoxy, $-CONR^5R^5$, OR^{13}, So_xR^6, O-(C_1-C_6 alkylene)-$CONR^5R^5$, O-(C_1-C_6 alkylene)-NR^5R^5, or O-(C_1-C_6 alkylene)-OR^6;

each R^5 is independently either H, C_1-C_6 alkyl or C_3-C_7 cycloalkyl or, when two R^5 groups are attached to the same nitrogen atom, those two groups taken together with the nitrogen atom to which they are attached represent azetidinyl, pyrrolidinyl, piperidinyl, homopiperidinyl, piperazinyl, homopiperazinyl or morpholinyl, said azetidinyl, pyrrolidinyl, piperidinyl, homopiperidinyl, piperazinyl, homopiperazinyl and morpholinyl being optionally substituted by C_1-C_6 alkyl or C_3-C_7 cycloalkyl;

each R^6 is independently either H, C_1-C_6 alkyl or C_3-C_7 cycloalkyl;

R^7 is C_1-C_6 alkyl or C_3-C_7 cycloalkyl;

R^8 is a five or six-membered, aromatic heterocyclic group containing (i) from 1 to 4 nitrogen heteroatom(s) or (ii) 1 or 2 nitrogen heteroatom(s) and 1 oxygen or 1 sulphur heteroatom or (iii) 1 or 2 oxygen or sulphur heteroatom(s), said heterocyclic group being optionally substituted by halo, oxo, -CN, $-COR^5$, $-CONR^5R^5$, $-SO_2NR^5R^5$, $-NR^5SO_2R^5$, $-OR^5$, $-NR^5R^5$, $-(C_1-C_6$ alkylene$)-NR^5R^5$, C_1-C_6 alkyl, fluoro(C_1-C_6)alkyl or C_3-C_7 cycloalkyl;

R^9 is a four to seven-membered, saturated or partially unsaturated heterocyclic group containing (i) 1 or 2 nitrogen heteroatom(s) or (ii) 1 nitrogen heteroatom and 1 oxygen or 1 sulphur heteroatom or (iii) 1 oxygen or sulphur heteroatom, said heterocyclic group being optionally substituted by oxo, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, $-SO_2R^5$, $-CONR^5R^5$, $-COOR^5$, $-CO-(C_1-C_6$ alkylene$)-OR^5$ or $-COR^5$ and optionally substituted on a carbon atom which is not adjacent to a heteroatom by halo, $-OR^5$, $-NR^5R^5$, $-NR^5COR^5$, $-NR^5COOR^5$, $-NR^5CONR^5R^5$, $-NR^5SO_2R^5$ or -CN;

R^{10} is H, R^8, R^9, R^{13}, C_1-C_6 alkyl, C_3-C_7 cycloalkyl or $-(C_1-C_6$ alkyl$)-(C_3-C_7$ cycloalkyl), said C_1-C_6 alkyl and C_3-C_7 cycloalkyl being optionally substituted by $-OR^5$, $-OR^{13}$, R^8, R^9, R^{13} or $-COR^{13}$;

R^{11} is H, C_1-C_6 alkyl or C_3-C_7 cycloalkyl, said C_1-C_6 alkyl and C_3-C_7 cycloalkyl being optionally substituted by $-OR^5$, $-NR^5R^5$, $-NR^5COR^5$, $-CONR^5R^5$, R^8 or R^9;

R^{12} is C_1-C_6 alkyl substituted by R^8, R^9, $-OR^5$, $-CONR^5R^5$, $-NR^5COR^5$ or $-NR^5R^5$;

R^{13} is phenyl optionally substituted by halo, -CN, $-COR^5$, $-CONR^5R^5$, $-SO_2NR^5R^5$, $-NR^5SO_2R^5$, $-OR^5$, $-NR^5R^5$, $-(C_1-C_6$ alkylene$)-NR^5R^5$, C_1-C_6 alkyl, halo(C_1-C_6)alkyl or C_3-C_7 cycloalkyl; and

x is 0, 1 or 2;

with the proviso that (a) when R^1 and R^3 are both phenyl, R^2 is not methyl; and (b) when R^1 is ethoxy and R^3 is ethoxycarbonyl, R^2 is not phenyl.

In the above definitions, halo means fluoro, chloro, bromo or iodo. Unless otherwise stated, alkyl, alkenyl, alkynyl, alkylene and alkoxy groups containing the requisite number of carbon atoms can be unbranched or branched chain. Examples of alkyl include methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl and t-butyl. Examples of alkenyl include ethenyl, propen-1-yl, propen-2-yl,

propen-3-yl, 1-buten-1-yl, 1-buten-2-yl, 1-buten-3-yl, 1-buten-4-yl, 2-buten-1-yl, 2-buten-2-yl, 2-methylpropen-1-yl or 2-methylpropen-3-yl. Examples of alkynyl include ethynyl, propyn-1-yl, propyn-3-yl, 1-butyn-1-yl, 1-butyn-3-yl, 1-butyn-4-yl, 2-butyn-1-yl. Examples of alkylene include methylene, 1,1-ethylene, 1,2-ethylene, 1,1-propylene, 1,2-propylene, 2,2-propylene and 1,3-propylene. Examples of alkoxy include methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, sec-butoxy and t-butoxy. Examples of cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. Where R^1 and R^2 are taken together, they form, along with the nitrogen atom and the carbon atom of the pyrazole ring to which they are attached, a 5- or 6-membered ring. Where a heterocyclic group R^8 or R^9 is attached to an oxygen, sulphur or nitrogen heteroatom the heterocyclic group R^8 or R^9 must be linked through a ring carbon atom. Further, where a heterocyclic group R^9 is attached to an oxygen, sulphur or nitrogen heteroatom the heterocyclic group R^9 must be linked through a ring carbon atom that is not adjacent to a ring heteratom.

The pharmaceutically acceptable salts of the compounds of the formula (I) include the acid addition and the base salts thereof.

Suitable acid addition salts are formed from acids which form non-toxic salts and examples are the hydrochloride, hydrobromide, hydroiodide, sulphate, bisulphate, nitrate, phosphate, hydrogen phosphate, acetate, maleate, fumarate, lactate, tartrate, citrate, gluconate, succinate, saccharate, benzoate, methanesulphonate, ethanesulphonate, benzenesulphonate, para-toluenesulphonate and pamoate salts.

Suitable base salts are formed from bases which form non-toxic salts and examples are the sodium, potassium, aluminium, calcium, magnesium, zinc and diethanolamine salts.

For a review on suitable salts see Berge *et al*, *J. Pharm. Sci.*, 66, 1-19, 1977.

The pharmaceutically acceptable solvates of the compounds of the formula (I) include the hydrates thereof.

Also included within the present scope of the compounds of the formula (I) are polymorphs thereof.

The compounds of formula (I) may be modified to provide pharmaceutically acceptable derivatives thereof at any of the functional groups in the compounds. Examples of such derivatives are described in: Drugs of Today, Volume 19, Number 9, 1983, pp 499 – 538; 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) and include: esters, carbonate esters, hemi-esters, phosphate esters, nitro esters, sulfate esters, sulfoxides, amides, sulphonamides, carbamates, azo-compounds, phosphamides, glycosides, ethers, acetals and ketals.

A compound of the formula (I) may contain one or more asymmetric carbon atoms and therefore exist in two or more stereoisomeric forms. The present invention includes the individual stereoisomers of the compounds of the formula (I) together with, where appropriate, the individual tautomers thereof, and mixtures thereof.

Separation of diastereoisomers may be achieved by conventional techniques, e.g. by fractional crystallisation, chromatography or high performance liquid chromatography (HPLC) of a stereoisomeric mixture of a compound of the formula (I) or a suitable salt or derivative thereof. An individual enantiomer of a compound of the formula (I) may also be prepared from a corresponding optically pure intermediate or by resolution, such as by HPLC 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.

Preferably, R^1, when taken separately, is H, C_1-C_8 alkyl, C_3-C_7 cycloalkyl or $-OR^7$, said C_1-C_8 alkyl and C_3-C_7 cycloalkyl being optionally substituted by halo, -CN, $-OR^{10}$, $S(O)_xR^{10}$, $-CO_2R^{10}$, $-CONR^5R^{10}$, $-OCONR^5R^{10}$, $-NR^5CO_2R^{10}$, $-NR^{10}R^{11}$, $-NR^5COR^{10}$, $-SO_2NR^5R^{10}$, $-NR^5CONR^5R^{10}$, $-NR^5SO_2R^{10}$ or R^{10}.
Preferably, R^1, when taken separately, is H, C_1-C_8 alkyl, C_3-C_7 cycloalkyl or $-OR^7$, said C_1-C_8 alkyl being optionally substituted by halo, $-OR^{10}$, $-NR^{10}R^{11}$, $-NR^5COR^{10}$ or R^{10}.
Preferably, R^1, when taken separately, is H, C_1-C_4 alkyl, cyclopropyl, or $-OCH_3$, said C_1-C_4 alkyl being optionally substituted by bromo, -OH, -O(C_1-C_2 alkyl), $-NR^{10}R^{11}$, $-NHCOR^{13}$ or R^{10}.
Preferably, R^1, when taken separately, is H, $-CH_3$, $-CH_2CH_3$, $-CH(CH_3)_2$, $-C(CH_3)_3$, cyclopropyl, $-OCH_3$, $-CH_2OH$, $-CH_2OCH_3$, $-CH_2OCH_2CH_3$, $-CH_2Br$, $-CH_2NH_2$, $-CH_2NHCH_3$, $-CH_2N(CH_3)_2$, $-CH_2NHCH_2$(cyclopropyl),

$-CH_2NHCH_2CH_2OCH_3$, $-CH_2NHCH_2CH_2NHCOCH_3$, $-CH_2NHCO$(4-cyanophenyl), $-CH_2NHCO$(3-cyanophenyl), $-CH_2NHCH_2$(4-cyanophenyl), $-CH_2NHCH_2$(4-fluorophenyl), $-CH_2NHCH_2$(4-methoxyphenyl), -CH2NHCH2(4-aminosulphonylphenyl), $-CH_2NHCH_2$(4-aminocarbonylphenyl), $-CH_2NHCH_2$(pyrid-3-yl), $-CH_2N(CH_3)$(4-cyanophenylmethyl), $-CH_2N(CH_2CH_2OH)$(4-cyanophenylmethyl), 4-methoxypiperidin-1-ylmethyl, 4-aminocarbonylpiperidin-1-ylmethyl, 4-methylcarbonylaminopiperidin-1-ylmethyl, piperazin-1-ylmethyl, 4-methylpiperazin-1-ylmethyl, 4-methylcarbonylpiperazin-1-ylmethyl, 4-methoxymethylcarbonylpiperazin-1-ylmethyl, 4-methoxycarbonylpiperazin-1-ylmethyl, 4-methylsulphonylpiperazin-1-ylmethyl, morpholin-4-ylmethyl, 2-methylimidazol-1-ylmethyl, pyrazol-1-ylmethyl or 1,2,4-triazol-1-ylmethyl.

Preferably, R^1, when taken separately, is, $-CH_3$, $-CH_2CH_3$, cyclopropyl, $-CH_2NHCH_2$(4-cyanophenyl), $-CH_2NHCH_2$(4-fluorophenyl), $-CH_2NHCH_2$(4-methoxyphenyl), $-CH_2NHCH_2$(4-aminosulphonylphenyl) or $-CH_2NHCH_2$(4-aminocarbonylphenyl).

Preferably, R^2, when taken separately, is H, C_1-C_6 alkyl, C_3-C_6 alkenyl or R^9, said C_1-C_6 alkyl being optionally substituted by halo, $-OR^5$, $-OR^{12}$, -CN, $-CO_2R^7$, $-OCONR^5R^5$, $-CONR^5R^5$, $-C(=NR^5)NR^5OR^5$, $-CONR^5NR^5R^5$, $-NR^5R^8$, $-NR^5R^{12}$, $-NR^5COR^5$, $-NR^5COR^8$, $-NR^5COR^{12}$, $-NR^5CO_2R^5$, $-NR^5CONR^5R^5$, $-SO_2NR^5R^5$, $-NR^5SO_2R^5$, R^8 or R^9.

Preferably, R^2, when taken separately, is H, C_1-C_6 alkyl, C_3-C_6 alkenyl or R^9, said C_1-C_6 alkyl being optionally substituted by $-OR^5$, $-OR^{12}$, -CN, $-CO_2R^7$, $-CONR^5R^5$, $-C(=NR^5)NR^5OR^5$, $-CONR^5NR^5R^5$, $-NR^5R^8$, $-NR^5R^{12}$, $-NR^5COR^8$, $-NR^5COR^{12}$, $-NR^5CO_2R^5$, R^8 or R^9.

Preferably, R^2, when taken separately, is H, C_1-C_3 alkyl, propenyl or R^9, said C_1-C_3 alkyl being optionally substituted by -OH, $-OCH_3$, $-OCH_2CH_2NH_2$, -CN, $-CO_2CH_3$, $-CO_2CH_2CH_3$, $-CONH_2$, $-C(=NH)NHOH$, $-CONHNH_2$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-NHCH_2CH_2NHCOCH_3$, $-NHCH_2CH_2OCH_3$, $-NHCH_2R^9$, $-NHCOR^8$, $-NHCOCH_2OCH_3$, $-NHCO_2C(CH_3)_3$, R^8 or R^9.

Preferably, R^2, when taken separately, is H, methyl, $-CH_2CH=CH_2$, $-CH_2CN$, $-CH_2OCH_3$, $-CH_2CONH_2$, $-CH_2CONHNH_2$, $-CH_2CO_2CH_3$, $-CH_2CO_2CH_2CH_3$, $-CH_2C(=NH)NHOH$, $-CH_2CH_2OH$, $-CH_2CH_2OCH_3$, $-CH_2CH_2NH_2$, $-CH_2CH_2NHCOCH_2OCH_3$, $-CH_2CH_2NHCO_2C(CH_3)_3$, 2-(pyrid-2-ylcarbonylamino)eth-1-yl, 2-(pyrazin-2-ylcarbonylamino)eth-1-yl, $-CH_2CH_2OCH_2CH_2NH_2$, $-CH_2CH_2NHCH_3$, $-CH_2CH_2N(CH_3)_2$, $-CH_2CH_2NHCH_2CH_2NHCOCH_3$, $-CH_2CH_2NHCH_2CH_2OCH_3$, $-CH_2CH(OH)CH_3$, (3-hydroxypyrazol-5-yl)methyl, 2-hydroxy-1,3,4-oxadiazol-5-ylmethyl, 2-amino-1,3,4-oxadiazol-5-yl, 5-hydroxy-1,2,4-oxadiazol-3-ylmethyl, 6-

hydroxy-2-methylpyrimidin-4-ylmethyl, 6-hydroxy-2-aminopyrimidin-4-ylmethyl, 2-(morpholin-4-yl)eth-1-yl, 2-(4-methylcarbonylpiperazin-1-yl)eth-1-yl, morpholin-3-ylmethyl, (2-(tetrahydrofuran-2-ylmethylamino)eth-1-yl, 1-methylazetidin-3-yl or azetidin-3-yl.

Preferably, R^2, when taken separately, is H, $-CH_2CH_2OH$ or $-CH_2CH_2NH_2$.

Preferably, R^1 and R^2, when taken together, represent unbranched C_3-C_4 alkylene, optionally substituted by oxo, wherein one methylene group of said C_3-C_4 alkylene is replaced by an oxygen atom or a nitrogen atom, said nitrogen atom being optionally substituted by R^{10}.

Preferably, R^1 and R^2, when taken together, represent unbranched propylene wherein one methylene group is replaced by an oxygen atom or unbranched butylene wherein one methylene group is replaced by a nitrogen atom, said propylene and butylene being optionally substituted by oxo and said nitrogen atom being optionally substituted by R^{10}.

Preferably, R^1 and R^2, when taken together, represent ^{x}-OCH_2CH_2-^{y}, ^{x}-$CONHCH_2CH_2$-^{y}, ^{x}-$CH_2NHCH_2CH_2$-^{y}, ^{x}-$CH_2N(CH_3)CH_2CH_2$-^{y}, ^{x}-CH_2N(4-cyanophenylmethyl)CH_2CH_2-^{y} or ^{x}-CH_2N(4-methoxyphenylmethyl)CH_2CH_2-^{y} wherein 'x' represents the point of attachment to the carbon atom of the pyrazole ring and 'y' represents the point of attachment to the nitrogen atom of the pyrazole ring.

Preferably, R^3 is H or C_1-C_6 alkyl, said C_1-C_6 alkyl being optionally substituted by halo, -CN, $-OR^5$, $-CO_2R^5$, $-CONR^5R^5$, $-OCONR^5R^5$, $-NR^5CO_2R^5$, $-NR^6R^6$, $-NR^5COR^5$, $-SO_2NR^5R^5$, $-NR^5CONR^6R^5$, $-NR^5SO_2R^5$, R^8 or R^9.

Preferably, R^3 is H or C_1-C_6 alkyl.

Preferably, R^3 is H or C_1-C_4 alkyl.

Preferably, R^3 is H, $-CH_3$, $-CH_2CH_3$, $-CH(CH_3)_2$ or $-C(CH_3)_3$.

Preferably, R^3 is $-CH_3$, $-CH_2CH_3$, $-CH(CH_3)_2$ or cyclopropyl.

Preferably, R^4 is phenyl optionally substituted by R^8, halo, -CN, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_7 cycloalkyl or C_1-C_6 alkoxy.

Preferably, R^4 is phenyl substituted by R^8, halo, -CN, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_7 cycloalkyl or C_1-C_6 alkoxy.

Preferably, R^4 is phenyl substituted by halo, -CN or C_1-C_6 alkyl.

Preferably, R^4 is phenyl substituted by fluoro, chloro, -CN or methyl.

Preferably, R^4 is 3-cyanophenyl, 4-chlorophenyl, 3-chlorophenyl, 2-chlorophenyl, 3-fluorophenyl, 2-fluorophenyl, 3,5-dichlorophenyl, 2,6-dichlorophenyl, 2,3-dichlorophenyl, 2,4-dichlorophenyl, 3,4-dichlorophenyl, 2,5-dichlorophenyl, 2,6-

difluorophenyl, 2,3-difluorophenyl, 3,5-difluorophenyl, 2,5-difluorophenyl, 3,5-dicyanophenyl, 3,5-dimethylphenyl, 4-fluoro-3-methylphenyl, 3-cyano-4-fluorophenyl, 3-cyano-5-fluorophenyl, 2-chloro-4-cyanophenyl, 3-chloro-5-cyanophenyl, 3-cyano-5-methylphenyl or 4-cyano-2,6-dimethylphenyl.

Preferably, R^4 is 3,5-dicyanophenyl, 3-cyano-5-fluorophenyl, 3-chloro-5-cyanophenyl or 3-cyano-5-methylphenyl.

In an alternative set of preferences:

Preferably, R^4 is phenyl optionally substituted by R^8, halo, -CN, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_7 cycloalkyl, C_1-C_6 alkoxy, $-CONR^5R^5$, OR^{13}, So_xR^6, O-(C_1-C_6 alkylene)-$CONR^5R^5$, O-(C_1-C_6 alkylene)-NR^5R^5, or O-(C_1-C_6 alkylene)-OR^6; or naphthyl.

Preferably, R^4 is phenyl substituted by R^8, halo, -CN, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_7 cycloalkyl, C_1-C_6 alkoxy, $-CONR^5R^5$, OR^{13}, So_xR^6, O-(C_1-C_6 alkylene)-$CONR^5R^5$, O-(C_1-C_6 alkylene)-NR^5R^5, or O-(C_1-C_6 alkylene)-OR^6.

Preferably, R^8 is pyrrolyl, imidazolyl, pyrazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, furanyl, thienyl, pyridinyl, pyridazinyl, pyrimidinyl or pyrazinyl, each being optionally substituted by halo, -CN, $-COR^5$, $-CONR^5R^5$, $-SO_2NR^5R^5$, $-NR^5SO_2R^5$, $-OR^5$, $-NR^5R^5$, -(C_1-C_6 alkylene)-NR^5R^5, C_1-C_6 alkyl, fluoro(C_1-C_6)alkyl or C_3-C_7 cycloalkyl.

Preferably, R^8 is imidazolyl, pyrazolyl, 1,2,4-triazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, pyridinyl, pyrazinyl or pyrimidinyl, each being optionally substituted by halo, -CN, $-COR^5$, $-CONR^5R^5$, $-SO_2NR^5R^5$, $-NR^5SO_2R^5$, $-OR^5$, $-NR^5R^5$, -(C_1-C_6 alkylene)-NR^5R^5, C_1-C_6 alkyl, fluoro(C_1-C_6)alkyl or C_3-C_7 cycloalkyl.

Preferably, R^8 is imidazolyl, pyrazolyl, 1,2,4-triazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, pyridinyl, pyrazinyl or pyrimidinyl, each being optionally substituted by $-OR^5$, $-NR^5R^5$ or C_1-C_6 alkyl.

Preferably, R^8 is imidazolyl, pyrazolyl, 1,2,4-triazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, pyridinyl, pyrazinyl or pyrimidinyl, each being optionally substituted by -OH, $-NH_2$ or methyl.

Preferably, R^8 is pyrazol-1-yl, 2-methylimidazol-1-yl, 1,2,4-triazol-1-yl, 3-hydroxypyrazol-5-yl, 2-hydroxy-1,3,4-oxadiazol-5-yl, 2-amino-1,3,4-oxadiazol-5-yl, 5-hydroxy-1,2,4-oxadiazol-3-yl, 2-methyl-4-hydroxypyrimidin-6-yl, 2-amino-4-hydroxypyrimidin-6-yl, pyridin-3-yl, pyridin-2-yl or pyrazin-2-yl.

Preferably, R^9 is azetidinyl, tetrahydropyrrolyl, piperidinyl, azepinyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, oxepinyl, morpholinyl, piperazinyl or

diazepinyl, each being optionally substituted by oxo, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, $-SO_2R^5$, $-CONR^5R^5$, $-COOR^5$, $-CO-(C_1-C_6$ alkylene$)-OR^5$ or $-COR^5$ and optionally substituted on a carbon atom which is not adjacent to a heteroatom by halo, $-OR^5$, $-NR^5R^5$, $-NR^5COR^5$, $-NR^5COOR^5$, $-NR^5CONR^5R^5$, $-NR^5SO_2R^5$ or -CN.

Preferably, R^9 is azetidinyl, piperidinyl, tetrahydrofuranyl, piperazinyl or morpholinyl, each being optionally substituted by oxo, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, $-SO_2R^5$, $-CONR^5R^5$, $-COOR^5$, $-CO-(C_1-C_6$ alkylene$)-OR^5$ or $-COR^5$ and optionally substituted on a carbon atom which is not adjacent to a heteroatom by halo, $-OR^5$, $-NR^5R^5$, $-NR^5COR^5$, $-NR^5COOR^5$, $-NR^5CONR^5R^5$, $-NR^5SO_2R^5$ or -CN.

Preferably, R^9 is azetidinyl, piperidinyl, tetrahydrofuranyl, piperazinyl or morpholinyl, each being optionally substituted by C_1-C_6 alkyl, $-SO_2R^5$, $-CONR^5R^5$, $-COOR^5$, $-CO-(C_1-C_6$ alkylene$)-OR^5$ or $-COR^5$ and optionally substituted on a carbon atom which is not adjacent to a heteroatom by $-OR^5$ or $-NR^5COR^5$.

Preferably, R^9 is azetidinyl, piperidinyl, tetrahydrofuranyl, piperazinyl or morphoninyl, each being optionally substituted by $-CH_3$, $-SO_2CH_3$, $-CONH_2$, $-COOCH_3$, $-COCH_2OCH_3$ or $-COCH_3$ and optionally substituted on a carbon atom which is not adjacent to a heteroatom by $-OCH_3$ or $-NHCOCH_3$.

Preferably, R^9 is 4-methoxypiperidin-1-yl, 4-aminocarbonylpiperidin-1-yl, 4-methylcarbonylaminopiperidin-1-yl, piperazin-1-yl, 4-methylpiperazin-1-yl, 4-methylcarbonylpiperazin-1-yl, 4-methoxymethylcarbonylpiperazin-1-yl, 4-methoxycarbonylpiperazin-1-yl, 4-methylsulphonylpiperazin-1-yl, morpholin-4-yl, tetrahydrofuran-2-yl, morpholin-3-yl, azetidin-3-yl or 1-methylazetidin-3-yl.

Preferably, R^{10} is H, R^8, R^9, R^{13}, C_1-C_6 alkyl or $-(C_1-C_6$ alkyl$)-(C_3-C_7$ cycloalkyl), said C_1-C_6 alkyl being optionally substituted by $-OR^5$, $-OR^{13}$, R^8, R^9, R^{13} or $-COR^{13}$.

Preferably, R^{10} is H, R^8, R^9, R^{13}, C_1-C_6 alkyl or $-(C_1-C_6$ alkyl$)-(C_3-C_7$ cycloalkyl), said C_1-C_6 alkyl being optionally substituted by $-OR^5$ or R^{13}.

Preferably, R^{10} is H, R^8, R^9, R^{13}, $-CH_3$, $-CH_2CH_3$ or $-CH_2$(cyclopropyl), said $-CH_3$ and $-CH_2CH_3$ being optionally substituted by $-OCH_3$ or R^{13}.

Preferably, R^{10} is H, R^8, R^9, R^{13}, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2OCH_3$, $-CH_2$(cyclopropyl), 4-cyanophenylmethyl, 4-fluorophenylmethyl, 4-methoxyphenylmethyl, 4-aminosulphonylphenylmethyl or 4-aminocarbonylphenylmethyl.

Preferably, R^{11} is H or C_1-C_6 alkyl, said C_1-C_6 alkyl being optionally substituted by $-OR^5$, $-NR^5R^5$, $-NR^5COR^5$, $-CONR^5R^5$, R^8 or R^9.

Preferably, R^{11} is H or C_1-C_6 alkyl, said C_1-C_6 alkyl being optionally substituted by $-OR^5$ or $-NR^5COR^5$.

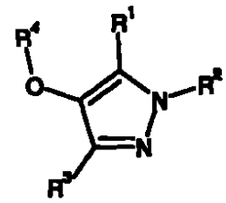
Preferably, R^{11} is H, $-CH_3$ or $-CH_2CH_3$, said $-CH_3$ and $-CH_2CH_3$ being optionally substituted by -OH or $-NHCOCH_3$.
Preferably, R^{11} is H, $-CH_3$, $-CH_2CH_2NHCOCH_3$ or $-CH_2CH_2OH$.

Preferably, R^{12} is C_1-C_4 alkyl substituted by R^8, R^9, $-OR^5$, $-CONR^5R^5$, $-NR^5COR^5$ or $-NR^5R^5$.
Preferably, R^{12} is C_1-C_4 alkyl substituted by R^9, $-OR^5$, $-NR^5COR^5$ or $-NR^5R^5$.
Preferably, R^{12} is C_1-C_2 alkyl substituted by tetrahydrofuranyl, $-OCH_3$, $-NHCOCH_3$ or $-NH_2$.
Preferably, R^{12} is $-CH_2CH_2NH_2$, $-CH_2CH_2OCH_3$, tetrahydrofuran-2-ylmethyl, $-CH_2CH_2NHCOCH_3$ or $-CH_2OCH_3$.

Preferably, R^{13} is phenyl substituted by halo, -CN, $-COR^5$, $-CONR^5R^5$, $-SO_2NR^5R^5$, $-NR^5SO_2R^5$, $-OR^5$, $-NR^5R^5$, $-(C_1$-C_6 alkylene$)-NR^5R^5$, C_1-C_6 alkyl, halo(C_1-C_6)alkyl or C_3-C_7 cycloalkyl.
Preferably, R^{13} is phenyl substituted by halo, -CN, $-CONR^5R^5$, $-SO_2NR^5R^5$ or $-OR^5$.
Preferably, R^{13} is phenyl substituted by fluoro, -CN, $-CONH_2$, $-SO_2NH_2$ or $-OCH_3$.
Preferably, R^{13} is 4-cyanophenyl, 3-cyanophenyl, 4-fluorophenyl, 1-methoxyphenyl, 4-aminocarbonylphenyl or 4-aminosulphonylphenyl.

Preferred groups of compounds according to the invention include all combinations of the preferred definitions for individual substituents given above.

Also preferred according to the invention are the compounds of formula (I)



(I)

or a pharmaceutically acceptable salt, solvate or derivative thereof, wherein:

R^1 is H, C_1-C_6 alkyl, $-OC_1$-C_6 alkyl, $-OC_3$-C_7 cycloalkyl, said C_1-C_6 alkyl being optionally substituted by R^{15};

R^2 is H, C_1-C_3 alkyl, propenyl or C-linked R^{15}, said C_1-C_3 alkyl being optionally substituted by -OH, $-OCH_3$, $-OCH_2CH_2NH_2$, -CN, $-CO_2CH_3$, $-CONH_2$, $-C(=NH)NH_2$, $-CONHNH_2$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-NHCH_2CH_2NHCOCH_3$, $-NHCH_2CH_2OCH_3$, $-NHCH_2R^{15}$, $-NHCOR^{15}$, $-NHCOCH_2OCH_3$, or R^{15}

R^3 is C_1-C_6 alkyl;

R^4 is phenyl optionally substituted by halo, -CN, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_7 cycloalkyl or C_1-C_6 alkoxy; and

R^{15} is azetidinyl, tetrahydrofuranyl, morpholinyl, piperazinyl, pyrazolyl, oxadiazolyl, pyridinyl or pyrimidinyl each being optionally substituted by -OH, -NH_2, oxo or C_1-C_6 alkyl or -CO(C_1-C_6 alkyl).

Preferred individual compounds according to the invention include the Examples below, particularly Examples 117, 118, 119, 120, 122, 123, 124, 125, 126, 127 and 128, and the pharmaceutically acceptable salts and solvates thereof.

All of the compounds of the formula (I) can be prepared by conventional routes such as the procedures described in the general methods presented below or by the specific methods described in the Examples section, or by similar methods thereto. The present invention also encompasses any one or more of these processes for preparing the compounds of formula (I), in addition to any novel intermediates used therein.

In the following general methods, R^1, R^2, R^3 and R^4 are as previously defined for a compound of the formula (I) unless otherwise stated.

Except where either R^1 or R^3 is halo, -OR^8 or -CN, compounds of the formula (I) may be prepared using the route shown in Scheme 1 that follows.

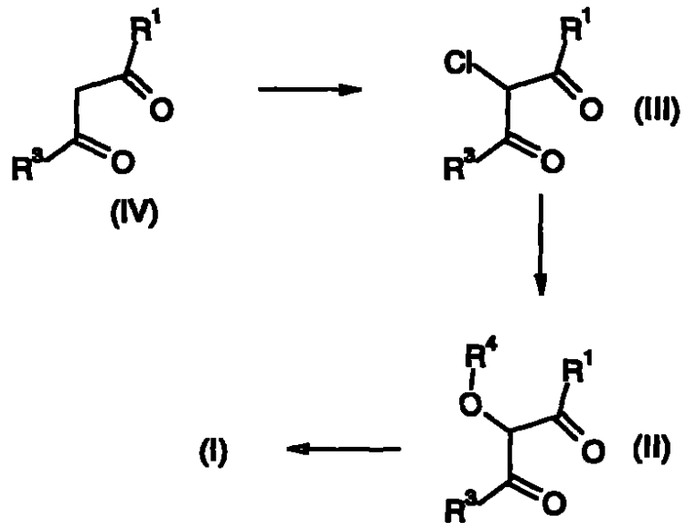
In Scheme 1, compounds of the formula (I) may be prepared by the condensation of a compound of the formula (II) with a compound of the formula

$$H_2NNHR^2 \text{ (V)},$$

or a salt or hydrate thereof, optionally in the presence of an acid or a base, the base preferably being a tertiary amine base such as triethylamine and the acid preferably being acetic acid. In a typical procedure, a solution of the compound of the formula (II) in a suitable solvent, such as ethanol, is treated with the compound of the formula (V), or the salt or hydrate thereof, and, if used, the appropriate acid or base, at a temperature of from room temperature to the reflux

temperature of the solvent. In a preferred procedure, the reaction mixture is heated under reflux.

Scheme 1



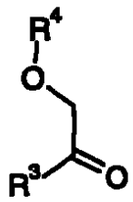
Functional equivalents of compounds of the formula (II) may also be used in this reaction. These include compounds of the formula (VI) or (VII), in which L^1 and L^2, respectively, are each suitable leaving groups, preferably -N(C_1-C_6 alkyl)$_2$, most preferably -N(CH_3)$_2$.



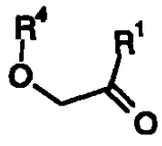
Thus, a compound of the formula (I) may be prepared by the condensation of a compound of the formula (VI) or (VII) with a compound of the formula (V), or a salt or hydrate thereof, optionally in the presence of an acid or a base, the base preferably being a tertiary amine base such as triethylamine and the acid preferably being acetic acid. In a typical procedure, a solution of the compound of the formula (VI) or (VII) in a suitable solvent, such as ethanol, is treated with the compound of the formula (V), or the salt or hydrate thereof, and, if used, the

appropriate acid or base, at a temperature of from room temperature to the reflux temperature of the solvent. In a preferred procedure, the reaction mixture is heated under reflux. Compounds of the formula (VI) or (VII) are particularly suitable for the synthesis of compounds of the formula (I) in which R^1 or R^3, respectively, is H.

Compounds of the formula (VI) in which R^1 is H and L^1 is dimethylamino may be prepared by the reaction of a compound of the formula (VIII) with dimethylformamide dimethylacetal at an elevated temperature, preferably at about 100°C. Compounds of the formula (VII) in which R^1 is H and L^1 is dimethylamino may be prepared by the reaction of a compound of the formula (IX) under the same conditions. Other compounds of the formula (VI) or (VII) in which L^1 or L^2 is dimethylamino may be prepared analogously.



(VIII)



(IX)

Compounds of the formula (VIII) are either commercially available or may be prepared by the reaction of a compound of the formula

$$R^3COCH_2Br \text{ (X)}$$

with a compound of the formula

$$R^4OH \text{ (XI)}.$$

In a typical procedure, a solution of the compound of the formula (XI) in a suitable solvent, such as acetone, is treated with a suitable base, such as caesium carbonate, and the compound of the formula (X). In a preferred procedure, the reaction mixture is heated, for example under reflux. Optionally, a nucleophilic catalyst such as sodium iodide or tetrabutylammonium iodide may be added

Compounds of the formula (IX) are either commercially available or may be prepared from a compound of the formula

R^1COCH_2Br (XII)

and a compound of the formula (XI) in the same way that a compound of the formula (VIII) may be prepared from a compound of the formula (X).

Compounds of the formula (II) may be prepared by the reaction of a compound of the formula (III) with a compound of the formula (XI).

In a typical procedure, a solution of the compound of the formula (III) in a suitable solvent such as acetone is treated with a compound of the formula (XI) and a suitable base, such as potassium or caesium carbonate, and heated, preferably under reflux. Optionally, a nucleophilic catalyst such as sodium iodide or tetrabutylammonium iodide may be added.

Compounds of the formula (III) are either commercially available or may be prepared by the reaction of a compound of the formula (IV) with a chlorinating reagent. In a typical procedure, a cooled solution of the compound of the formula (IV) in a suitable solvent such as acetonitrile is treated first with tetrabutylammonium bromide and chlorotrimethylsilane and then dry dimethylsulphoxide. In another typical procedure, the compound of the formula (IV) is treated with sulphuryl chloride, optionally in the presence of a suitable solvent such as dichloromethane.

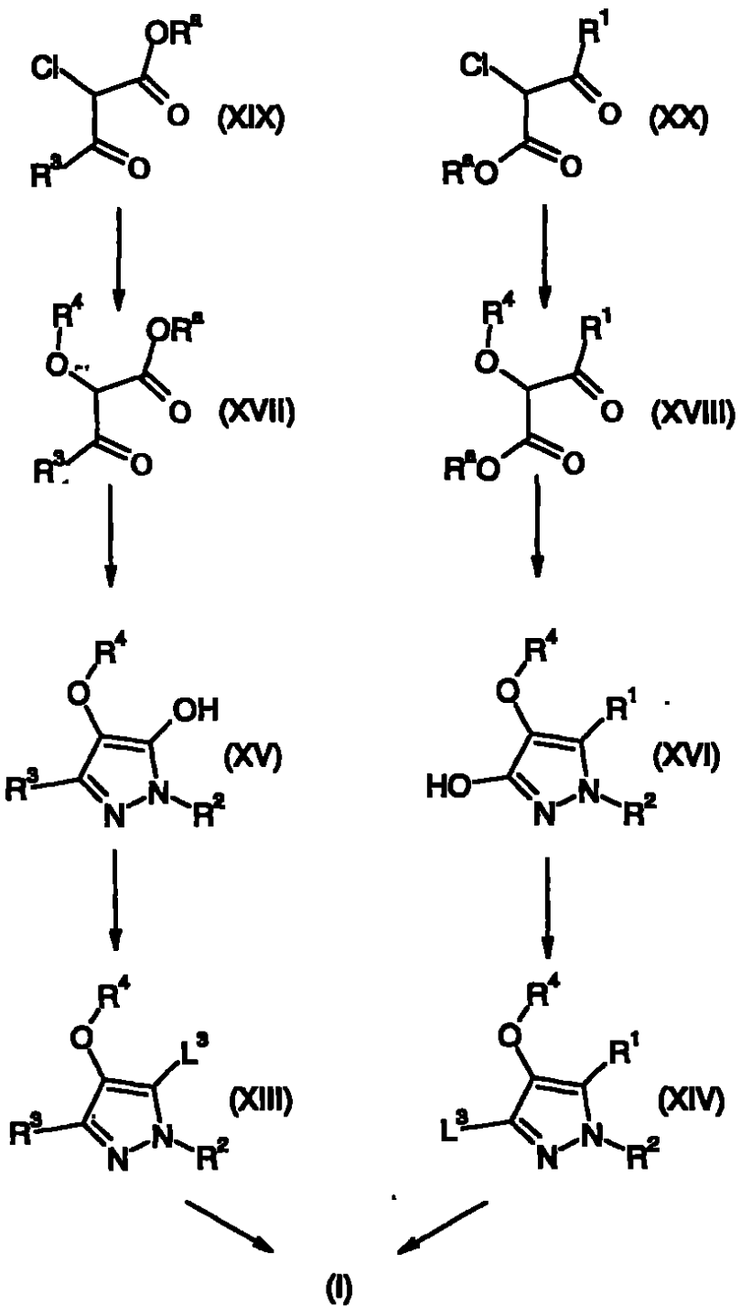
Compounds of the formula (I) in which R^1 or R^3 is $-OR^8$ may be prepared using the route shown in Scheme 2 that follows, in which R^8 is C_1-C_6 alkyl and L^3 is a suitable leaving group, preferably trifluoromethanesulphonate.

In Scheme 2, compounds of the formula (I) in which R^1 is $-OR^8$ may be prepared by the reaction of a compound of the formula (XIII) with an alcohol of the formula

R^8OH (XXI)

in the presence of a suitable palladium catalyst and carbon monoxide. In a typical procedure a mixture of the compound of the formula (XIII), a suitable palladium catalyst such as 1,1'-bis(diphenylphosphino)ferrocenepalladium(II)chloride, the alcohol of the formula (XXI) and, optionally, a suitable solvent such as N,N-dimethylformamide is heated, preferably to about 50°C, under an atmosphere of carbon monoxide, preferably at a pressure of 345 kPa.

Scheme 2



Compounds of the formula (XIII) may be prepared by the derivatisation of a compound of the formula (XV). In the case where L^3 is trifluoromethanesulphonate a suitable derivatising agent is phenyltriflamide. In a typical procedure, where L^3 is trifluoromethanesulphonate, a solution of the compound of the formula (XV) and a suitable base, preferably a trialkylamine base such as triethylamine, in a suitable solvent such as dichloromethane is treated with phenyltriflamide.

Compound of the formula (XV) may be prepared by the reaction of a compound of the formula (XVII) with a compound of the formula (V), or a salt or hydrate thereof, optionally in the presence of an acid or a base, the base preferably being a tertiary amine base such as triethylamine and the acid preferably being acetic acid. In a typical procedure, a solution of the compound of the formula (XVII) in a suitable solvent, such as ethanol, is treated with the compound of the formula (V), or the salt or hydrate thereof, and, if used, the appropriate acid or base, at a temperature of from room temperature to the reflux temperature of the solvent. In a preferred procedure, the reaction mixture is heated under reflux.

Compounds of the formula (XVII) may be prepared by the reaction of a compound of the formula (XIX) with a compound of the formula (XI). In a typical procedure, a solution of the compound of the formula (XVII) in a suitable solvent such as acetone is treated with a compound of the formula (XI) and a suitable base, such as potassium or caesium carbonate, and heated, preferably under reflux. Optionally, a nucleophilic catalyst such as sodium iodide or tetrabutylammonium iodide may be added.

In Scheme 2, compounds of the formula (I) in which R^3 is $-OR^8$ may be prepared from a compound of the formula (XX) in the same way that a compound of the formula (I) in which R^1 is $-OR^8$ is prepared from a compound of the formula (XIX), as set out above, *mutatis mutandis*.

Chloroketoesters of the formula (XIX) and (XX) are either commercially available or may be prepared by the chlorination of the corresponding ketoesters, for instance using sulphonyl chloride.

Alternatively, compounds of the formula (I) in which R^1 or R^3 is $-OR^8$ may be prepared from compounds of the formula (XV) or (XVI), respectively, by reaction with a compound of the formula (XXI) under dehydrating conditions, e.g. using the Mitsunobu reaction. In a typical procedure, a solution of the compound of the formula (XV) or (XVI) in a suitable solvent, such as tetrahydrofuran is treated with diethylazodicarboxylate, triphenylphosphine and a compound of the formula (XXI).

Compounds of the formula (I) in which R^1 or R^3 is halo can be prepared by the reaction, respectively, of a compound of the formula (XV) r a compound of the formula (XVI) with a suitable halogenating agent. In a typical procedure, the

compound of the formula (XV) or (XVI) is treated with $POCl_3$, optionally in the presence of a suitable solvent such as dimethylformamide, to give a compound of the formula (I) in which R^1 or R^3, respectively, is chloro.

It will be appreciated by those skilled in the art that, in many cases, compounds of the formula (I) may be converted into other compounds of the formula (I) by functional group transformations. For instance:

(a) compounds of the formula (I) in which R^2 is H may be converted into compounds of the formula (I) in which R^2 is optionally substituted C_1-C_6 alkyl by reaction with an appropriate alkylating agent. In a typical procedure, a solution of a compound of the formula (I) in which R^2 is H in a suitable solvent such as ethanol or N,N-dimethylformamide is treated with an alkyl bromide and a base such as sodium ethoxide or sodium hydride and heated at a temperature of from room temperature to the reflux temperature of the solvent. A preferred combination is N,N-dimethylformamide as the solvent, sodium hydride as the base and room temperature as the temperature. Examples of specific alkylating agents include bromoacetonitrile, ethyl 4-chloroacetoacetate, methyl bromoacetate and chloroethylamine hydrochloride. The use of further specific alkylating agents is illustrated by the Examples below;

(b) compounds of the formula (I) in which R^1, R^2 or R^3 contains an ester functionality may be reduced with a suitable reducing agent, such as lithium aluminium hydride, to give corresponding compounds of the formula (I) in which R^1, R^2 or R^3 contains a hydroxy group. In a typical procedure, a solution of the compound of the formula (I), in which R^1, R^2 or R^3 contains an ester group, in a suitable solvent, such as diethyl ether, is treated with lithium aluminium hydride, preferably with cooling to a temperature of from -78°C to 0°C;

(c) compounds of the formula (I) in which R^1, R^2 or R^3 are substituted by a heterocycle of the formula R^6 may be prepared by standard heterocycle-forming reactions well known to the skilled man (see, for example, Advanced Organic Chemistry, 3rd Edition, by Gerry March or Comprehensive Heterocyclic Chemistry, A.R. Katritzky, C.W. Rees, E.F.V. Scriven, Volumes 1-11). For instance, compounds of the formula (I) in which R^2 is (2-amino-6-hydroxypyrimidin-4-yl)methyl may be prepared by the sequential reaction of a compound of the formula (I) in which R^2 is H with chloroacetoacetate and then guanidine hydrochloride. This and other similar heterocyle-forming reactions are illustrated by the Examples below; and

(d) compounds of the formula (I) in which R^1 or R^3 is $-CO_2R^5$, wherein R^5 is other than H, may be converted into compounds of the formula (I) in which R^1 or R^3, respectively, is $-CO_2H$ by hydrolysis. Typically the reaction will be carried out in a suitable solvent, such as aqueous ethanol, or aqueous 1,4-dioxan and in the presence of a base such as sodium hydroxide. Such an acid may be converted to a primary amide by reaction with ammonia and a suitable coupling agent, such as a carbodiimide, e.g. dicyclohexylcarbodiimide. Such a primary amide may then be converted into a nitrile by dehydration with a suitable dehydrating agent, such as phosphoryl chloride.

(e) compounds of the formula (I) in which R^1 or R^3 is C_1-C_6 alkyl may be converted into the compounds of the formula (I) in which R^1 or R^3, respectively, is C_1-C_6 alkyl substituted by halo (such as bromo), by halogenation, using a suitable halogenating agent. Conveniently the reaction is effected in the presence of a solvent, such as a haloalkane (e.g. dichloromethane) and at ambient temperature. Suitable halogenating agents include halogens (e.g. bromine) or N-halosuccinimides (e.g. N-bromsuccinimide).

Compounds of the formula (I) containing an -OH, -NH- or $-NH_2$ group may be prepared by the deprotection of the corresponding compound bearing an $-OP^1$, $-NP^1$- or $-NHP^1$ group, respectively, wherein the group P^1 is a suitable protecting group. Examples of suitable protecting groups will be apparent to the skilled person [see, for instance, 'Protecting groups in Organic Synthesis (Second Edition)' by Theodora W. Green and Peter G. M. Wuts, 1991, John Wiley and Sons]. Such compounds bearing an $-OP^1$, $-NP^1$- or $-NHP^1$ group may be prepared using the routes described above, *mutatis mutandis*.

Compounds of the formula (IV), (V) and (XXI) are either commercially available or easily prepared by methods well known to those skilled in the art.

The compounds of the formula (I) can be administered alone but will generally be administered in admixture with a suitable pharmaceutical excipient, diluent or carrier selected with regard to the intended route of administration and standard pharmaceutical practice.

For example, the compounds of the formula (I) can be administered orally, buccally or sublingually in the form of tablets, capsules, multi-particulates, gels, films, ovules, elixirs, solutions or suspensions, which may contain flavouring or colouring agents, for immediate-, delayed-, modified-, sustained-, pulsed- or

controlled-release applications. The compounds of the formula (I) may also be administered as fast-dispersing or fast-dissolving dosage forms or in the form of a high energy dispersion or as coated particles. Suitable formulations of the compounds of the formula (I) may be in coated or uncoated form, as desired.

Such solid pharmaceutical compositions, for example, 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.

General Example

A formulation of the tablet could typically contain from 0.01mg to 500mg of active compound whilst tablet fill weights may range from 50mg to 1000mg. An example of a formulation for a 10mg tablet is illustrated below:

Ingredient	%w/w
Compound of the formula (I) or salt	10.000*
Lactose	64.125
Starch	21.375
Croscarmellose sodium	3.000
Magnesium Stearate	1.500

* Quantity adjusted in accordance with drug activity.

The tablets are manufactured by a standard process, for example, direct compression or a wet or dry granulation process. The tablet cores may be coated with appropriate overcoats.

Solid compositions of a similar type may also be employed as fillers in gelatin or HPMC capsules. Preferred excipients in this regard include lactose, starch, a cellulose, milk sugar or high molecular weight polyethylene glycols. For aqueous suspensions and/or libirs, the compounds of the formula (I) 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.

The compounds of the formula (I) 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 or needleless injection techniques. For such parenteral administration they are best used in the form of a sterile aqueous solution which may contain other substances, 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.

For oral and parenteral administration to human patients, the daily dosage level of the compounds of the formula (I) will usually be from 0.01 to 30 mg/kg, preferably from 0.01 to 5 mg/kg (in single or divided doses).

Thus tablets or capsules of the compound of the formula (I) may contain from 1 to 500 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 appreciate that, in the treatment of certain conditions the compounds of the formula (I) may be taken as a single dose as needed or desired.

The compounds of formula (I) 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, atomiser or nebuliser, with or without the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, 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, atomiser or nebuliser 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 formula (I) and a suitable powder base such as lactose or starch.

Alternatively, the compounds of the formula (I) 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 formula (I) may also be dermally or transdermally administered, for example, by the use of a skin patch. They may also be administered by the pulmonary or rectal routes.

They may also be administered by the ocular route. For ophthalmic use, the compounds can be formulated as micronised 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 formula (I) 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 formula (I) 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.

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

Oral administration is preferred.

Included within the scope of the present invention are embodiments comprising the co-administration of a compound of the present invention with one or more additional therapeutic agents, and compositions containing a compound of the present invention along with one or more additional therapeutic agents. Such a combination therapy is especially useful for the prevention and/or treatment of infection by HIV and related *retroviruses* which may evolve rapidly into strains resistant to any monotherapy. Alternatively, additional therapeutic agents may be desirable to treat diseases and conditions which result from or accompany the disease being treated with the compound of the present invention. For example, in the treatment of an HIV or related retroviral infection, it may be desirable to additionally treat opportunistic infections, neoplasms and other conditions which occur as a result of the immuno-compromised state of the patient being treated.

Preferred combinations of the present invention include simultaneous or sequential treatment with a compound of the formula (I), as defined above, or a pharmaceutically acceptable salt thereof, and:

(a) one or more reverse transcriptase inhibitors such as zidovudine, didanosine, zalcitabine, stavudine, lamivudine, abacavir and adefovir;

(b) one or more non-nucleoside reverse transcriptase inhibitors such as nevirapine, delavirdine and efavirenz;

(c) one or more HIV protease inhibitors such as indanivir, ritonavir, saquinavir and nelfinavir;

(d) one or more CCR5 antagonists such as TAK-779;

(e) one or more CXCR4 antagonists such as AMD-3100;

(f) one or more integrase inhibitors;

(g) one or more inhibitors of viral fusion such as T-20;

(h) one or more investigational drugs such as trizivir, KNI-272, amprenavir, GW-33908, FTC, PMPA, S-1153, MKC-442, MSC-204, MSH-372, DMP450, PNU-140690, ABT-378, KNI-764, DPC-083, TMC-120 or TMC-125; or

(l) one or more antifungal or antibacterial agents such as fluconazole.

The activity of the compounds of the invention as reverse transcriptase inhibitors and as agents for treating HIV infections may be measured using the following assays.

A. Inhibition of HIV-1 reverse transcriptase enzyme

The reverse transcriptase activity of the compounds of the invention may be assayed as following. Using the purified recombinant HIV-1 reverse transcriptase (RT, EC, 2.7.7.49) obtained by expression in Escherichia Coli, a 96-well plate assay system was established for assaying a large number of samples using either the Poly(rA)-oligo(dT) Reverse Transcriptase [3H]-SPA enzyme assay system (Amersham NK9020) or the [3H]-flashplate enzyme assay system (NEN - SMP 103) and following the manufacturer's recommendations. The compounds were dissolved in 100% DMSO and diluted with the appropriate buffer to a 5% final DMSO concentration. The inhibitory activity was expressed in percent inhibition relative to the DMSO control. The concentration at which the compound inhibited the reverse transcriptase by 50% was expressed as the IC_{50} of the compound. The compounds of examples 7, 20 and 51, when tested according to the above procedure, had IC_{50} values of, respectively, 39000, 3200 and 248 nanomolar.

B. Anti-Human Immunodeficiency Virus (HIV-1) cell culture assay

The anti-HIV activity of selected Examples of the invention was assayed by the following procedures.

1) SupT1 cells were cultured in an RPMI-1640 medium supplemented with 10% foetal calf serum and were split so that they were in growth phase on the day of use.

2) The compounds were dissolved in 100% DMSO and diluted with the above culture medium to predetermined concentrations and distributed in 20µl aliquots into a 96-well microtiter plate (0.1% DMSO final concentration).

3) To prepare infected cells, 100µl of RF viruses (TCID50 of 10^7/ml) were added to 10^6 cells and incubated for 1 hour at 37°C. The cells were then washed twice in PBS and resuspended in the culture medium at a density of 2.2 x10^5cells/ml. 180µl of these infected cells was transferred to wells of the 96 well plate containing the compounds.

4) The plate was incubated in a CO_2 incubator at 37°C for 4 days. The cell survival rates were measured following the manufacturer's recommendations (CellTiter 96® AQ_{ueous} Non-Radioactive Assay - Promega (cat no: G5430)). The

concentration at which the compound inhibited the cytotoxic effect of the virus by 50% was expressed as the EC_{50}.

Thus the invention provides:

(i) a compound of the formula (I) or a pharmaceutically acceptable salt, solvate or derivative thereof;

(ii) a process for the preparation of a compound of the formula (I) or a pharmaceutically acceptable salt, solvate or derivative thereof;

(iii) a pharmaceutical composition including a compound of the formula (I) or a pharmaceutically acceptable salt, solvate or derivative thereof, together with a pharmaceutically acceptable excipient, diluent or carrier;

(iv) a compound of the formula (I) or a pharmaceutically acceptable salt, solvate or composition thereof, for use as a medicament;

(v) a compound of the formula (I) or a pharmaceutically acceptable salt, solvate or composition thereof, for use as a reverse transcriptase inhibitor or modulator;

(vi) a compound of the formula (I) or a pharmaceutically acceptable salt, solvate or composition thereof, for use in the treatment of an HIV, or genetically-related retroviral, infection or a resulting acquired immune deficiency syndrome (AIDS);

(vii) the use of a compound of the formula (I) or of a pharmaceutically acceptable salt, solvate or composition thereof, for the manufacture of a medicament having reverse transcriptase inhibitory or modulating activity;

(viii) the use of a compound of the formula (I) or of a pharmaceutically acceptable salt, solvate or composition thereof, for the manufacture of a medicament for the treatment of an HIV, or genetically-related retroviral, infection or a resulting acquired immune deficiency syndrome (AIDS);

(ix) a method of treatment of a mammal, including a human being, with a reverse transcriptase inhibitor or modulator including treating said mammal with an effective amount of a compound of the formula (I) or with a pharmaceutically acceptable salt, solvate or composition thereof;

(x) a method of treatment of a mammal, including a human being, to treat an HIV, or genetically-related retroviral, infection or a resulting acquired immune deficiency syndrome (AIDS) including treating said mammal with an effective amount of a compound of the formula (I) or with a pharmaceutically acceptable salt, solvate or composition thereof; and

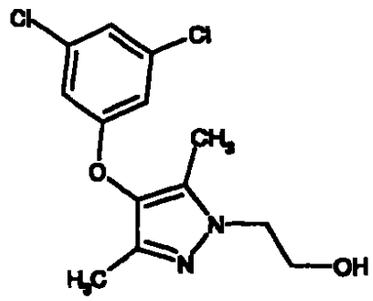
(xi) certain novel intermediates disclosed herein.

The following Examples illustrate the preparation of the compounds of the formula (I). The synthesis of certain intermediates used therein are described in the Preparations section that follows the Examples.

^{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: HRMS, high resolution mass spectrometry; hplc, high performance liquid chromatography; nOe, nuclear Overhauser effect; m.p., melting point; $CDCl_3$, deuterochloroform; D_6-DMSO, deuterodimethylsulphoxide; CD_3OD, deuteromethanol. 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.

EXAMPLE 1

2-[4-(3,5-Dichlorophenoxy)-3,5-dimethyl-1*H*-pyrazol-1-yl]ethanol



2-Hydroxyethyl hydrazine (21.5μL, 0.316mmol) was added to a stirred solution of the β-diketone of Preparation 1 (75mg, 0.287mmol) in ethanol (2.9ml) at room temperature under nitrogen and the resulting orange solution was heated under reflux for 18 hours. After cooling, the mixture was concentrated under reduced pressure. The residue was dissolved in dichloromethane (20ml) and washed with 2M hydrochloric acid (10ml) and brine (10ml) and then dried over magnesium sulphate, filtered and concentrated under reduced pressure to leave a viscous orange oil. The crude product was purified by flash chromatography on silica gel eluting with pentane:ethyl acetate (10:1, by volume) then dichloromethane to provide the title compound (32mg) as a white powder, m.p. 114-115°C.

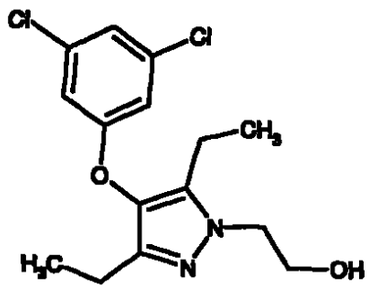
^{1}H-NMR (400MHz, $CDCl_3$): δ = 2.08 (s, 3H), 2.10 (s, 3H), 3.30 (t, 1H), 4.06 (m, 4H), 6.79 (s, 2H), 7.01 (s, 1H).

LRMS (thermospray): m/z [MH^+] 301.

Microanalysis: Found: C, 51.76; H, 4.64; N, 9.20. $C_{13}H_{14}Cl_2N_2O_2$ requires C, 51.85; H, 4.69; N, 9.30%.

EXAMPLE 2

2-[4-(3,5-Dichlorophenoxy)-3,5-diethyl-1*H*-pyrazol-1-yl]ethanol



3,5-Dichlorophenol (501mg, 3.07mmol), potassium carbonate (467mg, 3.38mmol) and finally sodium iodide (461mg, 3.07mmol) were added sequentially to a stirred solution of the chloroketone of Preparation 2 (500mg, 3.07mmol) in acetone (15ml), at room temperature and under nitrogen, producing an orange/red suspension. The mixture was heated under reflux for 22½ hours producing a yellow suspension. After cooling the mixture was diluted with water (10ml) and the acetone was removed under reduced pressure in a fumehood (caution: possible residual lachrymator). The residue was diluted with 2M hydrochloric acid and extracted with dichloromethane (1x20ml, 2x10ml). The combined organic layers were washed with brine (20ml), dried over magnesium sulphate, filtered and concentrated under reduced pressure to leave crude 4-(3,5-dichlorophenoxy)-3,5-heptanedione as an orange oil (777mg). A portion of the crude 4-(3,5-dichlorophenoxy)-3,5-heptanedione (250mg, *ca.* 0.865mmol) was dissolved in ethanol (8.6ml) and treated with 2-hydroxethyl hydrazine (65µL, 0.951mmol). The resulting solution was heated under reflux for 16 hours producing a red solution. After cooling, the mixture was concentrated under reduced pressure and the residue was dissolved in dichloromethane (20ml). The resulting solution was washed with 2M hydrochloric acid (10ml), 1N sodium hydroxide solution (10ml) and brine (10ml), dried over magnesium sulphate, filtered and concentrated under reduced pressure to leave an orange oil (102mg). The crude product was purified by flash chromatography n silica gel

eluting with methanol:dichloromethane (5:95, by volume) to provide the title compound (23mg) as an orange oil which solidified to a waxy solid on standing.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.08 (t, 3H), 1.12 (t, 3H), 2.38 (q, 2H), 2.48 (q, 2H), 3.69 (br.s, 1H), 4.02 (m, 4H), 6.76 (s, 2H), 6.97 (s, 1H).
LRMS (thermospray): m/z [MH^+] 329.

EXAMPLE 3

4-(3,5-Dichlorophenoxy)-3,5-diethyl-1*H*-pyrazole

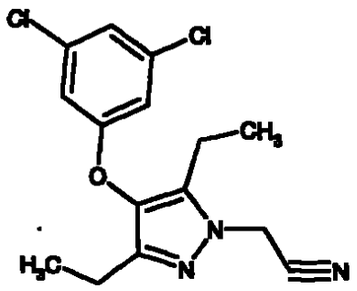


A mixture of the chloroketone of Preparation 2 (5g, 30.8mmol), 3,5-dichlorophenol (5g, 30.8mmol), caesium carbonate (10g, 30.8mmol) and acetone (40ml) was heated under reflux for 18 hours. After cooling, a solid was removed by filtration and washed with dichloromethane (100ml). The combined filtrates were concentrated under reduced pressure. The crude product was dissolved in ethanol (20ml), hydrazine hydrate (1.5ml, 30.8mmol) was added and the mixture was heated at 60°C for 30 minutes under nitrogen. After cooling, the mixture was concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel eluting with ether:pentane (1:1, by volume) to provide the title compound (5.5g) as a yellow oil which solidified on standing to leave a yellow solid, m.p. 114-115°C.

^{1}H-NMR (300MHz, $CDCl_3$): δ = 1.15 (6H, t), 2.48 (4H, q), 6.78 (2H, s), 6.95 (1H, s).
LRMS (thermospray): m/z [MH^+] 285.
Microanalysis: Found: C, 54.93; H, 5.05; N, 9.94. $C_{13}H_{14}Cl_2N_2O$ requires C, 54.75; H, 4.95; N, 9.82%.

EXAMPLE 4

[4-(3,5-Dichlorophenoxy)-3,5-diethyl-1*H*-pyrazol-1-yl]acetonitrile



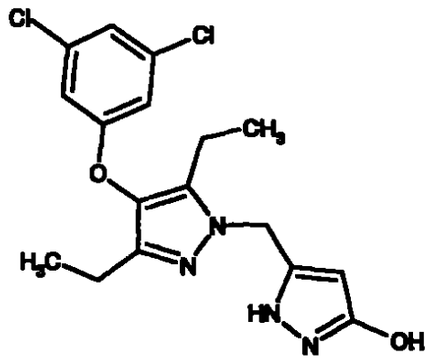
Sodium hydride (60% dispersion in oil, 470mg, 11.8mmol) was added to a stirred solution of 4-(3,5-dichlorophenoxy)-3,5-diethyl-1*H*-pyrazole (3g, 10.5mmol, Example 3) in dry N,N-dimethylformamide (20ml) at 0°C under nitrogen. The mixture was stirred for 5 minutes during which time hydrogen was evolved and then bromoacetonitrile (0.81ml, 11.6mmol) was added. The yellow solution turned dark brown and a precipitate formed. Further dry N,N-dimethylformamide (5ml) was added to aid dissolution and after 45 minutes the reaction mixture was quenched by the addition of water (1ml). The mixture was partitioned between water (150ml) and diethyl ether (2x150ml). The combined organic layers were washed with water (50ml) and brine (100ml), dried over magnesium sulphate and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with dichloromethane to provide the title compound (3.2g) as a yellow powder, m.p. 70-72°C.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.14 (6H, m), 2.38 (2H, q), 2.56 (2H, q), 4.92 (2H, s), 6.75 (2H, s), 7.00 (1H, s).

Microanalysis: Found: C, 55.43; H, 4.69; N, 12.71. $C_{16}H_{15}Cl_2N_3O$ requires C, 55.57; H, 4.60; N, 12.96%.

EXAMPLE 5

5-[[4-(3,5-Dichlorophenoxy)-3,5-diethyl-1*H*-pyrazol-1-yl]methyl]-1*H*-pyrazol-3-ol



A mixture of the ester (120mg, 0.29mmol) of Preparation 3, hydrazine hydrate (16mg, 0.29mmol) and ethanol (5ml) was stirred and heated at 60°C for 2 hours under nitrogen. After cooling, the mixture was concentrated under reduced pressure and the resulting white solid was stirred in ethyl acetate and then collected by filtration to give the title compound (60mg) as a white solid, m.p. 142-144°C.

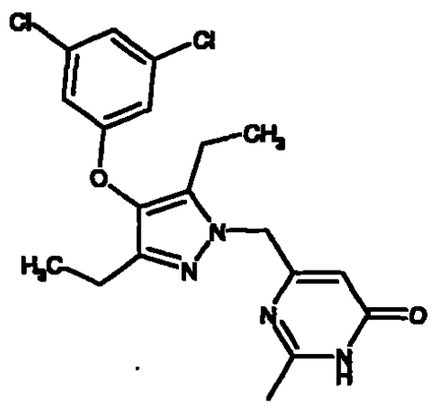
^{1}H-NMR (400MHz, DMSO-d_6): δ = 0.89 (3H, t). 0.99 (3H, t), 2.26 (2H, q), 2.45 (2H, q), 5.01 (2H, s), 5.19 (1H, s), 6.88 (2H, s), 7.21 (1H, s).

LRMS (electrospray): m/z [M-H$^+$] 379.

Microanalysis: Found: C, 55.39; H, 4.72; N, 14.69. $C_{17}H_{18}Cl_2N_4O_2$ requires C, 53.56; H, 4.76; N, 14.69%.

EXAMPLE 6

6-[[4-(3,5-Dichlorophenoxy)-3,5-diethyl-1*H*-pyrazol-1-yl]methyl]-2-methyl-4(3*H*)-pyrimidinone

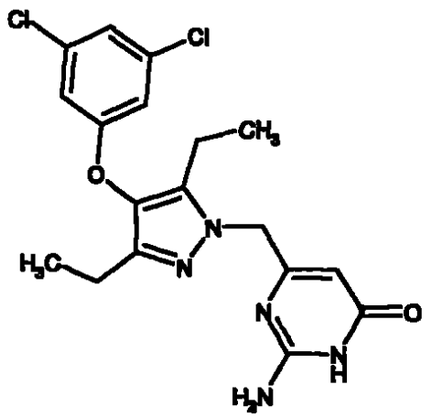


A mixture of the ester (140mg, 0.34mmol) of Preparation 3, acetamidine hydrochloride (95mg, 1.0mmol), sodium ethoxide (68mg, 1.0mmol) and ethanol (5ml) was stirred and heated at 70°C for 1 hour under nitrogen. After cooling, the mixture was concentrated under reduced pressure. The resulting oil was dissolved in dichloromethane (50ml), washed with water (20ml), dried over magnesium sulphate and concentrated under reduced pressure to leave the title compound as a white foam (100mg).

^{1}H-NMR (300MHz, $CDCl_3$): δ = 1.10 (3H, t), 1.19 (3H, t), 2.48 (7H, m), 5.08 (2H, s), 5.72 (1H, s), 6.82 (2H, s), 7.03 (1H, s).
LRMS (thermospray): m/z [MH^+] 407.

EXAMPLE 7

2-Amino-6-[[4-(3,5-dichlorophenoxy)-3,5-diethyl-1*H*-pyrazol-1-yl]methyl]-4(3*H*)-pyrimidinone

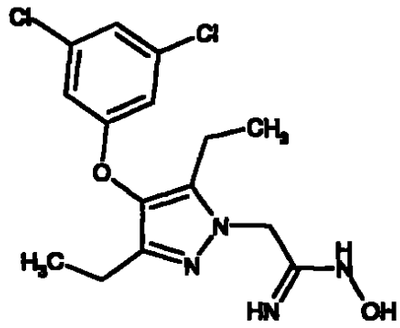


A mixture of the ester (150mg, 0.365mmol) from Preparation 3 and guanidine hydrochloride (104mg, 1.08mmol) and sodium ethoxide (73mg, 1.08mmol) in ethanol (5ml) was stirred and heated at 70°C for 3 hours under nitrogen. After cooling the mixture was concentrated under reduced pressure and the resulting oil was dissolved in dichloromethane (50ml), washed with water (20ml), dried over magnesium sulphate and concentrated under reduced pressure. The crude product was purified by chromatography on silica gel eluting with dichloromethane:methanol:ammonia (90:10:1, by volume) to give the title compound as a white solid (30mg), m.p. 238-240°C.

^{1}H-NMR (400MHz, DMSO-d_6): δ = 0.91 (3H, t), 0.99 (3H, t), 2.29 (2H, q), 2.44 (2H, q), 4.75 (1H, s), 4.81 (2H, s), 6.58 (2H, br.s), 6.87 (2H, s), 7.22 (1H, s).
LRMS (thermospray): m/z [MH^+] 408.

EXAMPLE 8

2-[4-(3,5-Dichlorophenoxy)-3,5-diethyl-1*H*-pyrazol-1-yl]-*N*-hydroxyethanimidamide

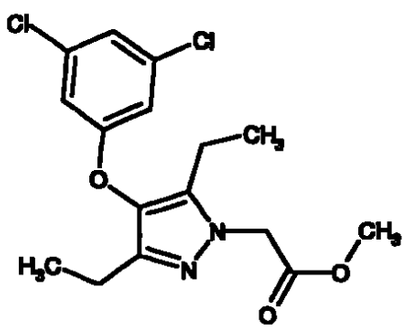


Hydroxylamine hydrochloride (1.1g, 15.8mmol) and potassium carbonate (2.1g, 15.2mmol) were added to a suspension of the nitrile (1g, 3.1mmol) of Example 4 in a mixture of methanol (25ml) and water (10ml) which was then heated under reflux for 3 days. After cooling, the mixture was extracted with dichloromethane (2x250ml) and the combined organic layers were washed with brine (100ml), dried over magnesium sulphate, filtered and concentrated under reduced pressure to afford the product as a white solid (1.1g), m.p. 128-130°C.

^{1}H-NMR (300MHz, CD_3OD): δ = 1.10 (6H, m), 2.40 (2H, q), 2.60 (2H, q), 4.65 (2H, s), 6.90 (2H, s), 7.10 (1H, s).
LRMS (electrospray): m/z [MH^+] 357.

EXAMPLE 9

Methyl [4-(3,5-dichlorophenoxy)-3,5-diethyl-1*H*-pyrazol-1-yl]acetate

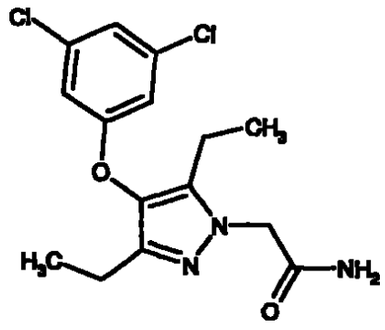


Methyl bromoacetate (984µL, 10mmol) and then sodium hydride (60% dispersion in oil, 801mg, 20.1mmol) were added to a stirred solution of the pyrazole (2.6g, 9.12mmol) of Example 3 in dry N,N'-dimethylformamide (25ml) at 0°C under nitrogen. After stirring for 1 hour at 0°C ice-water (100ml) was added and the mixture was extracted with ether (3x50ml). The combined ether layers were dried over magnesium sulphate, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with ethyl acetate:pentane (20:80, by volume) to provide the title compound (780mg) as a yellow oil which partly crystallised on standing.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.10 (6H, m), 2.44 (4H, m), 3.78 (3H, s), 4.80 (2H, s), 6.69 (2H, s), 6.99 (1H, s).
LRMS (thermospray): m/z [MH^+] 357.

EXAMPLE 10

2-[4-(3,5-Dichlorophenoxy)-3,5-diethyl-1*H*-pyrazol-1-yl]acetamide



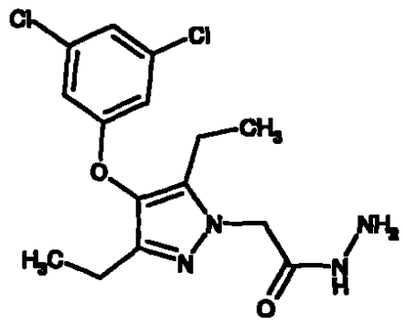
1,1'-Carbonyl diimidazole (71mg, 0.44mmol) was added to stirred solution of the acid (125mg, 0.36mmol) of Preparation 4 in dry N,N-dimethylformamide at room temperature and the reaction mixture was stirred for 30 minutes. Concentrated aqueous ammonia (d=0.880g/cm^3, *ca.* 0.1ml, *ca.* 1.8mmol) was added and stirring was continued for 10 minutes. The solvent was removed under reduced pressure and the residue was partitioned between water (10ml) and ethyl acetate (10ml). The organic layer was concentrated under reduced pressure and the residue was purified by chromatography on silica gel, eluting with ethyl acetate, to give the title compound as a white solid (60mg), m.p. 164-166°C.

^{1}H-NMR (300MHz, $CDCL_3$): δ = 1.15 (6H, m), 2.50 (4H, m), 4.70 (2H, s), 5.50 (1H, br. s), 6.21 (1H, br. s), 6.78 (2H, s), 7.04 (1H, s).

LRMS (thermospray): m/z [MH$^+$] 342.

EXAMPLE 11

2-[4-(3,5-Dichlorophenoxy)-3,5-diethyl-1*H*-pyrazol-1-yl]acetohydrazide

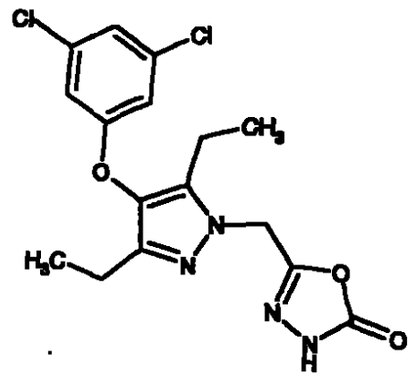


Hydrazine hydrate (520µL, 10.9mmol) was added to a solution of the ester (780mg, 2.18mmol) of Example 9 in ethanol (25ml) and the resulting mixture was heated under reflux for 18 hours. After cooling, the precipitate was collected by filtration and washed with ether (50ml) to afford the title compound (550g) as a white solid, m.p. >250°C.

^{1}H-NMR (300MHz, CD_3OD): δ = 1.10 (6H, m), 2.39 (2H, q), 2.55 (2H, q), 4.72 (2H, s), 6.93 (2H, s), 7.09 (1H, s).
LRMS (electrospray): m/z [MH$^+$] 357.

EXAMPLE 12

5-[[4-(3,5-Dichlorophenoxy)-3,5-diethyl-1*H*-pyrazol-1-yl]methyl]-1,3,4-oxadiazol-2(3*H*)-one

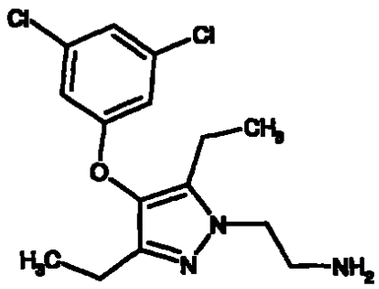


A stirred solution of the hydrazide (275mg, 0.77mmol) of Example 11 and 1,1'-carbonyl diimidazole 187mg, 1.16mmol) in dioxane (50ml) was heated under reflux for 18 hours. After cooling, the mixture was concentrated under reduced pressure and the residue was dissolved in dichloromethane (50ml) and washed with water (25ml). The organic layer was dried over magnesium sulphate, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with dichloromethane:methanol (95:5, by volume) to afford the title compound (112mg) as a white solid m.p. 138-142°C.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.10 (6H, m), 2.40 (2H, q), 2.55 (2H, q), 5.07 (2H, s), 6.76 (2H, s), 6.98 (1H, s), 10.45 (1H, br. s).
LRMS (electrospray): m/z [MH^+] 383.

EXAMPLE 13

2-[4-(3,5-Dichlorophenoxy)-3,5-diethyl-1*H*-pyrazol-1-yl]ethylamine

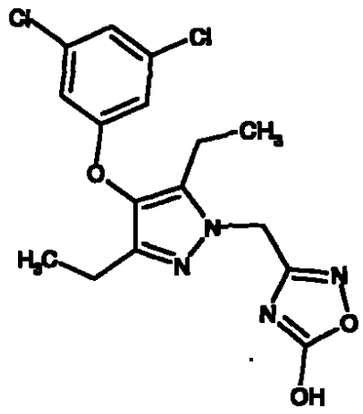


A mixture of the pyrazole (390mg, 1.37mmol) of Example 3 and chloroethylamine hydrochloride (238mg, 2.05mmol) was stirred and heated at 150°C for 24 hours. After cooling, the mixture was partitioned between saturated aqueous sodium bicarbonate solution (100ml) and dichloromethane (2x50ml). The combined organic layers were washed with brine (30ml), dried over magnesium sulphate, filtered and concentrated under reduced pressure. The resulting brown oil was purified by flash chromatography on silica gel eluting with dichloromethane:methanol (90:10, by volume) to afford the title compound (244mg) as a brown oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.09 (6H, m), 2.41 (2H, q), 2.52 (2H, q), 3.18 (2H, t), 4.02 (2H, t), 6.78 (2H, s), 6.99 (1H, s).
LRMS (electrospray): m/z [MH^+] 330.
Microanalysis: Found: C, 52.28; H, 5.70; N, 11.75. $C_{15}H_{19}Cl_2N_3O.H_2O$ requires C, 52.03; H, 6.11; N, 12.14%.

EXAMPLE 14

3-[[4-(3,5-Dichlorophenoxy)-3,5-diethyl-1*H*-pyrazol-1-yl]methyl]-1,2,4-oxadiazol-5-ol



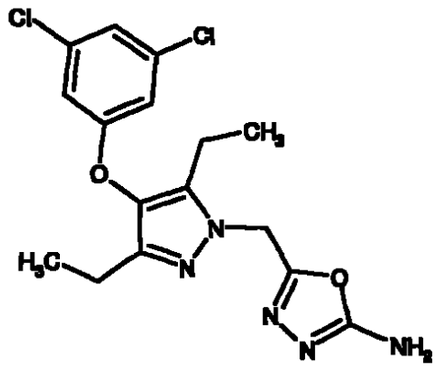
Ethylchloroformate (0.30ml, 3.08mmol) was added to a stirred solution of the amidoxime of Example 8 (500mg, 1.39mmol) in pyridine (8ml) at 0°C under nitrogen and the resulting solution was stirred for 10 minutes. The mixture was concentrated under reduced pressure and the residue was dissolved in a mixture of water (4ml), tetrahydrofuran (4ml) and 1M aqueous sodium hydroxide solution (2ml). The mixture was heated under reflux for 1 hour, cooled to room temperature and stirred for a further 2 days. The resulting solution was diluted with 2M aqueous hydrochloric acid (20ml) and extracted with ethyl acetate (2x50ml). The combined organic layers were washed with brine (50ml), dried over magnesium sulphate, filtered and evaporated under reduced pressure to leave a yellow oil. The oil was purified by flash column chromatography on silica gel eluting with pentane:ethyl acetate (50:50, by volume) to yield a white solid. The solid was dissolved in a mixture of tetrahydrofuran (1ml) and 1M aqueous sodium hydroxide solution (10ml) and then heated under reflux for 24 hours. The resulting solution was diluted with 2M hydrochloric acid (20ml) and extracted with dichloromethane (2x50ml). The combined organic layers were washed with brine (50ml), dried over magnesium sulphate, filtered and evaporated under reduced pressure to give the title compound (113mg) as a white solid m.p. 94-96°C.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.14 (m, 6H), 2.56 (m, 4H), 5.06 (s, 2H), 6.75 (s, 2H), 7.03 (s, 1H).

LRMS (electrospray): m/z [M-(H^+)] 381.

EXAMPLE 15

5-[[4-(3,5-Dichlorophenoxy)-3,5-diethyl-1*H*-pyrazol-1-yl]methyl]-1,3,4-oxadiazol-2-amine

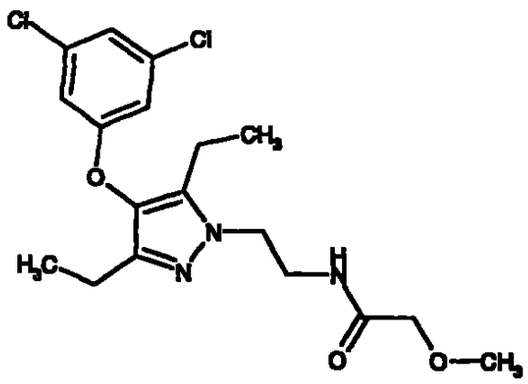


Cyanogen bromide (49mg, 0.462mmol) was added to a stirred solution of the hydrazide of Example 11 (150mg, 0.420mmol) in ethanol (30ml), at room temperature, under nitrogen and the resulting solution was heated to reflux for 2.5 hours. After cooling, the mixture was concentrated under reduced pressure to leave a brown oil. The crude product was purified by flash column chromatography on silica gel eluting with dichloromethane:methanol:ammonia (98:1.75:0.25, by volume) to provide the title compound (71mg) as a white powder, m.p. 226-228°C.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.00 (m, 6H), 2.29 (m, 2H), 2.55 (m, 2H), 5.34 (s, 2H), 6.90 (s, 2H), 7.07 (s, 2H), 7.24 (s, 1H).
LRMS (electrospray): m/z [MH^+] 382.
Microanalysis: Found: C, 49.82; H, 4.52; N, 17.81. $C_{16}H_{17}Cl_2N_5O_2.0.25H_2O$ requires C, 49.69; H, 4.56; N, 18.11%.

EXAMPLE 16

N-[2-[4-(3,5-Dichlorophenoxy)-3,5-diethyl-1*H*-pyrazol-1-yl]ethyl]-2-methoxyacetamide



A solution of the pyrazole of Example 13 (53mg, 0.161mmol), 1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide hydrochloride (34mg, 0.178mmol) and 4-(dimethylamino)pyridine (22mg, 0.178mmol) in dichloromethane (1ml) was added to a stirred solution of methoxyacetic acid (14.2µL, 0.178mmol) in dichloromethane (1ml) at room temperature. The reaction was stirred for 12 hours and then concentrated under a stream of nitrogen to leave a yellow solid. The crude product was purified by flash column chromatography on silica gel eluting with dichloromethane:methanol (98:2, by volume) to provide the title compound (54mg) as a brown solid, m.p. 75-76°C.

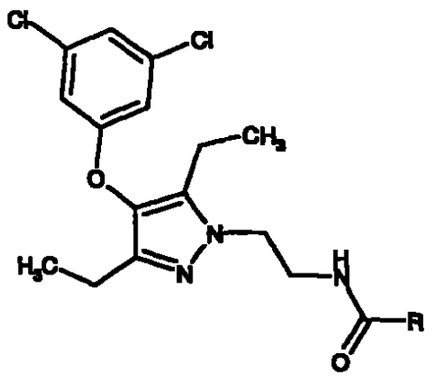
^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.08 (t, 3H), 1.18 (t, 3H), 2.42 (q, 2H), 2.52 (q, 2H), 3.39 (s, 3H), 3.75 (m, 2H), 3.90 (s, 2H), 4.13 (t, 2H), 6.79 (s, 2H), 6.99 (s, 1H), 7.21 (br s, 1H).

LRMS (electrospray): m/z [MH^+] 400; [M-(H^+)] 398.

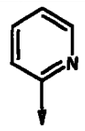
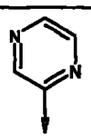
Microanalysis: Found: C, 54.09; H, 5.79; N, 10.39. $C_{18}H_{23}Cl_2N_3O_3$ requires C, 54.01; H, 5.79; N, 10.50%.

EXAMPLES 17 AND 18

The compounds of the following tabulated Examples of the general formula:



were prepared by a similar method to that of Example 16 using the appropriate acid starting material and the pyrazole of Example 13.

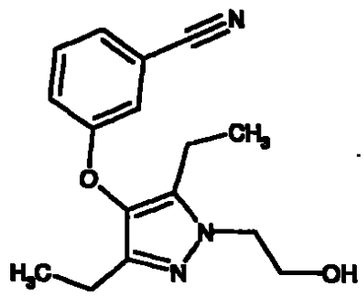
Example No	R	LRMS (thermospray)	Analytical Data
17		m/z [MH$^+$] 433	^{1}H-NMR (400MHz, $CDCl_3$) δ = 1 06 (t, 3H), 1 18 (t, 3H), 2 44 (q, 2H), 2 52 (q, 2H), 3 92 (m, 2H), 4 24 (t, 2H), 6 79 (s, 2H), 6 99 (s, 1H), 7 40 (m, 1H), 7 82 (m, 1H), 8 19 (m, 1H), 8 52 (br s, 2H), 8 55 (m, 1H) Microanalysis Found C, 57 01, H, 5 08, N, 11 94 $C_{21}H_{22}Cl_2N_4O_2$ requires C, 58 21, H, 5 12, N, 12 03%
18		m/z [MH$^+$] 434	^{1}H-NMR (400MHz, $CDCl_3$) δ = 1 08 (t, 3H), 1 18 (t, 3H), 2 42 (q, 2H), 2 52 (q, 2H), 3 96 (m, 2H), 4 24 (t, 2H), 6 79 (s, 2H), 7 01 (s, 1H), 8 22 (br s, 1H), 8 54 (d, 1H), 8 78 (d, 1H), 9 40 (s, 1H)





EXAMPLE 19

3-{[3,5-Diethyl-1-(2-hydroxyethyl)-1*H*-pyrazol-4-yl]oxy}benzonitrile

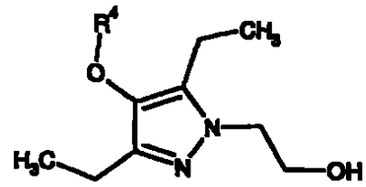


A mixture of the chloroketone of Preparation 2 (243mg, 1.50mmol), 3-cyanophenol (155mg, 1.50mmol), cesium carbonate (488mg, 1.50mmol) and acetone (10ml) was heated under reflux for 2 hours. After cooling, the solid was removed by filtration and the filtrate was concentrated under reduced pressure to leave a brown oil. The oil was dissolved in ethanol (10ml), hydroxyethylhydrazine (114mg, 1.50mmol) was added and the mixture was heated at 60°C for 18 hours. After cooling, the mixture was concentrated under reduced pressure. A solution of the residue in dichloromethane (10ml) was washed with 2M aqueous hydrochloric acid (5ml) and water (5ml), dried over magnesium sulphate, filtered and concentrated under reduced pressure to leave a yellow oil. The crude product was purified by flash column chromatography on silica gel eluting with ethyl acetate to provide the title compound (80mg) as a colourless oil.

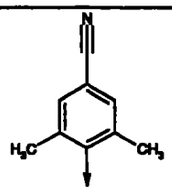
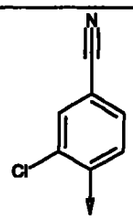
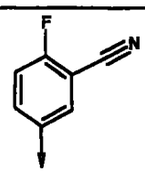
^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.10 (m, 6H), 2.40 (q, 2H), 2.50 (q, 2H), 3.68 (br s, 1H), 4.07 (m, 4H), 7.12 (s, 1H), 7.14 (d, 1H), 7.28 (d, 2H).
LRMS (electrospray): m/z [MH^+] 286; [MNa^+] 308.

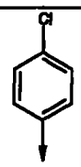
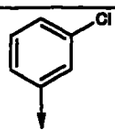
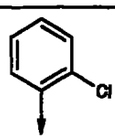
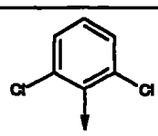
EXAMPLES 20 TO 38

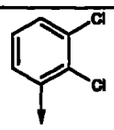
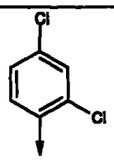
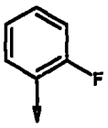
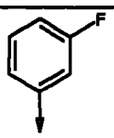
The compounds of the following tabulated Examples of the general formula:

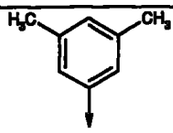
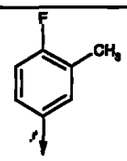
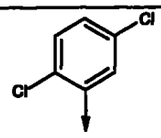
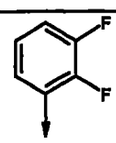


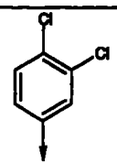
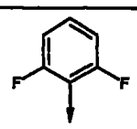
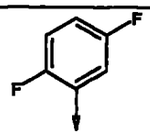
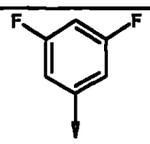
were prepared by a similar method to that of Example 19 using the appropriate phenols and the chloroketone of Preparation 2.

Example No	R^4	LRMS (electrospray)	Analytical Data
20		m/z [MH^+] 314	^{1}H-NMR (400MHz, $CDCl_3$) δ = 0 99 (t, 3H), 1 09 (t,3H), 2 18 (s, 6H), 2.25 (q, 2H), 2 40 (q, 2H), 3 78 (br s, 1H), 4 00 (m, 4H), 7 34 (s, 2H)
21		m/z [MH^+] 320	^{1}H-NMR (400MHz, $CDCl_3$) δ = 1 10 (m, 6H), 2 40 (q, 2H), 2 53 (q, 2H), 3 56 (br s, 1H), 4 04 (m, 2H), 4 08 (m, 2H), 6 80 (d, 1H), 7 44 (d, 1H), 7 72 (s, 1H) Accurate Mass Found 320 1165 [MH^+], $C_{16}H_{18}ClN_3O_2$ requires 320 1161 [MH^+]
22		m/z [MH^+] 304	^{1}H-NMR (400MHz, $CDCl_3$) δ = 1 10 (m, 6H), 2 39 (q, 2H), 2 50 (q, 2H), 4 60 (m, 4H), 7 05 (m, 1H), 7 14 (m, 2H)

Example No	R^4	LRMS (electrospray)	Analytical Data
23		m/z [MH^+] 295	^{1}H-NMR (400MHz, $CDCl_3$) δ = 1 09 (m, 6H), 2 41 (m, 2H), 2 51 (m, 2H), 3 78 (br s, 1H), 4 06 (m, 4H), 6 81 (m, 2H), 7 21 (m, 2H) Microanalysis Found C, 60 88, H, 6 49, N, 9 40 $C_{15}H_{19}ClN_2O_2$ requires C, 61 12, H, 6 50, N, 9 50%
24		m/z [MH^+] 295	^{1}H-NMR (400MHz, $CDCl_3$) δ = 1 09 (t, 3H), 1 14 (t, 3H), 2 41, (q, 2H), 2 52 (q, 2H), 3 79 (br s, 1H), 4 05 (m, 4H), 6 78 (d, 1H), 6 88 (s, 1H), 6 98 (d, 1H), 7 19 (t, 1H)
25		M/z [MH^+] 295	^{1}H-NMR (400MHz, $CDCl_3$) δ = 1 08 (t, 3H), 1 15 (t, 3H), 2 44 (q, 2H), 2 54 (q, 2H), 4 02 (m, 2H), 4 09 (m, 2H), 6 69 (d, 1H), 6 94 (t, 1H), 7 10 (t, 1H), 7 40 (d, 1H)
26		M/z [MH^+] 329	^{1}H-NMR (400MHz, $CDCl_3$) δ = 1 01 (t, 3H), 1 10 (t, 3H), 2 38 (q, 2H), 2 49 (q, 2H), 3 84 (br s, 1H), 3 99 (m, 4H), 7 01 (t, 1H), 7 30 (d, 2H) Accurate Mass Found 329 0822 [MH^+], $C_{15}H_{18}Cl_2N_2O_2$ requires 329 0818 [MH^+]

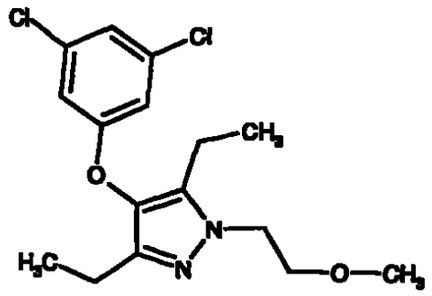
Example No	R^4	LRMS (electrospray)	Analytical Data
27		m/z [M-(H^+)] 328	^{1}H-NMR (400MHz, $CDCl_3$) δ = 1 09 (t, 3H), 1 14 (t, 3H), 2 41 (q, 2H), 2 51 (q, 2H), 4 03 (m, 2H), 4 07 (m, 2H), 6 60 (d, 1H), 7 04 (t, 1H), 7 10 (t, 1H)
28		m/z [MH^+] 329	^{1}H-NMR (400MHz, $CDCl_3$) δ = 1 08 (t, 3H), 1 14 (t, 3H), 2 41 (q, 2H), 2 51 (q, 2H), 4 03 (m, 2H), 4 08 (m, 2H), 6 62 (d, 1H), 7 09 (d, 1H) Microanalysis Found C, 54 66, H, 5 54, N, 8 12 $C_{15}H_{18}Cl_2N_2O_2$ requires C, 54 72, H, 5 51, N, 8 51%
29		m/z [MH^+] 279	^{1}H-NMR (400MHz, $CDCl_3$) δ = 1 10 (t, 3H), 1 14 (t, 3H), 2 44 (q, 2H), 2 55 (q, 2H), 3 79 (br s, 1H), 4 06 (m, 4H), 6 71 (m, 1H), 6 98 (m, 2H), 7 12 (m, 1H)
30		m/z [MH^+] 279	^{1}H-NMR (400MHz, $CDCl_3$) δ = 1 09 (t, 3H), 1 12 (t, 3H), 2 43 (q, 2H), 2 52 (q, 2H), 3 78 (br s, 1H), 4 04 (m, 4H), 6 59 (m, 1H), 6 75 (m, 2H), 7 20 (m, 2H)

Example No	R^4	LRMS (electrospray)	Analytical Data
31		m/z [MH^+] 289	^{1}H-NMR (400MHz, $CDCl_3$) δ = 1 10 (t, 3H), 1 17 (t, 3H), 2 25 (s, 6H), 2 42 (q, 2H), 2 52 (q, 2H), 3 90 (br s, 1H), 4 05 (m, 4H), 6 49 (s, 2H), 6 62 (s, 1H)
32		m/z [MH^+] 293	^{1}H-NMR (400MHz, $CDCl_3$) δ = 1 09 (t, 3H), 1 14 (t, 3H), 2 22 (s, 3H), 2 42 (q, 2H), 2 31 (q, 2H), 3 83 (br s, 1H), 4 03 (m, 4H), 6 60 (m, 1H), 6 70 (m, 1H), 6 88 (m, 1H)
33		m/z [MH^+] 329	^{1}H-NMR (400MHz, $CDCl_3$) δ = 1 11 (t, 3H), 1 17 (t, 3H), 2 42 (q, 2H), 2 54 (q, 2H), 4 06 (m, 4H), 6 69 (s, 1H), 6 94 (d, 1H), 7 34 (d, 1H) Microanalysis Found C, 54 84, H, 5 67, N, 8 48 $C_{15}H_{18}Cl_2N_2O_2$ requires C, 54 72, H, 5 51, N, 8 51%.
34		m/z [MH^+] 297	^{1}H-NMR (400MHz, $CDCl_3$) δ = 1 09 (3, 3H), 1 12 (t, 3H), 2 42 (q, 2H), 2 50 (q, 2H), 3 68 (br s, 1H), 4 01 (m, 4H), 6 47 (m, 1H), 6 77 (m, 1H), 6 86 (m, 1H) Microanalysis Found C, 60 57, H, 6 23, N, 9 52 $C_{15}H_{18}F_2N_2O_2$ requires C, 60 80, H, 6 12, N, 9 45%

Example No	R^4	LRMS (electrospray)	Analytical Data
35		m/z [MH$^+$] 329	^{1}H-NMR (400MHz, $CDCl_3$) δ = 1 08 (t, 3H), 1 12 (t, 3H), 2.41 (q, 2H), 2 51 (q, 2H), 3 73 (br s, 1H), 4 08 (m, 4H), 6 75 (d, 1H), 6 98 (s, 1H), 7 31 (d, 1H) Microanalysis Found C, 54 70, H, 5 54, N, 8 50 $C_{15}H_{18}Cl_2N_2O_2$ requires C, 54 72, H, 5 51, N, 8 51%
36		m/z [MH$^+$] 297	^{1}H-NMR (400MHz, $CDCl_3$) δ = 1 08 (t, 3H), 1 12 (t, 3H), 2 49 (q, 2H), 2 60 (q, 2H), 3 81 (br s, 1H), 3 99 (m, 4H), 6 91 (m, 2H), 6 99 (m, 1H)
37		m/z [MH$^+$] 297	^{1}H-NMR (400MHz, $CDCl_3$) δ = 1 09 (t, 3H), 1 15 (t, 3H), 2 45 (q, 2H), 2 55 (q, 2H), 3 70 (br s, 1H), 4 06 (m, 4H), 6.46 (m, 1H), 6 62 (m, 1H), 7 08 (m, 1H)
38		m/z [MH$^+$] 297	^{1}H-NMR (400MHz, $CDCl_3$) δ = 1 08 (t, 3H), 1 14 (t, 3H), 2 41 (q, 2H), 2 53 (q, 2H), 3 72 (br s, 1H), 4 05 (m, 4H), 6 43 (m, 3H)

EXAMPLE 39

4-(3,5-Dichlorophenoxy)-3,5-diethyl-1-(2-methoxyethyl)-1*H*-pyrazole



Sodium hydride (60% dispersion in oil, 34mg, 0.850mmol) was added to a stirred solution of 4-(3,5-dichlorophenoxy)-3,5-diethyl-1*H*-pyrazole of Example 3 (200mg, 0.701mmol) and methoxyethyl bromide (117mg, 0.850mmol) in dry *N,N*-dimethylformamide (2ml) at 0°C under nitrogen. The mixture was stirred at 0°C for 45 minutes during which time hydrogen was evolved and the yellow solution turned dark brown. The reaction mixture was quenched by the addition of water (5ml) and the mixture concentrated under reduced pressure. The residue was dissolved in ethyl acetate (20ml) and washed with water (10ml) and brine (10ml) and then dried over magnesium sulphate, filtered and concentrated under reduced pressure to leave a brown oil. The crude product was purified by flash column chromatography on silica gel eluting with pentane:diethyl ether (80:20, by volume) to provide the title compound (140mg) as a colourless oil.

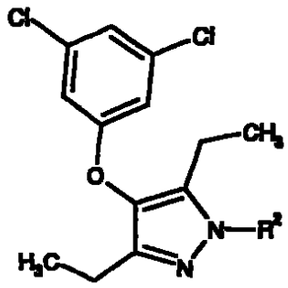
^{1}H-NMR (300MHz, $CDCl_3$): δ = 1.09 - 1.15 (m, 6H), 2.41 - 2.49 (q, 2H), 2.51 - 2.57 (q, 2H), 3.34 (s, 3H), 3.74 - 3.78 (t, 2H), 4.15 - 4.17 (t, 2H), 6.81 (s, 2H), 7.01 (s, 1H).

LRMS (thermospray): m/z [MH^+] 343.

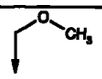
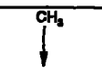
Microanalysis: Found: C, 56.25; H, 5.94; N, 7.95. $C_{16}H_{20}Cl_2N_2O_2$ requires C, 55.99; H, 5.87; N, 8.16%.

EXAMPLES 40 AND 41

The compounds of the following tabulated Examples of the general formula:

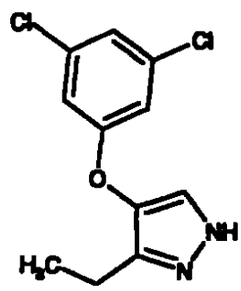


were prepared by a similar method to that of Example 39 using the appropriate halides and the pyrazole of Example 3.

Example No	R^2	LRMS (thermospray)	Analytical Data
40		m/z [MH^+] 329	^{1}H-NMR (300MHz, $CDCl_3$) δ = 1 13 - 1 18 (m, 6H), 2 45 (q, 2H), 2 60 (q, 2H), 3 37 (s, 3H), 5 34 (s, 2H), 6 80 (s, 2H), 7 02 (s, 1H) Microanalysis Found C, 54 72, H, 5 46, N, 8 40 $C_{15}H_{18}Cl_2N_2O_2$ requires C, 54 72, H, 5 51, N, 8 51%
41		m/z [MH^+] 299	^{1}H-NMR (300MHz, $CDCl_3$) δ = 1 15 (m, 6H), 2 48 (m, 4H), 3 79 (s, 3H), 6 82 (s, 2H), 7 01 (s, 1H) Microanalysis Found C, 56 08, H, 5 37, N, 9 29 $C_{14}H_{16}Cl_2N_2O$ requires C, 56 20, H, 5 39, N, 9 36%

EXAMPLE 42

4-(3,5-Dichlorophenoxy)-3-ethyl-1*H*-pyrazole

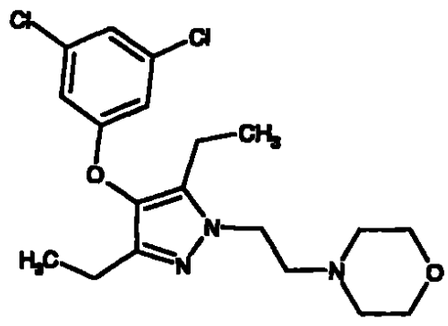


A solution of the enamine of Preparation 6 (2.88g, 10.0mmol) and hydrazine hydrate (0.49ml, 10.0mmol) in ethanol (10ml) was heated under reflux for 12 hours. After cooling further hydrazine hydrate (0.49ml, 10.0mmol) was added and the reaction was heated under reflux for 3 hours. After cooling the mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel eluting with cyclohexane:ethyl acetate (80:20, by volume) and then cyclohexane:ethyl acetate (60:40, by volume) to provide the title compound (620mg) as a yellow oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.23 (t, 3H), 2.66 (q, 2H), 6.87 (s, 2H), 7.02 (s, 1H), 7.40 (s, 1H).
LRMS (electrospray): m/z [MH^+] 257; [M-(H^+)] 255.

EXAMPLE 43

4-[2-[4-(3,5-Dichlorophenoxy)-3,5-diethyl-1*H*-pyrazol-1-yl]ethyl]morpholine



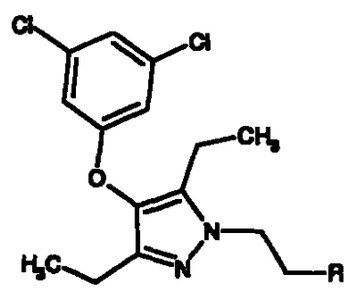
Osmium tetroxide (1.00ml of a 2.5% w/v solution in *tert*-butanol) was added dropwise to a stirred solution of the pyrazole of Example 64 (3.00g, 9.23mmol) and sodium periodate (4.93g, 23.1mmol) in acetone (90ml) and water (30ml) at

room temperature. A white precipitate formed after 5 minutes and the suspension was stirred for a further 3 hours. The solid was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was partitioned between ethyl acetate (300ml) and water (100ml) and the organic phase was separated, dried over magnesium sulphate, filtered and concentrated under reduced pressure to yield an intermediate aldehyde. An aliquot of the aldehyde (100mg, 0.305mmol) was dissolved in dichloromethane (5ml) and morpholine (30mg, 0.344mmol) and glacial acetic acid (17.1µL, 0.305mmol) were added. After stirring at room temperature for 5 minutes sodium triacetoxyborohydride (95mg, 0.451mmol) was added in one portion and the reaction was stirred for 1 hour. After this time the resultant mixture was diluted with dichloromethane (20ml) and partitioned between water (30ml) and dichloromethane (20ml). The organic phase was washed with 2M aqueous sodium hydroxide solution (10ml), dried over magnesium sulphate, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with dichloromethane:methanol:ammonia (95:4:1, by volume) to provide the title compound (125mg) as a colourless oil.

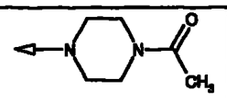
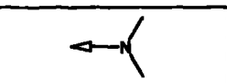
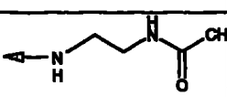
^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.06 (m, 6H), 2.12 (m, 8H), 2.75 (t, 2H), 3.64 (m, 4H), 4.04 (t, 2H), 6.73 (s, 2H), 6.95 (s, 1H).
LRMS (thermospray): m/z [MH^+] 398.
Microanalysis: Found: C, 57.18; H, 6.31; N, 10.36. $C_{19}H_{25}Cl_2N_3O_2$ requires C, 57.29; H, 6.33; N, 10.55%.

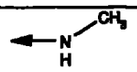
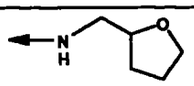
EXAMPLES 44 TO 49

The compounds of the following tabulated Examples of the general formula:



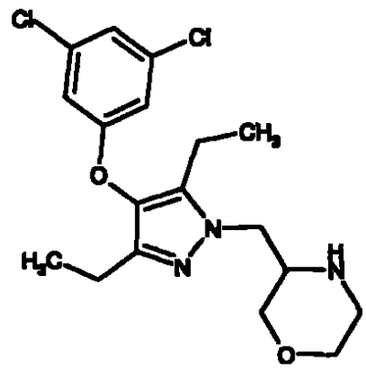
were prepared by a similar method to that of Example 43 using the appropriate amine starting material and the pyrazole of Example 64.

Example No	R	LRMS (thermospray)	Analytical Data
44		m/z [MH+] 386	^{1}H-NMR (300MHz, $CDCl_3$) δ = 1 09 - 1 17 (m, 6H), 2.40 - 2 47 (q, 2H), 2 50 - 2 56 (q, 2H), 2 80 - 2 82 (t, 2H), 3 07 - 3 11 (t,2H), 3 36 (s, 3H), 3 47 - 3 51 (t, 2H), 4 09 - 4 11 (t, 2H), 6 81 (s, 2H), 7 01 (s, 1H)
45		m/z [MH+] 439	^{1}H-NMR (400MHz, $CDCl_3$) δ = 1 04 (m, 6H), 2 00 (s, 3H), 2 38 (m, 6H), 2 44 (q, 2H), 2 77 (q, 2H), 3 38 (m, 2H), 3 55 (m, 2H), 4 05 (m, 2H), 6 71 (s, 2H), 6 92 (s, 1H)
46		m/z [MH+] 356	^{1}H-NMR (400MHz, $CDCl_3$) δ = 1 05 (m, 6H), 2 23 (s, 6H), 2 38 (q, 2H), 2 45 (q, 2H), 2,69 (m, 2H), 4 03 (m, 2H), 6 75 (s, 2H), 6 95 (s, 1H)
47		m/z [MH+] 413	^{1}H-NMR (400MHz, $CDCl_3$) δ = 1 08 (m, 6H), 1.59 (br s, 1H), 1 91 (s, 3H), 2 38 (q, 2H), 2 48 (q, 2H), 2 71 (m, 2H), 2 99 (m, 2H), 3 28 (m, 2H), 4 02 (m, 2H), 6 09 (br s, 1H), 6 71 (s, 2H), 6 95 (s, 1H) Microanalysis Found C, 54 86, H, 6 32, N, 13 33 $C_{19}H_{28}Cl_2N_4O_2$ requires C, 55 21, H, 6 34, N, 13 55% m p 69-70°C

Example No	R	LRMS (thermospray)	Analytical Data
48		m/z [MH$^+$] 342	^{1}H-NMR (400MHz, $CDCl_3$) δ = 1 08 (m, 7H), 2 39 (m, 2H), 2 42 (s, 3H), 2 49 (q, 2H), 3 00 (m, 2H), 4 05 (m, 2H), 6 78 (s, 2H), 6 96 (s, 1H)
49		m/z [MH$^+$] 412	^{1}H-NMR (400MHz, $CDCl_3$) δ = 1 05 (m, 6H), 1 49 (m, 1H), 1 81 (m, 4H), 2 42 (q, 2H), 2 52 (q, 2H), 2 64 (m, 2H), 3 08 (t, 2H), 3 76 (m, 1H), 3 79 (m, 1H), 4 00 (m, 1H), 6 78 (s, 2H), 6 98 (s, 1H) Microanalysis Found C, 57 78, H, 6 68, N, 9 90 $C_{20}H_{27}Cl_2N_3O_2$ requires C, 58 13, H, 6 61, N, 10 17%

EXAMPLE 50

3-[[4-(3,5-Dichlorophenoxy)-3,5-diethyl-1*H*-pyrazol-1-yl]methyl]morpholine

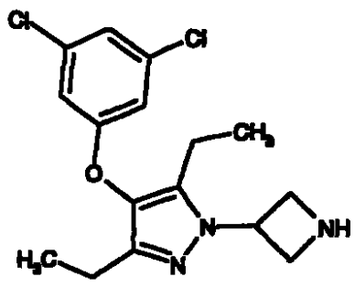


Sodium hydride (60% dispersion in oil, 37mg, 0.925mmol) was added to a stirred solution of the mesylate of Preparation 11 (273mg, 0.925mmol) and the pyrazole of Example 3 (220mg, 0.772mmol) in dry *N,N*-dimethylformamide (4ml) at 0°C under nitrogen. The mixture was heated at 50°C for 3 hours during which time the yellow solution turned dark brown. The reaction mixture was quenched by the addition of water (5ml) and the mixture was concentrated under reduced pressure. A solution of the residue in ethyl acetate (20ml) was washed with water (10ml) and brine (10ml), dried over magnesium sulphate, filtered and concentrated under reduced pressure to leave a brown oil. The oil was dissolved in dichloromethane (3ml), trifluoroacetic acid (1ml) was added and the reaction was stirred at room temperature for 12 hours. The mixture was concentrated under reduced pressure and the residue was dissolved in ethyl acetate (10ml) and washed with 1M aqueous hydrochloric acid (2x5ml). The combined aqueous phases were neutralised with solid sodium carbonate and extracted with ethyl acetate (3x20ml). The combined ethyl acetate layers were dried over magnesium sulphate, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel eluting with dichloromethane:methanol:ammonia (95:4:1, by volume) to provide the title compound (3mg) as a colourless oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.15 (m, 6H), 2.41 (q, 2H), 2.51 (q, 2H), 2.89 (m, 2H), 3.30 (m, 2H), 3.58 (m, 1H), 3.78 (m, 2H), 3.87 (d, 2H), 6.88 (s, 2H), 7.00 (1H, s).
LRMS (thermospray): m/z [MH^+] 384.

EXAMPLE 51

1-(3-Azetidinyl)-4-(3,5-dichlorophenoxy)-3,5-diethyl-1*H*-pyrazole

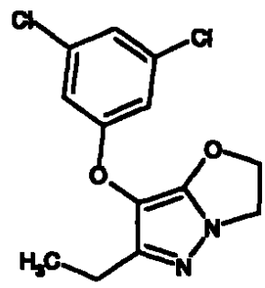


Sodium hydride (60% dispersion in oil, 30mg, 0.750mmol) was added to a stirred solution of the pyrazole of Example 3 (200mg, 0.702mmol) and 1-benzhydryl-3-azetidinyl methanesulfonate (222mg, 0.702mmol) (see J. Org. Chem., 1972, *37*, 3953) in *N,N*-dimethylformamide (5ml) at 0°C under nitrogen. The mixture was heated at 50°C for 4 hours and then cooled to room temperature. The reaction mixture was quenched by the addition of water (30ml) and the aqueous mixture was extracted with ether (2x50ml). The combined organic phases were washed with water (10ml) and brine (10ml), dried over magnesium sulphate, filtered and concentrated under reduced pressure to leave a brown oil. The oil was purified by flash column chromatography on silica gel eluting with dichloromethane to provide the intermediate (60mg) as a yellow oil. The oil was dissolved in dichloromethane (5ml) and 1-chloroethylchloroformate (20µL, 0.182mmol) was added at room temperature under nitrogen. The mixture was heated under reflux for 4 hours, cooled to room temperature and concentrated under reduced pressure to leave a yellow oil. The oil was dissolved in methanol (5ml) and the resulting solution was heated under reflux for 1 hour, cooled to room temperature and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel eluting with dichloromethane:methanol:ammonia (95:4:1, by volume) to provide the title compound (17mg) as a colourless oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.08 (t, 3H), 1.16 (t, 3H), 2.48 (m, 4H), 3.87 (t, 2H), 4.40 (t, 2H), 5.07 (q, 1H), 6.79 (s, 2H), 7.01 (m, 1H).
LRMS (thermospray): m/z [MH^+] 340.

EXAMPLE 52

7-(3,5-Dichlorophenoxy)-6-ethyl-2,3-dihydropyrazolo[5,1-*b*][1,3]oxazole

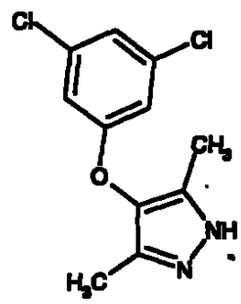


The triflate of Preparation 15 (282mg, 0.500mmol), tributylvinyltin (175µL, 0.600mmol), palladium dibenzylidene acetone (23mg, 0.025mmol), triphenyl arsine (12mg, 0.040mmol) and lithium chloride (64mg, 1.50mmol) were heated in *N,N*-dimethylformamide (3ml) at 80°C under nitrogen for 12 hours. The reaction was cooled to room temperature and partitioned between water (20ml) and ethyl acetate (20ml). The organic layer was washed with brine (10ml), dried over magnesium sulphate, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel eluting with pentane:ethyl acetate (90:10, by volume) to provide the title compound (34mg) as a colourless oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.16 (t, 3H), 2.45 (q, 2H), 4.29 (t, 2H), 5.03 (t, 2H), 6.89 (s, 2H), 7.02 (s, 1H).
LRMS (thermospray): m/z [MH^+] 299.

EXAMPLE 53

4-(3,5-Dichlorophenoxy)-3,5-dimethyl-1*H*-pyrazole

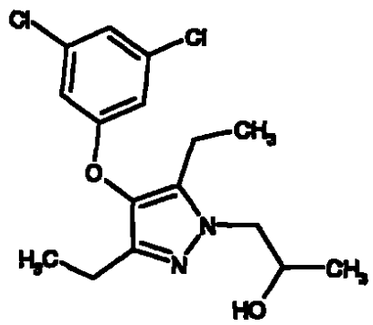


A mixture of 3-chloro-2,4-pentanedione (5.00g, 37.0mmol), 3,5-dichlorophenol (6.03g, 37.0mmol), cesium carbonate (12.0g, 37.0mmol) and acetone (40ml) was heated under reflux for 18 hours. After cooling the solid was removed by filtration and the filtrate concentrated under reduced pressure. The intermediate was dissolved in ethanol (30ml) and hydrazine hydrate (1.85g, 37.0mmol) was added and the mixture heated at 60°C for 30 minutes. After cooling the mixture was concentrated under reduced pressure and the residue purified by flash column chromatography on silica gel eluting with ethyl acetate:pentane (30:70, by volume) to provide the title compound (3.00g) as a yellow oil which solidified on standing to leave a yellow solid, m.p. 85-87°C.

^{1}H-NMR (300MHz, $CDCl_3$): δ = 2.14 (s, 6H), 5.24 (br s, 1H), 6.81 (s, 2H), 7.02 (s, 1H).
LRMS (thermospray): m/z [MH^+] 257.
Microanalysis: Found: C, 49.58; H, 4.06; N, 11.05. $C_{11}H_{10}Cl_2N_2O.0.4H_2O$ requires C, 49.98; H, 4.12; N, 10.60%.

EXAMPLE 54

1-[4-(3,5-Dichlorophenoxy)-3,5-diethyl-1*H*-pyrazol-1-yl]-2-propanol



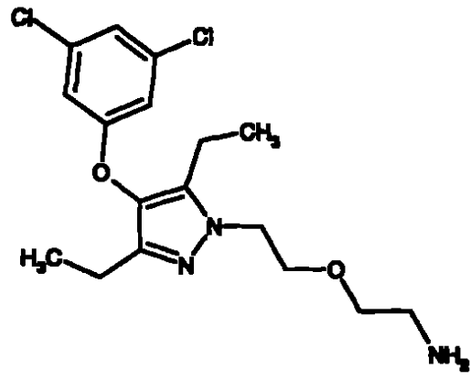
Osmium tetroxide (1.00ml of a 2.5% w/v solution in *tert*-butanol) was added dropwise to a stirred solution of the pyrazole of Example 64 (3.00g, 9.23mmol) and sodium periodate (4.93g, 23.1mmol) in acetone (90ml) and water (30ml) at room temperature. A white precipitate formed after 5 minutes and the suspension was stirred for a further 3 hours. The solid was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was partitioned between ethyl acetate (300ml) and water (100ml) and the organic phase was separated, dried over

magnesium sulphate, filtered and concentrated under reduced pressure to yield the intermediate aldehyde. An aliquot of the aldehyde (250mg, 0.765mmol) was dissolved in tetrahydrofuran (5ml) and stored under nitrogen. In a separate flask, anhydrous cerium trichloride (377mg, 1.53mmol) was added to a stirred solution of methyl magnesium bromide (0.51ml of a 3M solution in ether, 1.53mmol) in tetrahydrofuran (5ml) at room temperature under nitrogen. The mixture was stirred at room temperature for 1.5 hours and the aldehyde in tetrahydrofuran was added dropwise. The mixture was stirred for 12 hours and the reaction was then quenched with 1M aqueous acetic acid at room temperature. The mixture was diluted with dichloromethane (20ml), washed with water (5ml) and brine (5ml), dried over magnesium sulphate, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel eluting with pentane:ethyl acetate (70:30, by volume) to provide the title compound (30mg) as a colourless oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.05 (t, 3H), 1.10 (t, 3H), 1.21 (d, 2H), 2.40 (q, 2H), 2.47 (q, 2H), 3.79 (dd, 1H), 3.97 (dd, 1H), 4.24 (s, 1H), 6.76 (s, 2H), 6.98 (s, 1H).
LRMS (thermospray): m/z [MH^+] 343.

EXAMPLE 55

2-[2-[4-(3,5-Dichlorophenxoy)-3,5-diethyl-1*H*-pyrazol-1-yl)ethoxy]ethanamine



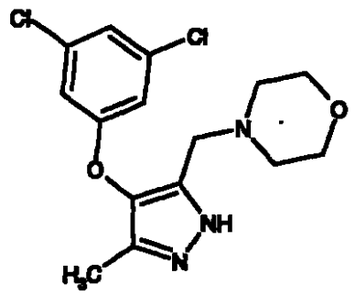
Sodium hydride (60% dispersion in oil, 24mg, 0.600mmol) was added to a stirred solution of the pyrazole of Example 2 (100mg, 0.303mmol) in dry *N,N*-dimethylformamide (4ml) at 0°C under nitrogen. The mixture was stirred at 0°C for 30 minutes and 2-chloroethylamine hydrochloride (53mg, 0.455mmol) was added.

The reaction mixture was stirred at 0°C for 30 minutes and then stirred at room temperature for 30 minutes. The reaction was cooled to 0°C, further sodium hydride (60% dispersion in oil, 24mg, 0.600mmol) and 2-chloroethylamine hydrochloride (53mg, 0.455mmol) were added and the reaction was stirred for 1 hour. The reaction was quenched by the addition of water (5ml) and extracted with ether (10ml). The organic layer was washed with 2M aqueous hydrochloric acid (30ml). The acid was neutralised with solid sodium carbonate and extracted with ether (3x20ml). The combined ether layers were dried over magnesium sulphate, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel eluting with dichloromethane:methanol:ammonia (95:4:1, by volume) to provide the title compound (21mg) as a colourless oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.19 (m, 6H), 2.42 (q, 2H), 2.58 (q, 2H), 2.80 (t, 2H), 3.38 (t, 2H), 3.81 (t, 2H), 4.18 (t, 2H), 6.78 (s, 2H), 7.02 (s, 1H).
LRMS (thermospray): m/z [MH^+] 372.

EXAMPLE 56

4-[[4-(3,5-Dichlorophenoxy)-3-methyl-1*H*-pyrazol-5-yl]methyl]morpholine

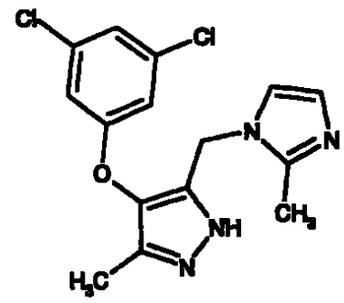


Morpholine (140µL, 1.59mmol) was added in one portion to a stirred solution of the bromide of Preparation 8 (200mg, 0.531mmol) in isopropanol (4ml) at room temperature. The mixture was heated at 50°C for 1 hour, cooled to room temperature and concentrated under reduced pressure to leave a yellow oil. The crude product was purified by flash column chromatography on silica gel eluting with ethyl acetate to provide the title compound (60mg) as a colourless oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 2.13 (s, 3H), 2.42 (m, 4H), 3.38 (s, 2H), 3.64 (m, 4H), 6.79 (s, 2H), 7.02 (s, 1H).
LRMS (thermospray): m/z [MH^+] 342.

EXAMPLE 57

4-(3,5-Dichlorophenoxy)-3-methyl-5-[(2-methyl-1*H*-imidazol-1-yl)methyl]-1*H*-pyrazole

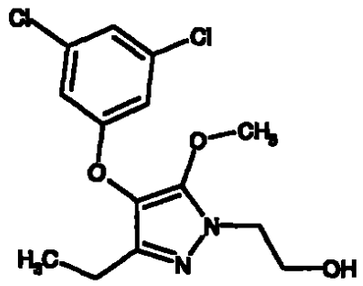


Sodium hydride (60% dispersion in oil, 32mg, 0.800mmol) was added to a stirred solution of 2-methylimidazole (65mg, 0.800mmol) in *N,N*-dimethylformamide (5ml) at 0°C under nitrogen. The mixture was stirred for 10 minutes and then the bromide of Preparation 8 (100mg, 0.261mmol) was added and the reaction was stirred at room temperature for 1 hour. The reaction mixture was quenched by the addition of 1M aqueous sodium hydroxide solution (5ml) and the mixture was concentrated under reduced pressure. A solution of the residue in ethyl acetate (20ml) was washed with water (10ml) and brine (10ml), dried over magnesium sulphate, filtered and concentrated under reduced pressure to leave a brown oil. The crude product was purified by flash column chromatography on silica gel eluting with dichloromethane:methanol:ammonia (95:4.5:0.5, by volume) to provide the title compound (10mg) as a colourless oil.

^{1}H-NMR (300MHz, $CDCl_3$): δ = 2.14 (s, 3H), 2.35 (s, 3H), 4.89 (s, 2H), 6.68 (s, 2H), 6.78 (s, 1H), 6.82 (s, 1H), 7.03 (s, 1H).
LRMS (thermospray): m/z [MH^+] 337.

EXAMPLE 58

2-[4-(3,5-Dichlorophenoxy)-3-ethyl-5-methoxy-1*H*-pyrazol-1-yl]ethanol

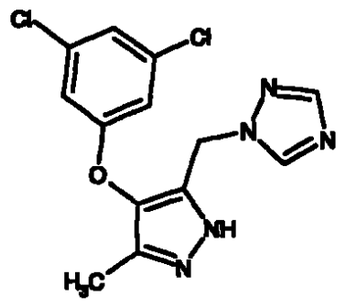


The triflate of Preparation 15 (282mg, 0.500mmol) was dissolved in methanol (3ml) and 1,1'-bis(diphenylphosphino)ferrocenepalladium(II)chloride (18mg, 0.025mmol) was added in one portion at room temperature. The mixture was heated at 50°C under an atmosphere of carbon monoxide (345 kPa, 50 psi) for 10 hours. The reaction was cooled to room temperature and concentrated under reduced pressure to leave a brown oil. The oil was dissolved in a mixture of tetrahydrofuran (0.5ml), glacial acetic acid (1.0ml) and water (0.5ml) and stirred at room temperature for 12 hours. The solvent was removed under a stream of nitrogen to leave a yellow solid and the crude product was purified by flash column chromatography on silica gel eluting with dichloromethane:acetonitrile (95:5, by volume) and then dichloromethane:acetonitrile (90:10, by volume) to provide the title compound (6mg) as a colourless oil.

^{1}H-NMR (300MHz, $CDCl_3$): δ = 1.13 (t, 3H), 2.41 (q, 2H), 3.44 (br s, 1H), 3.94 (s, 3H), 4.23 (m, 4H), 6.87 (s, 2H), 7.09 (s, 1H).
LRMS (thermospray): m/z [MH^+] 331.

EXAMPLE 59

1-[[4-(3,5-Dichlorophenoxy)-3-methyl-1*H*-pyrazol-5-yl]methyl]-1*H*-1,2,4-triazole

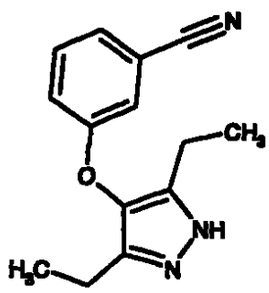


A suspension of the bromide of Preparation 8 (100mg, 0.264mmol), 1,2,4-triazole (92mg, 1.32mmol) and sodium carbonate (140mg, 1.32mmol) in toluene (5ml) was heated at 100°C for 12 hours. The suspension was cooled to room temperature and 1M aqueous sodium hydroxide solution (5ml) was added. The mixture was extracted with ethyl acetate (3x20ml) and the combined organic phases were dried over magnesium sulphate, filtered and concentrated under reduced pressure to leave a clear oil. The crude product was purified by flash column chromatography on silica gel eluting with dichloromethane:methanol:ammonia (95:4.5:0.5, by volume) to provide the title compound (62mg) as a colourless oil.

^{1}H-NMR (300MHz, $CDCl_3$): δ = 2.16 (s, 3H), 5.25 (s, 2H), 6.70 (s, 2H), 7.04 (s, 1H), 7.89 (s, 1H), 8.04 (s, 1H).
LRMS (thermospray): m/z [MH^+] 324.

EXAMPLE 60

3-[(3,5-Diethyl-1*H*-pyrazol-4-yl)oxy]benzonitrile

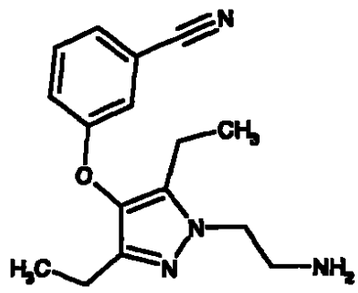


Hydrazine hydrate (153µL, 3.14mmol) was added to a stirred solution of the β-diketone of Preparation 9 (771mg, 3.14mmol) in ethanol (16ml) and the resulting solution was heated under reflux for 12 hours. After cooling the mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel eluting with pentane:ethyl acetate (75:25, by volume) to provide the title compound (712mg) as a yellow solid, m.p. 81-84°C.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.15 (t, 6H), 2.47 (q, 4H), 7.11 (m, 2H), 7.24 (d, 1H), 7.35 (t, 1H).
LRMS (thermospray): m/z [MH^+] 242.
Microanalysis: Found: C, 69.03; H, 6.43; N, 17.20. $C_{14}H_{15}N_3O_3.0.13H_2O$ requires C, 69.02; H, 6.31; N, 17.25%.

EXAMPLE 61

3-[[1-(2-Aminoethyl)-3,5-diethyl-1*H*-pyrazol-4-yl]oxy]benzonitrile

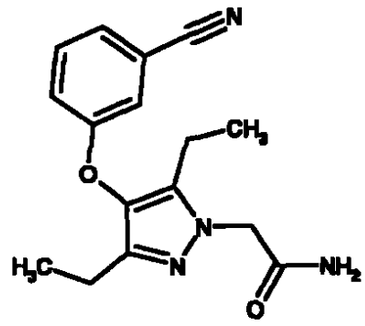


The pyrazole of Example 60 (200mg, 0.829mmol) and 2-chloroethylamine hydrochloride (144mg, 1.24mmol) were heated as a melt at 150°C for 17 hours. After cooling the solid was dissolved in saturated aqueous sodium hydrogencarbonate (15ml) and extracted with dichloromethane (2x10ml). The combined organic phases were washed with 2M aqueous hydrochloric acid (20ml) and the aqueous layer was neutralised with solid sodium carbonate and extracted with dichloromethane (3x10ml). The combined organic phases were dried over magnesium sulphate, filtered and concentrated under reduced pressure to leave an orange gum. The crude product was purified by flash column chromatography on silica gel eluting with dichloromethane:methanol (90:10) then dichloromethane:methanol:ammonia (90:9:1, by volume) to provide the title compound (124mg) as a pale yellow oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.11 (m, 6H), 2.41 (q, 2H), 2.52 (q, 2H), 3.18 (t, 2H), 4.04 (t, 2H), 7.15 (m, 2H), 7.29 (d, 1H), 7.38 (t, 1H).
LRMS (thermospray): m/z [MH^+] 285.

EXAMPLE 62

2-[4-(3-Cyanophenoxy)-3,5-diethyl-1*H*-pyrazol-1-yl]acetamide



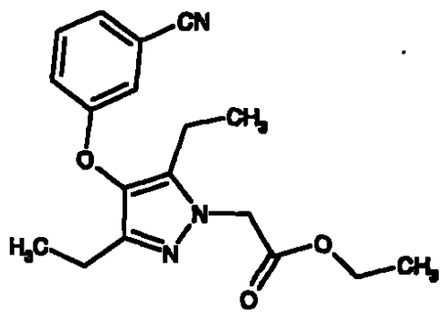
A saturated solution of ammonia in methanol (2.3ml) was added to the ester of Example 63 (75mg, 0.229mmol) in a vial at room temperature then the vial was sealed and heated at 75°C for 17 hours. After cooling to room temperature the mixture was concentrated under reduced pressure to leave a cream solid. The crude product was purified by flash column chromatography on silica gel eluting with dichloromethane then dichloromethane:methanol (99:1, by volume) to provide the title compound (49mg) as a white solid, m.p. 159-160°C.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.10 (t, 3H), 1.17 (t, 3H), 2.44 (q, 2H), 2.53 (q, 2H), 4.69 (s, 2H), 5.44 (br s, 1H), 6.22 (br s, 1H), 7.14 (m, 2H), 7.31 (d, 1H), 7.40 (t, 1H).
LRMS (thermospray): m/z [MH^+] 299.
Microanalysis: Found: C, 64.20; H, 6.12; N, 18.79. $C_{16}H_{18}N_4O_2$ requires C, 64.41; H, 6.08; N, 18.78%.

EXAMPLE 63

Ethyl [4-(3-cyanophenoxy)-3,5-diethyl-1*H*-pyrazol-1-yl]acetate

65

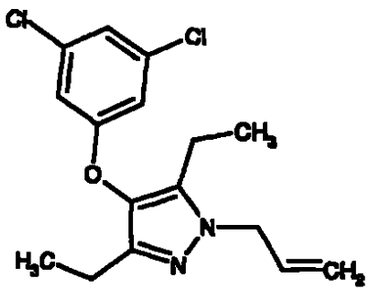


A solution of ethylhydrazinoacetate (88mg, 0.571mmol) in ethanol (2.0ml) was added to a stirred solution of the β-diketone of Preparation 9 (140mg, 0.571mmol) and triethylamine (88µL, 0.628ml) in ethanol (1.0ml) and the resulting solution was heated under reflux for 18 hours. After cooling, the mixture was concentrated under reduced pressure and the residue was partitioned between dichloromethane (20ml) and water (10ml). The organic layer was separated, washed with brine (10ml), dried over magnesium sulphate, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel eluting with pentane:ethyl acetate (75:25, by volume) and then ethyl acetate to provide the title compound (131mg) as a yellow oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.08 (m, 6H), 1.25 (t, 3H), 2.40 (m, 4H), 4.20 (q, 2H), 4.77 (s, 2H), 7.12 (m, 2H), 7.23 (d, 1H), 7.34 (t, 1H).
LRMS (thermospray): *m/z* [MH^+] 328.

EXAMPLE 64

1-Allyl-4-(3,5-dichlorophenoxy)-3,5-diethyl-1*H*-pyrazole



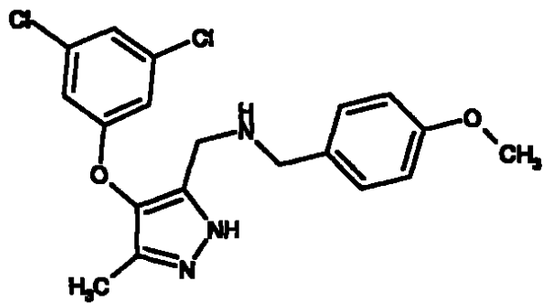
Sodium hydride (60% dispersion in oil, 770mg, 19.2mmol) was added to a stirred solution of allyl bromide (1.70ml, 19.2mmol) and the pyrazole of Example 3 (5.00g,

17.5mmol) in *N,N*-dimethylformamide (20ml) at 0°C under nitrogen. The reaction was warmed to room temperature and stirred for 1 hour. The reaction mixture was quenched by the addition of water (100ml) and the aqueous phase was extracted with ether (2x50ml). The combined organic phases were washed with water (30ml) and brine (30ml), dried over magnesium sulphate, filtered and concentrated under reduced pressure to leave a brown oil. The crude product was purified by flash column chromatography on silica gel eluting with pentane:ethyl acetate (80:20, by volume) to provide the title compound (5.00g) as a yellow oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.11 (m, 6H), 2.46 (m, 4H), 4.65 (d, 2H), 5.04 (d, 1H), 5.22 (d, 1H), 5.99 (m, 1H), 6.79 (s, 2H), 6.99 (s, 1H).
LRMS (thermospray): m/z [MH^+] 325.

EXAMPLE 65

N-[[4-(3,5-Dichlorophenoxy)-3-methyl-1*H*-pyrazol-5-yl]methyl]-*N*-(4-methoxybenzyl)amine

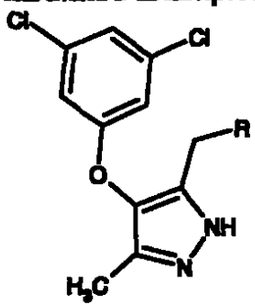


4-Methoxybenzylamine (0.104ml, 0.800mmol) was added in one portion to a stirred solution of the bromide of Preparation 8 (100mg, 0.265mmol) in isopropanol (2ml) at room temperature. The mixture was heated at 50°C for 1 hour, cooled to room temperature and concentrated under reduced pressure to leave a yellow oil. The oil was diluted with diethyl ether (20ml), washed with saturated aqueous sodium hydrogen carbonate (5ml) and water (5ml), dried over magnesium sulphate, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel eluting with dichloromethane:methanol:ammonia (95:4:1, by volume) to provide the title compound (50mg) as a colourless oil.

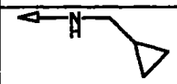
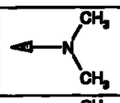
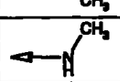
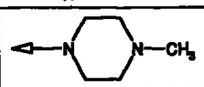
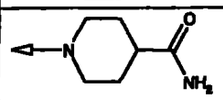
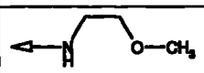
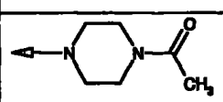
^{1}H-NMR (300MHz, $CDCl_3$): δ = 2.13 (s, 3H), 3.68 (s, 2H), 3.71 (s, 2H), 3.80 (s, 3H), 6.83 (m, 4H), 7.03 (s, 1H), 7.17 (m, 2H).
LRMS (thermospray): m/z [MH^+] 392.

EXAMPLES 66 TO 75

The compounds of the following tabulated Examples of the general formula:

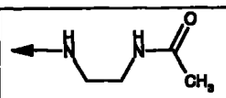
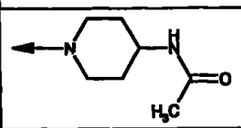
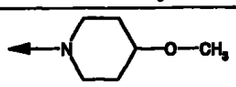


were prepared by a similar method to that of Example 65 using the appropriate amine starting material and the bromide of Preparation 8.

Example No	R	LRMS (thermospray)	Analytical Data
66		m/z [MH$^+$] 326	^{1}H-NMR (300MHz, $CDCl_3$) δ = 0 09 (m, 2H), 0.49 (q, 2H), 0 90 (m, 1H), 2 34 (s, 3H), 2 47 (d, 2H), 3 73 (s, 2H), 6 82 (s, 2H), 7 03 (s, 1H)
67		m/z [MH$^+$] 300	^{1}H-NMR (400MHz, $CDCl_3$) δ = 2 08 (s, 3H), 2 20 (s, 6H), 3 31 (s, 2H), 6 76 (s, 2H), 6 97 (s, 1H)
68		m/z [MH$^+$] 286	^{1}H-NMR (400MHz, $CDCl_3$) δ = 2 12 (s, 3H), 2 42 (s, 3H), 3 65 (s, 2H), 6 80 (s, 2H), 7 02 (s, 1H)
69		m/z [MH$^+$] 355	^{1}H-NMR (400MHz, $CDCl_3$) δ = 2 08 (s, 3H), 2 22 (s, 3H), 2 31 (m, 8H), 3 36 (s, 2H), 6 76 (s, 2H), 6 97 (s, 1H)
70		m/z [MH$^+$] 385	^{1}H-NMR (400MHz, $CDCl_3$) δ = 1 50 (m, 2H), 1 60 (m, 2H), 1 90 (m, 4H), 2 41 (m, 2H), 3 25 (s, 2H), 3 75 (m, 2H), 5 52 (s, 1H), 5 80 (s, 1H), 6 67 (s, 2H), 6 86 (s, 1H)
71		m/z [MH$^+$] 330	^{1}H-NMR (400MHz, $CDCl_3$) δ = 2 08 (s, 3H), 2 74 (m, 2H), 3 30 (s, 3H), 3 44 (m, 2H), 3 68 (s, 2H), 6 76 (s, 2H), 6 98 (s, 1H)
72		m/z [MH$^+$] 383	^{1}H-NMR (400MHz, $CDCl_3$) δ = 2 02 (s, 3H), 2 10 (s, 3H), 2 38 (m, 4H), 3 34 (m, 2H), 3 38 (s, 2H), 3 51 (m, 2H), 6 76 (s, 2H), 6 98 (s, 1H)

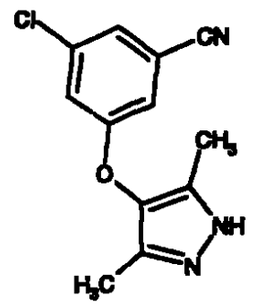




73		m/z [MH$^+$] 357	^{1}H-NMR (400MHz, $CDCl_3$) δ = 1 92 (s, 3H), 2 09 (s, 3H), 2 70 (m, 2H), 3 29 (m, 2H), 3 65 (s, 2H), 6 01 (s, 1H), 6 76 (s, 2H), 6 99 (s, 1H)
74		m/z [MH$^+$] 397	^{1}H-NMR (400MHz, $CDCl_3$) δ = 1 30 (m, 2H), 1 80 (m, 2H), 1 92 (s, 3H), 2 09 (m, 5H), 2 70 (m, 2H), 3 34 (s, 2H), 3 71 (m, 1H), 6 76 (s, 2H), 6 98 (s, 1H)
75		m/z [MH$^+$] 370	^{1}H-NMR (300MHz, $CDCl_3$) δ = 1 60 (m, 2H), 1 80 (m, 2H), 2 13 (s, 3H), 2 20 (m, 2H), 2 71 (m, 2H), 3 22 (m, 1H), 3 33 (s, 3H), 3 39 (s, 2H), 6 81 (s, 2H), 7 03 (s, 1H)

EXAMPLE 76

3-Chloro-5-[(3,5-dimethyl-1*H*-pyrazol-4-yl)oxy]benzonitrile

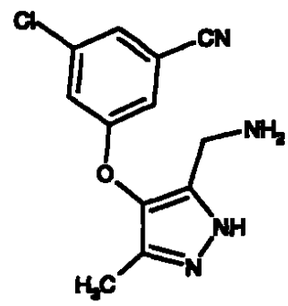


Hydrazine hydrate (1.10ml, 21.9mol) was added to a stirred solution of the β-diketone of Preparation 16 (5.50g, 21.9mmol) in glacial acetic acid (22ml) and the resulting solution was stirred at room temperature for 14 hours. The mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel eluting with dichloromethane and then dichloromethane:ethyl acetate (85:15, by volume) to provide the title compound (4.80g) as a yellow solid, m.p. 136-140°C.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 2.09 (s, 6H), 7.02 (m, 1H), 7.10 (m, 1H), 7.25 (m, 1H).
LRMS (electrospray): m/z [MH^+] 248.
Microanalysis: Found: C, 57.91; H, 4.03; N, 16.79. $C_{12}H_{10}N_3OCl$ requires C, 58.19; H, 4.07; N, 16.97%.

EXAMPLE 77

3-[[5-(Aminomethyl)-3-methyl-1*H*-pyrazol-4-yl]oxy]-5-chlorobenzonitrile



The bromide of Preparation 18 (300mg, 0.800mmol) was added to a saturated solution of ammonia in isopropanol (50ml) at 0°C. The reaction was stirred for 2 hours and allowed to slowly warm to room temperature. The mixture was concentrated under reduced pressure and the resulting yellow oil was dissolved in dichloromethane (50ml). The dichloromethane solution was washed with 1M aqueous sodium carbonate solution (20ml), dried over magnesium sulphate, filtered and concentrated under reduced pressure to provide the title compound (220mg) as a white foam.

^{1}H-NMR (300MHz, $CDCl_3$): δ = 2.14 (s, 3H), 3.79 (s, 2H), 7.08 (1H, s), 7.16 (1H, s), 7.31 (1H, s).
LRMS (thermospray): m/z [MH^+] 263.

EXAMPLE 78

3-Chloro-5-[[3-methyl-5-(1-piperazinylmethyl)-1*H*-pyrazol-4-yl]oxy]benzonitrile



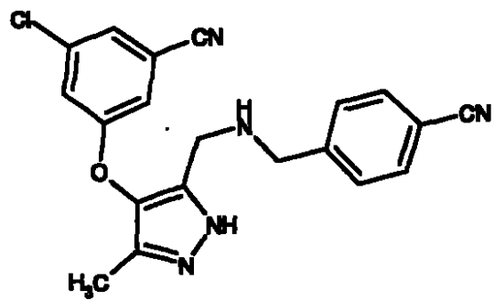
t-Butyl-1-piperazinecarboxylate (1.17g, 6.30mmol) was added in one portion to a stirred solution of the bromide of Preparation 18 (500mg, 1.40mmol) in isopropanol (20ml) at room temperature. The mixture was heated at 60°C for 1 hour, cooled to room temperature and concentrated under reduced pressure to leave a yellow oil. The oil was dissolved in dichloromethane (100ml) and the resulting solution was washed with 1M aqueous sodium carbonate (20ml) and brine (20ml), dried over magnesium sulphate, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel eluting with dichloromethane:methanol:ammonia (95:4:1, by volume) to provide a yellow foam. The foam was dissolved in dichloromethane (10ml), the resulting solution was cooled to 0°C and trifluoroacetic acid (2ml) was added. The reaction was allowed to warm to room temperature and stirred for 24 hours. The mixture was diluted with

dichloromethane (50ml), washed with 1M aqueous sodium carbonate (20ml) and brine (20ml), dried over magnesium sulphate, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel eluting with dichloromethane:methanol:ammonia (90:9:1, by volume) to provide the title compound (400mg) as a white foam.

^{1}H-NMR (300MHz, $CDCl_3$): δ = 2.14 (s, 3H), 2.40 (m, 4H), 2.83 (m, 4H), 3.38 (s, 2H), 7.09 (s, 1H), 7.16 (s, 1H), 7.30 (s, 1H).
LRMS (thermospray): m/z [MH^+] 332.

EXAMPLE 79

3-Chloro-5-[(5-[[(4-cyanobenzyl)amino]methyl]-3-methyl-1*H*-pyrazol-4-yl)oxy]benzonitrile

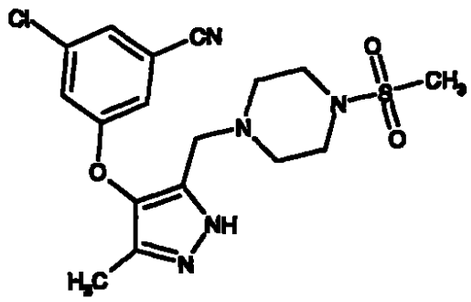


A mixture of 4-cyanobenzaldehyde (60mg, 0.460mmol), the amine of Example 77 (120mg, 0.460mmol), magnesium sulphate (500mg) and dichloromethane (5ml) was stirred under nitrogen at room temperature for 3 days. The mixture was concentrated under reduced pressure and the crude product was purified by flash column chromatography on silica gel eluting with methanol:ethyl acetate (5:95, by volume) to provide a foam. The foam was dissolved in methanol (5ml), sodium borohydride (50mg, 1.31mmol) was added in one portion at room temperature and the reaction was stirred for 30 minutes. The mixture was concentrated under reduced pressure and the residue was dissolved in dichloromethane (20ml). The resulting solution was washed with 1M aqueous sodium carbonate solution (10ml) and brine (10ml), dried over magnesium sulphate, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel eluting with dichloromethane:methanol:ammonia (95:4:1, by volume) to provide the title compound (35mg) as a white foam.

^{1}H-NMR (300MHz, $CDCl_3$): δ = 2.15 (s, 3H), 3.69 (s, 2H), 3.84 (s, 2H), 7.06 (s, 1H), 7.15 (s, 1H), 7.31 (s, 1H), 7.38 (d, 2H), 7.60 (d, 2H).
LRMS (thermospray): m/z [MH^+] 378.

EXAMPLE 80

3-Chloro-5-[(3-methyl-5-[[4-(methylsulfonyl)-1-piperazinyl]methyl]-1*H*-pyrazol-4-yl)oxy]benzonitrile

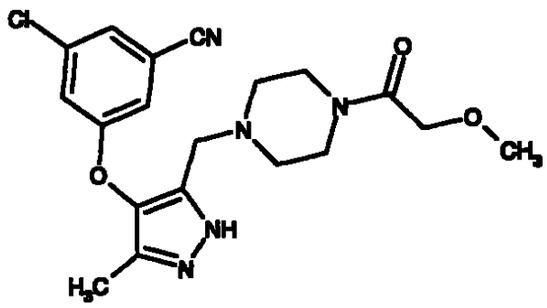


Methanesulphonyl chloride (19µl, 0.240mmol) was added dropwise to a stirred solution of the amine of Example 78 (80mg, 0.240mmol) and triethylamine (45µL, 0.288mmol) in dichloromethane (3ml) at room temperature under nitrogen. The reaction was stirred for 30 minutes and then concentrated under reduced pressure to leave a yellow oil. The crude product was purified by flash column chromatography on silica gel eluting with dichloromethane and then dichloromethane:methanol:ammonia (95:4:1, by volume) to provide the title compound (65mg) as a white foam.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 2.14 (s, 3H), 2.51 (m, 4H), 2.72 (s, 3H), 3.12 (m, 4H), 3.39 (s, 2H), 7.08 (m, 1H), 7.13 (m, 1H), 7.26 (s, 1H).
LRMS (thermospray): m/z [MH^+] 410.

EXAMPLE 81

3-Chloro-5-[(5-[[4-(methoxyacetyl)-1-piperazinyl]methyl]-3-methyl-1*H*-pyrazol-4-yl)oxy]benzonitrile

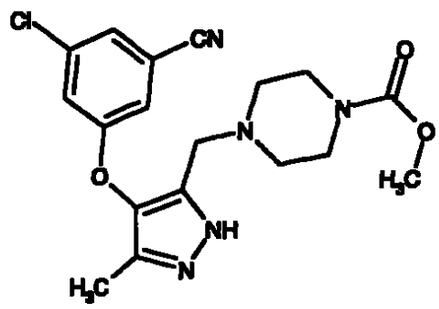


N-Benzyl-*N*'-cyclohexylcarbodiimide polymer bound (624mg of 1.3mmol/g, 0.480mmol) was added in one portion to a stirred solution of methoxyacetic acid (37μL, 0.480mmol) and the amine of Example 78 (80mg, 0.240mmol) in dichloromethane (5ml) at room temperature under nitrogen. The reaction was stirred for 1 hour and the polymer bound reagent was removed by filtration. The filtrate was concentrated under reduced pressure and the crude product was purified by flash column chromatography on silica gel eluting with dichloromethane:methanol:ammonia (95:4:1, by volume) to provide the title compound (45mg) as a white foam.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 2.11 (s, 3H), 2.38 (m, 4H), 3.37 (m, 7H), 3.51 (m, 2H), 4.04 (s, 2H), 7.04 (m, 1H), 7.10 (m, 1H), 7.26 (m, 1H).
LRMS (thermospray): m/z [MH^+] 404.

EXAMPLE 82

Methyl 4-[[4-(3-chloro-5-cyanophenoxy)-3-methyl-1*H*-pyrazol-5-yl]methyl]-1-piperazinecarboxylate

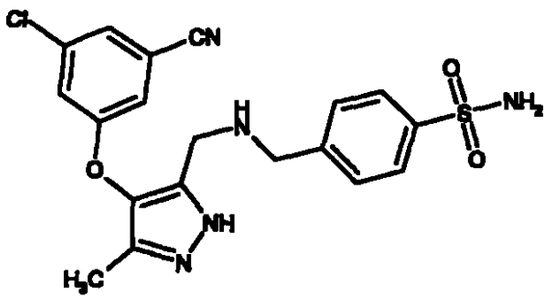


Methyl chloroformate (19µl, 0.240mmol) was added dropwise to a stirred solution of the amine of Example 78 (80mg, 0.240mmol) and triethylamine (45µl, 0.288mmol) in dichloromethane (5ml) at room temperature under nitrogen. The reaction was stirred for 90 minutes and then concentrated under reduced pressure to leave a yellow oil. The crude product was purified by flash column chromatography on silica gel eluting with dichloromethane and then dichloromethane:methanol:ammonia (95:4:1, by volume) to provide the title compound (55mg) as a white foam.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 2.09 (s, 3H), 2.34 (m, 4H), 3.36 (m, 6H), 3.64 (s, 3H), 7.02 (m, 1H), 7.10 (m, 1H), 7.25 (m, 1H).
LRMS (thermospray): m/z [MH^+] 390.

EXAMPLE 83

4-[({[4-(3-Chloro-5-cyanophenoxy)-3-methyl-1*H*-pyrazol-5-yl]methyl}amino)methyl]benzenesulfonamide

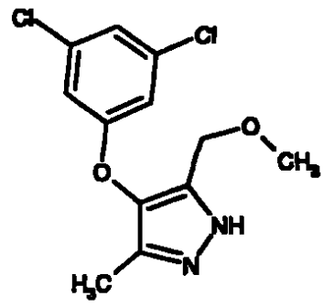


Triethylamine (125µl, 0.860mmol) was added in one portion to a stirred suspension of 4-aminomethylbenzenesulphonamide hydrochloride (144mg, 0.590mmol) and the bromide of Preparation 18 (100mg, 0.270mmol) in isopropanol (5ml) at room temperature under nitrogen. The reaction was heated at 70°C for 1 hour and then cooled to room temperature. The mixture was concentrated under reduced pressure and the crude product was purified by flash column chromatography on silica gel eluting with dichloromethane and then dichloromethane:methanol:ammonia (90:9:1, by volume) to provide a foam. The foam was further purified using a Phenomenex Luna C18 column eluting with diethylamine:methanol (0.1:99.1, by volume) to provide the title compound (8mg) as a white foam.

^{1}H-NMR (400MHz, CD_3OD): δ = 2.06 (s, 3H), 3.27 (s, 2H), 3.62 (s, 2H), 3.79 (s, 2H), 7.17 (s, 1H), 7.21 (s, 1H), 7.40 (m, 3H), 7.77 (d, 2H).
LRMS (thermospray): m/z [MH^+] 432.

EXAMPLE 84

4-(3,5-Dichlorophenoxy)-5-(methoxymethyl)-3-methyl-1*H*-pyrazole

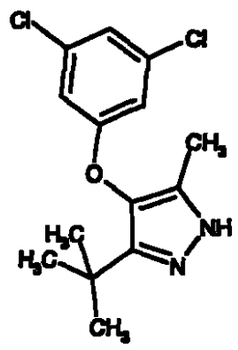


Tetrakis(triphenylphosphine)palladium (60mg) was added in one portion to a stirred solution of the bromide of Preparation 8 (590mg, 1.56mmol) in methanol (20ml) and tetrahydrofuran (20ml) at room temperature. The mixture was heated at 80°C under an atmosphere of carbon monoxide (690kPa, 100psi) for 18 hours. The reaction was cooled to room temperature and concentrated under reduced pressure to leave a brown oil. The oil was dissolved in dichloromethane (100ml) and the resulting solution was washed with water (50ml), dried over magnesium sulphate, filtered and evaporated under reduced pressure. The crude product was purified by flash column chromatography on silica gel eluting with ether to provide the title compound (110mg) as a colourless oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 2.15 (s, 3H), 3.34 (s, 3H), 4.35 (s, 2H), 6.83 (s, 2H), 7.03 (s, 1H).
LRMS (thermospray): m/z [MH^+] 287.

EXAMPLE 85

3-*tert*-Butyl-4-(3,5-dichlorophenoxy)-5-methyl-1*H*-pyrazole

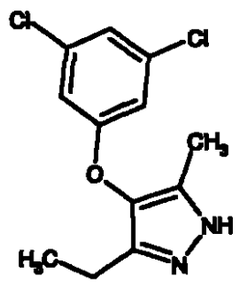


A mixture of the dione of Preparation 19 (1.00g, 5.68mmol), 3,5-dichlorophenol (930mg, 5.68mmol), cesium carbonate (1.85g, 5.68mmol) and acetone (20ml) was heated at reflux for 18 hours. After cooling the solid was removed by filtration and the filtrate was concentrated under reduced pressure. The intermediate was dissolved in ethanol (20ml), hydrazine hydrate (284mg, 5.68mmol) was added and the mixture was heated at 60°C for 1 hour. After cooling the mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel eluting with ethyl acetate:pentane (25:75, by volume) to provide the title compound (200mg) as a yellow oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.30 (s, 9H), 2.06 (s, 3H), 6.81 (s, 2H), 7.02 (s, 1H).
LRMS (thermospray): m/z [MH^+] 299.

EXAMPLE 86

4-(3,5-Dichlorophenoxy)-3-ethyl-5-methyl-1*H*-pyrazole

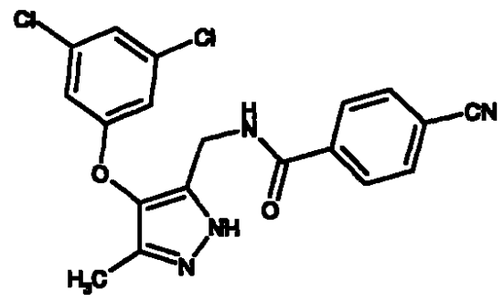


A mixture of the dione of Preparation 50 (4.50g, 30.8mmol), 3,5-dichlorophenol (5.00g, 30.8mmol), caesium carbonate (10.0g, 30.8mmol) and acetone (40ml) was heated at reflux for 18 hours. After cooling the solid was removed by filtration and the filtrate was concentrated under reduced pressure. The intermediate was dissolved in ethanol (40ml), hydrazine hydrate (1.00ml, 30.8mmol) was added and the mixture was heated at 60°C for 1 hour. After cooling the mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel eluting with ethyl acetate:pentane (20:80, by volume) to provide the title compound (1.50g) as an orange oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.18 (t, 3H), 2.11 (s, 3H), 2.53 (q, 2H), 6.79 (s, 2H), 7.01 (s, 1H).
LRMS (thermospray): m/z [MH^+] 271.

EXAMPLE 87

4-Cyano-*N*-[[4-(3,5-dichlorophenoxy)-3-methyl-1*H*-pyrazol-5-yl]methyl]benzamide

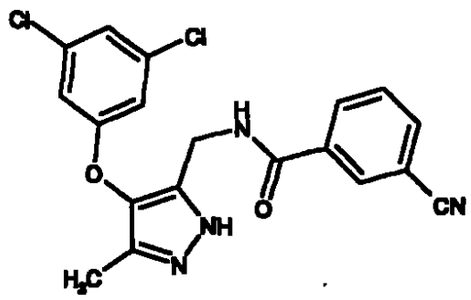


1-(3-(Dimethylamino)propyl)-3-ethylcarbodiimide (93mg, 0.490mmol) was added in one portion to a stirred solution of the amine of Example 109 (120mg, 0.440mmol) and 4-cyanobenzoic acid (71mg, 0.490mmol) in dichloromethane (5ml) at room temperature under nitrogen. The reaction was stirred for 20 minutes and then washed with 1M aqueous sodium hydroxide solution (10ml), 1M aqueous hydrochloric acid (10ml) and water (10ml). The organic layer was dried over magnesium sulphate, filtered and evaporated under reduced pressure to leave a yellow foam. The crude product was purified by flash column chromatography on silica gel eluting with dichloromethane:methanol:ammonia (95:4:1, by volume) to provide the title compound (110mg) as a white foam.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 2.09 (s, 3H), 4.91 (d, 2H), 6.74 (s, 2H), 6.95 (s, 1H), 6.98 (d, 1H), 7.65 (d, 2H), 7.77 (d, 2H).
LRMS (thermospray): m/z [MNH_4^+] 418.

EXAMPLE 88

3-Cyano-*N*-[[4-(3,5-dichlorophenoxy)-3-methyl-1*H*-pyrazol-5-yl]methyl]benzamide

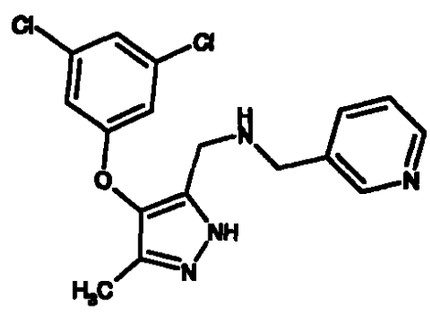


1-(3-(Dimethylamino)propyl)-3-ethylcarbodiimide (93mg, 0.490mmol) was added in one portion to a stirred solution of the amine of Example 109 (120mg, 0.440mmol) and 3-cyanobenzoic acid (71mg, 0.490mmol) in dichloromethane (5ml) at room temperature under nitrogen. The reaction was stirred for 10 minutes and then washed with 1M aqueous sodium hydroxide solution (10ml), 1M aqueous hydrochloric acid (10ml) and brine (10ml). The organic layer was dried over magnesium sulphate, filtered and evaporated under reduced pressure to leave a cream foam. The crude product was purified by flash column chromatography on silica gel eluting with dichloromethane:methanol:ammonia (95:4:1, by volume) to provide the title compound (100mg) as a white foam.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 2.14 (s, 3H), 4.53 (d, 2H), 6.78 (s, 2H), 6.98 (m, 2H), 7.54 (dd, 1H), 7.76 (d, 1H), 7.95 (d, 1H), 7.99 (s, 1H).
LRMS (thermospray): m/z [MH^+] 401.

EXAMPLE 89

N-[[4-(3,5-Dichlorophenoxy)-3-methyl-1*H*-pyrazol-5-yl]methyl]-*N*-(3-pyridinylmethyl)amine

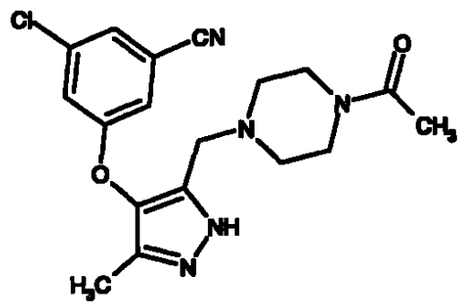


A mixture of 3-pyridinecarboxaldehyde (55mg, 0.514mmol), the amine of Example 109 (140mg, 0.514mmol), magnesium sulphate (500mg) and dichloromethane (5ml) was stirred under nitrogen at room temperature for 18 hours. Sodium triacetoxyborohydride (163mg, 0.771mmol) was added in one portion and then acetic acid (3 drops) was added. After 5 minutes the mixture was filtered. Tthe filtrate was washed with 1M aqueous sodium carbonate solution (10ml), water (10ml) and brine (10ml), dried over magnesium sulphate, filtered and concentrated under reduced pressure to leave a clear oil. The crude product was purified by flash column chromatography on silica gel eluting with dichloromethane:methanol:ammonia (95:4:1, by volume) to provide the title compound (60mg) as a colourless oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 2.09 (s, 3H), 3.66 (s, 2H), 3.74 (s, 2H), 6.75 (s, 2H), 6.97 (s, 1H), 7.17 (m, 1H), 7.55 (d, 1H), 8.49 (m, 2H).
LRMS (electrospray): m/z [MH^+] 363.

EXAMPLE 90

3-({5-[(4-Acetyl-1-piperazinyl)methyl]-3-methyl-1*H*-pyrazol-4-yl}oxy)-5-chlorobenzonitrile

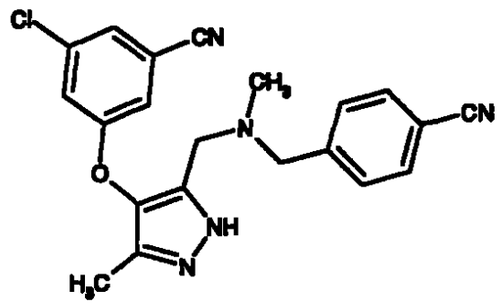


N-Acetylpiperazine (104mg, 0.810mmol) was added in one portion to a stirred solution of the bromide of Preparation 18 (100mg, 0.271mmol) in isopropanol (5ml) at room temperature. The mixture was heated at 50°C for 1 hour, cooled to room temperature and concentrated under reduced pressure to leave a yellow oil. The crude product was purified by flash column chromatography on silica gel eluting with dichloromethane:methanol:ammonia (95:4:1, by volume) to provide the title compound (90mg) as a colourless oil.

^{1}H-NMR (300MHz, $CDCl_3$): δ = 2.08 (s, 3H), 2.16 (s, 3H), 2.43 (m, 4H), 3.42 (m, 4H), 3.55 (m, 2H), 7.08 (s, 1H), 7.16 (s, 1H), 7.31 (s, 1H).
LRMS (thermospray): m/z [MH^+] 374.

EXAMPLE 91

3-Chloro-5-[(5-{[(4-cyanobenzyl)(methyl)amino]methyl}-3-methyl-1*H*-pyrazol-4-yl)oxy]benzonitrile

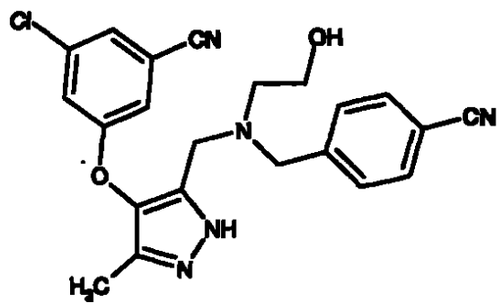


The amine of Preparation 20 (127mg, 0.870mmol) was added in one portion to a stirred solution of the bromide of Preparation 18 (100mg, 0.271mmol) in isopropanol (5ml) at room temperature. The mixture was heated at 50°C for 12 hours, cooled to room temperature and concentrated under reduced pressure to leave a yellow oil. The oil was dissolved in 1M hydrochloric acid and the aqueous solution was washed with ethyl acetate (10ml). Solid sodium carbonate was added until effervescence ceased and the mixture was extracted with ethyl acetate (3x20ml). The combined organic phases were dried over magnesium sulphate, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with dichloromethane:methanol:ammonia (95:4:1, by volume) to provide the title compound (45mg) as a colourless oil.

^{1}H-NMR (300MHz, $CDCl_3$): δ = 2.14 (s, 3H), 2.17 (s, 3H), 3.45 (s, 2H), 3.55 (s, 2H), 7.05 (s, 1H), 7.14 (s, 1H), 7.31 (m, 3H), 7.59 (d, 2H).
LRMS (thermospray): m/z [MH^+] 392.

EXAMPLE 92

3-Chloro-5-[(5-[[(4-cyanobenzyl)(2-hydroxyethyl)amino]methyl]-3-methyl-1*H*-pyrazol-4-yl)oxy]benzonitrile



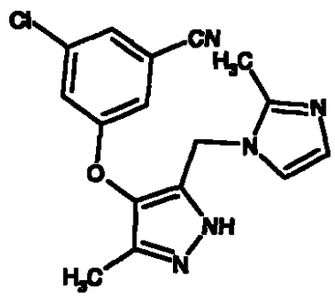
The amine of Preparation 21 (153mg, 0.870mmol) was added in one portion to a stirred solution of the bromide of Preparation 18 (100mg, 0.271mmol) in isopropanol (5ml) at room temperature. The mixture was heated at 50°C for 12 hours, cooled to room temperature and concentrated under reduced pressure to leave a yellow oil. The oil was dissolved in 1M aqueous sodium hydroxide solution and the resulting solution was stirred at room temperature for 1 hour. The aqueous was extracted with ethyl acetate (3x20ml) and the combined organic phases were dried over magnesium sulphate, filtered and concentrated under reduced pressure. The

residue was purified by flash column chromatography on silica gel eluting with dichloromethane:methanol:ammonia (95:4:1, by volume) to provide the title compound (20mg) as a colourless oil.

^{1}H-NMR (300MHz, $CDCl_3$): δ = 2.14 (s, 3H), 2.71 (m, 2H), 3.50 (s, 1H), 3.58 (s, 2H), 3.67 (m, 2H), 3.72 (s, 2H), 6.99 (s, 1H), 7.09 (s, 1H), 7.31 (s, 1H), 7.41 (d, 2H), 7.58 (d, 2H).
LRMS (thermospray): m/z [MH^+] 422.

EXAMPLE 93

3-Chloro-5-({3-methyl-5-[(2-methyl-1*H*-imidazol-1-yl)methyl]-1*H*-pyrazol-4-yl}oxy)benzonitrile

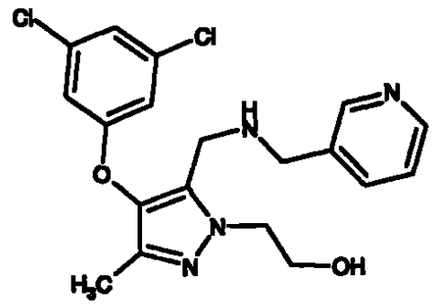


A suspension of the bromide of Preparation 18 (100mg, 0.264mmol), 2-methylimidazole (111mg, 1.35mmol) and sodium carbonate (143mg, 1.35mmol) in toluene (5ml) was heated at 100°C for 12 hours. The suspension was cooled to room temperature, 1M aqueous sodium hydroxide solution (5ml) was added and the mixture was stirred for 1 hour. The mixture was extracted with ethyl acetate (3x20ml) and the combined organic phases were dried over magnesium sulphate, filtered and concentrated under reduced pressure to leave a white solid. The crude product was purified by flash column chromatography on silica gel eluting with dichloromethane:methanol:ammonia (95:4.5:0.5, by volume) to provide the title compound (77mg) as a white solid, m.p. 212-214°C.

^{1}H-NMR (300MHz, $CDCl_3$): δ = 2.14 (s, 3H), 2.33 (s, 3H), 4.92 (s, 2H), 6.76 (s, 1H), 6.79 (s, 1H), 6.86 (s, 1H), 7.27 (s, 2H).
LRMS (thermospray): m/z [MH^+] 328.

EXAMPLE 94

2-(4-(3,5-Dichlorophenoxy)-3-methyl-5-[[(3-pyridinylmethyl)amino]methyl]-1*H*-pyrazol-1-yl)ethanol

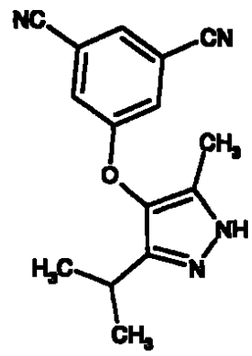


Tetrabutylammonium fluoride (0.58ml of a 1.0M solution in tetrahydrofuran, 0.580mmol) was added in one portion to a stirred solution of the amine of Preparation 22 (150mg, 0.290mmol) in dichloromethane (5ml) at room temperature. The reaction was stirred for 12 hours and concentrated under reduced pressure to leave a colourless oil. The crude product was purified by flash column chromatography on silica gel eluting with dichloromethane:methanol:ammonia (95:4:1, by volume) to provide the title compound (100mg) as a colourless oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 2.07 (s, 3H), 3.65 (s, 2H), 3.76 (s, 2H), 3.96 (m, 2H), 4.24 (m, 2H), 6.76 (s, 2H), 7.02 (s, 1H), 7.26 (m, 1H), 7.59 (d, 1H), 8.50 (m, 2H).
LRMS (thermospray): m/z [MH^+] 407.

EXAMPLE 95

5-[(3-Isopropyl-5-methyl-1*H*-pyrazol-4-yl)oxy]isophthalonitrile

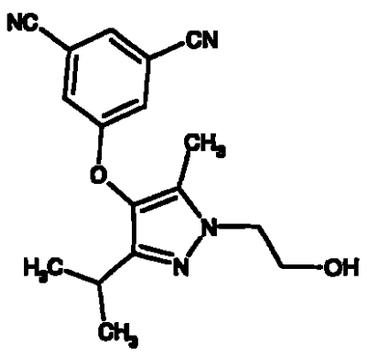


Hydrazine hydrate (110µl, 2.24mmol) was added to a stirred solution of the β-diketone of Preparation 24 (550mg, 2.04mmol) in glacial acetic acid (5ml) and the resulting solution was stirred at room temperature for 1 hour. The mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel eluting with pentane:ethyl acetate (60:40, by volume) to provide the title compound (350mg) as a yellow solid, m.p. 142-144°C.

^{1}H-NMR (300MHz, $CDCl_3$): δ = 1.21 (d, 6H), 2.09 (s, 3H), 2.90 (sept, 1H), 7.40 (s, 2H), 7.60 (s, 1H).
LRMS (thermospray): m/z [MH^+] 267.

EXAMPLE 96

5-[[1-(2-Hydroxyethyl)-3-isopropyl-5-methyl-1*H*-pyrazol-4-yl]oxy]isophthalonitrile



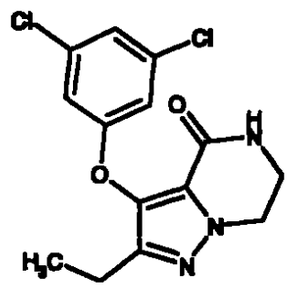
Tetrabutylammonium fluoride (0.28ml of a 1.0M solution in tetrahydrofuran, 0.280mmol) was added in one portion to a stirred solution of the pyrazole of Preparation 25 (60mg, 0.140mmol) in dichloromethane (5ml) at room temperature. The reaction was stirred for 12 hours and concentrated under reduced pressure to leave a colourless oil. The crude product was purified by flash column chromatography on silica gel eluting with pentane:ethyl acetate (20:80, by volume) to provide the title compound (30mg) as a white solid.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.17 (d, 6H), 2.08 (s, 3H), 2.76 (sept, 1H), 3.52 (m, 2H), 4.10 (m, 2H), 7.40 (s, 2H), 7.59 (s, 1H).
LRMS (electrospray): m/z [MH^+] 311.

Microanalysis: Found: C, 65.44; H, 5.87; N, 17.91. $C_{17}H_{18}N_4O_2$ requires C, 65.79; H, 5.85; N, 18.05%.

EXAMPLE 97

3-(3,5-Dichlorophenoxy)-2-ethyl-6,7-dihydropyrazolo[1,5-*a*]pyrazin-4(5*H*)-one

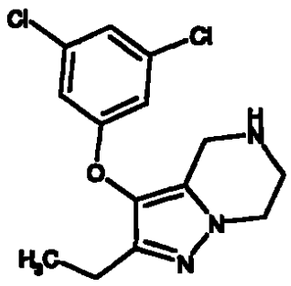


Lithium diisopropylamide (18.0ml of a 1.5M solution in cyclohexane, 27.0mmol) was added dropwise to a stirred solution of the pyrazole of Preparation 26 (12.0g, 24.6mmol) in tetrahydrofuran (120ml) at -78°C under nitrogen. The reaction was stirred for 14 hours, slowly warming to room temperature, and cautiously quenched with saturated aqueous ammonium chloride solution (20ml). The mixture was concentrated under reduced pressure and the residue was dissolved in dichloromethane (200ml). The resulting solution was washed with saturated aqueous ammonium chloride solution (100ml), dried over magnesium sulphate, filtered and concentrated under reduced pressure to leave a white solid. The solid was triturated with a mixture of dichloromethane and pentane (100ml and 100ml) to give the title compound (2.63g) as a white solid, m.p. 220-223°C.

^{1}H-NMR (400MHz, D_6 DMSO): δ = 1.08 (t, 3H), 2.44 (q, 2H), 3.60 (m, 2H), 4.24 (t, 2H), 7.00 (s, 2H), 7.26 (s, 1H), 8.15 (s, 1H).
LRMS (thermospray): m/z [MNH_4^+] 343.
Microanalysis: Found: C, 51.52; H, 3.98; N, 12.74. $C_{14}H_{31}Cl_2N_3O_2$ requires C, 51.55; H, 4.02; N, 12.88%.

EXAMPLE 98

3-(3,5-Dichlorophenoxy)-2-ethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine

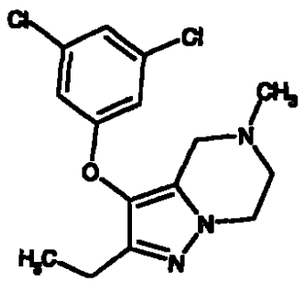


Borane (2.00ml of a 1.0M solution in tetrahydrofuran, 2.00mmol) was added to a stirred solution of the pyrazole of Example 97 (328mg, 1.00mmol) in tetrahydrofuran (10ml) at room temperature under nitrogen. The reaction was heated under reflux for 5 hours and further borane (3.00ml of a 1.0M solution in tetrahydrofuran, 3.00mmol) was added. The reaction was heated under reflux for 14 hours and further borane (2.00ml of a 1.0M solution in tetrahydrofuran, 2.00mmol) was added. The reaction was heated under reflux for 3 hours and further borane (2.00ml of a 1.0M solution in tetrahydrofuran, 2.00mmol) was added. The mixture was cooled to room temperature, 2M hydrochloric acid (10ml) was added and the mixture was heated under reflux for 1 hour. The mixture was cooled to room temperature and concentrated under reduced pressure. The residue was dissolved in dichloromethane (40ml), washed with 1M aqueous potassium carbonate solution (30ml), dried over magnesium sulphate, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel eluting with dichloromethane:methanol (98:2, by volume), then dichloromethane:methanol (95:5, by volume) and then dichloromethane:methanol:ammonia (90:9:1, by volume) to provide the title compound (219mg) as a white solid, m.p. 76-77°C.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.10 (t, 3H), 2.42 (q, 2H), 3.24 (t, 2H), 3.80 (s, 2H), 4.05 (t, 2H), 6.76 (s, 2H), 6.95 (s, 1H).
LRMS (thermospray): m/z [MH^+] 312.
Microanalysis: Found: C, 53.79; H, 4.88; N, 13.14. $C_{14}H_{15}Cl_2N_3O$ requires C, 53.86; H, 4.84; N, 13.46%.

EXAMPLE 99

3-(3,5-Dichlorophenoxy)-2-ethyl-5-methyl-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrazine

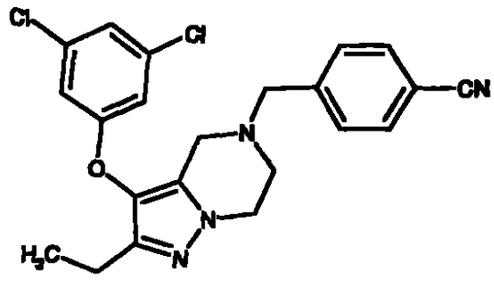


Methyl iodide (11µl, 0.176*mmol*) was added to a stirred solution of potassium carbonate (24mg, 0.176mmol) and the amine of Example 98 (50mg, 0.160mmol) in *N,N*-dimethylformamide (2ml) at room temperature under nitrogen. The reaction was stirred for 3 hours and then concentrated under reduced pressure. The residue was dissolved in ethyl acetate (20ml), washed with 1M aqueous potassium carbonate solution (20ml), dried over magnesium sulphate, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography *on silica gel eluting with dichloromethane:methanol* (98:2, by volume) to provide the title compound (18mg) as a colourless oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.11 (t, 3H), 2.42 (m, 5H), 2.84 (t, 2H), 3.37 (s, 2H), 4.11 (t, 2H), 6.77 (s, 2H), 6.98 (s, 1H).
LRMS (thermospray): *m/z* [MH^+] 326.

EXAMPLE 100

4-[(3-(3,5-Dichlorophenoxy)-2-ethyl-6,7-dihydropyrazolo[1,5-*a*]pyrazin-5(4*H*)-yl)methyl]benzonitrile

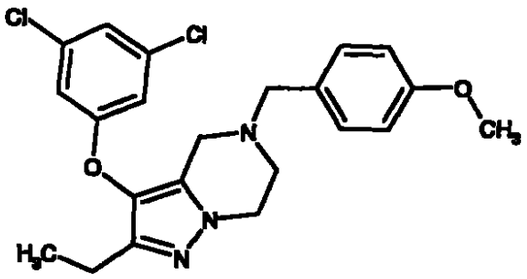


4-Cyanobenzylbromide (35mg, 0.176mmol) was added to a stirred solution of potassium carbonate (24mg, 0.176mmol) and the amine of Example 98 (50mg, 0.160mmol) in *N,N*-dimethylformamide (2ml) at room temperature under nitrogen. The reaction was stirred for 14 hours and then concentrated under reduced pressure. The residue was dissolved in ethyl acetate (20ml) and the resulting solution was washed with 1M aqueous potassium carbonate solution (15ml), dried over magnesium sulphate, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel eluting with dichloromethane:methanol (98:2, by volume) to provide the title compound (66mg) as a white solid, m.p. 149-150°C.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.13 (t, 3H), 2.44 (q, 2H), 2.92 (t, 2H), 3.42 (s, 2H), 3.71 (s, 2H), 4.13 (t, 2H), 6.74 (s, 2H), 6.97 (s, 1H), 7.42 (d, 2H), 7.60 (d, 2H).
LRMS (thermospray): m/z [MH^+] 427.

EXAMPLE 101

3-(3,5-Dichlorophenoxy)-2-ethyl-5-(4-methoxybenzyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine



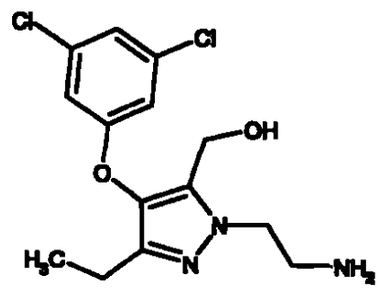
4-Methoxybenzylchloride (24µl, 0.176mmol) was added to a stirred solution of potassium carbonate (24mg, 0.176mmol) and the amine of Example 98 (50mg, 0.160mmol) in *N,N*-dimethylformamide (6ml) at room temperature under nitrogen. The reaction was stirred for 14 hours and then potassium carbonate (12mg, 0.088mmol) and 4-methoxybenzylchloride (12µl, 0.088mmol) added. The reaction was stirred for 3 hours and then concentrated under reduced pressure. The residue was dissolved in ethyl acetate (20ml) and the resulting solution was washed with 1M aqueous potassium carbonate solution (20ml), dried over magnesium sulphate, filtered and concentrated under reduced pressure. The crude product was purified

by flash column chromatography on silica gel eluting with dichloromethane:methanol (99:1, by volume) to provide the title compound (50mg) as a colourless oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.13 (t, 3H), 2.45 (q, 2H), 2.92 (t, 2H), 3.44 (s, 2H), 3.60 (s, 2H), 3.80 (s, 3H), 4.10 (t, 2H), 6.77 (s, 2H), 6.85 (d, 2H), 7.00 (s, 1H), 7.23 (d, 2H).
LRMS (thermospray): m/z [MH^+] 432.

EXAMPLE 102

[1-(2-Aminoethyl)-4-(3,5-dichlorophenoxy)-3-ethyl-1*H*-pyrazol-5-yl]methanol

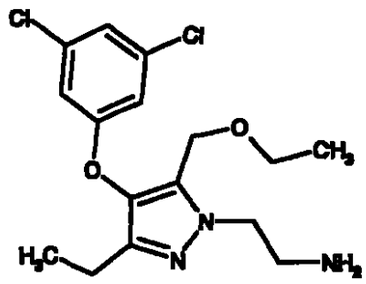


Hydrogen chloride (0.50ml of a 4.0M solution in dioxane, 2.00mmol) was added to a stirred solution of the pyrazole of Example 135 (86mg, 0.200mmol) in dioxane (0.5ml) at room temperature under nitrogen. The reaction was stirred for 24 hours and concentrated under reduced pressure. The residue was dissolved in dichloromethane (20ml) and the resulting solution was washed with 1M aqueous potassium carbonate solution (10ml), dried over magnesium sulphate, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with dichloromethane:methanol (99:1, by volume) to provide the title compound (40mg) as a white solid, m.p. 105-107°C.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.10 (t, 3H), 2.42 (q, 2H), 2.55 (s, 2H), 3.13 (t, 2H), 4.13 (t, 2H), 4.37 (s, 2H), 6.79 (s, 2H), 6.98 (s, 1H).
LRMS (thermospray): m/z [MH^+] 330.
Microanalysis: Found: C, 50.61; H, 5.23; N, 12.31. $C_{14}H_{17}Cl_2N_3O_2$ requires C, 50.92; H, 5.19; N, 12.73%.

EXAMPLE 103

2-[4-(3,5-Dichlorophenoxy)-5-(ethoxymethyl)-3-ethyl-1*H*-pyrazol-1-yl]ethylamine

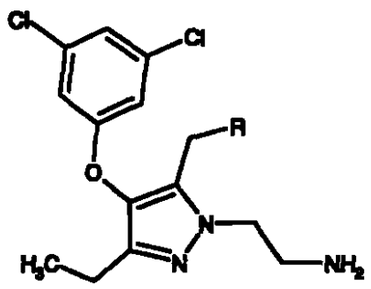


Hydrogen chloride (0.50ml of a 4.0M solution in dioxane, 2.00mmol) was added to a stirred solution of the pyrazole of Example 136 (60mg, 0.130mmol) in dioxane (0.5ml) at room temperature under nitrogen. The reaction was stirred for 2 days and concentrated under reduced pressure. The residue was dissolved in dichloromethane (20ml) and the resulting solution was washed with 1M aqueous potassium carbonate solution (10ml), dried over magnesium sulphate, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with dichloromethane:methanol:ammonia (99:9:1, by volume) to provide the title compound (32mg) as a colourless oil.

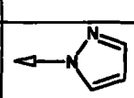
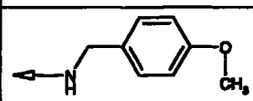
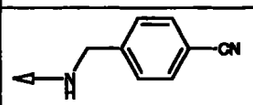
^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.10 (m, 6H), 2.42 (q, 2H), 3.15 (t, 2H), 3.40 (q, 2H), 4.11 (t, 2H), 4.29 (s, 2H), 6.79 (s, 2H), 6.98 (s, 1H).
LRMS (thermospray): *m/z* [MH^+] 358.

EXAMPLES 104 TO 106

The compounds of the following tabulated Examples of the general formula:



were prepared by a similar method to that of Example 103 using the appropriate starting material.

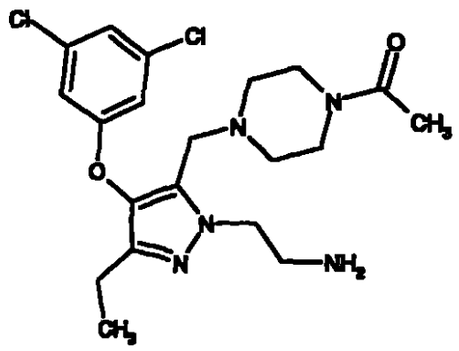
Example No (Starting material)	R	LRMS (thermospray)	Analytical Data
104 (Example 140)		m/z [MH$^+$] 380	^{1}H-NMR (400MHz, $CDCl_3$) δ = 1 10 (t, 3H), 2 40 (q, 2H), 2 97 (t, 2H), 4 15 (t, 2H), 5 20 (s, 2H), 6 16 (s, 1H), 6 71 (d, 2H), 6 97 (s, 1H), 7 15 (s, 1H), 7 42 (s, 1H) Microanalysis Found C, 52 78, H, 5 09, N, 17 86 $C_{17}H_{18}Cl_2N_5O$ 0 12CH_2Cl_2 requires C, 52 66, H, 4 97, N, 17 94%
105 (Example 142)		m/z [MH$^+$] 449	^{1}H-NMR (400MHz, $CDCl_3$) δ = 1 10 (t, 3H), 2 42 (q, 2H), 3 11 (t, 2H), 3 55 (s, 2H), 3 60 (s, 2H), 3 75 (s, 3H), 4 07 (t, 2H), 6 73 (s, 2H), 6 79 (d, 2H), 6 97 (s, 1H), 7 10 (d, 2H) Microanalysis Found C, 56 88, H, 5 67, N, 11 88 $C_{22}H_{28}Cl_2N_4O_2$.0 23CH_2Cl_2 requires C, 56 94, H, 5 69, N, 11 95%
106 (Example 143)		m/z [MH$^+$] 444	^{1}H-NMR (400MHz, $CDCl_3$) δ = 1 10 (t, 3H), 2 41 (q, 2H), 3 15 (t, 2H), 3 60 (s, 2H), 3 74 (s, 2H), 4 10 (d, 2H), 6 73 (s, 2H), 6 97 (s, 1H), 7 29 (d, 2H), 7 53 (d, 2H) Microanalysis Found C, 57 53, H, 5 09, N, 15 05 $C_{22}H_{23}Cl_2N_5O$ 0 22CH_2Cl_2 requires C, 57 64, H, 5 10, N, 15 12%





EXAMPLE 107

2-[5-[(4-Acetyl-1-piperazinyl)methyl]-4-(3,5-dichlorophenoxy)-3-ethyl-1*H*-pyrazol-1-yl]ethylamine



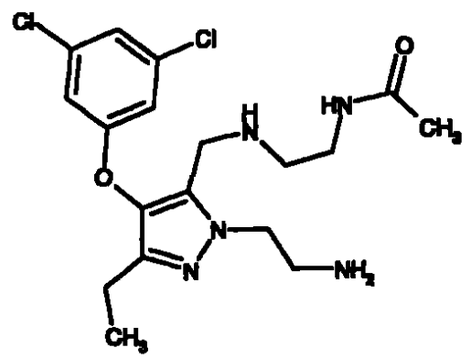
Trifluoroacetic acid (1ml) was added to a stirred solution of the pyrazole of Example 139 (150mg, 0.28mmol) in dichloromethane (2ml) at room temperature under nitrogen. The reaction was stirred for 3 hours and the mixture was concentrated under reduced pressure. The residue was dissolved in dichloromethane (20ml) and the resulting solution was washed with 1M aqueous potassium carbonate solution (30ml), dried over magnesium sulphate, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with dichloromethane:methanol:ammonia (90:9:1, by volume) to provide the title compound (103mg) as a colourless oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.11 (t, 3H), 2.05 (s, 3H), 2.32 (m, 4H), 2.42 (q, 2H), 3.13 (m, 2H), 3.33 (s, 2H), 3.34 (m, 2H), 3.52 (m, 2H), 4.15 (t, 2H), 6.73 (s, 2H), 6.97 (s, 1H).

LRMS (thermospray): m/z [MH^+] 440.

EXAMPLE 108

N-[2-({[1-(2-Aminoethyl)-4-(3,5-dichlorophenoxy)-3-ethyl-1*H*-pyrazol-5-yl]methyl}amino)ethyl]acetamide



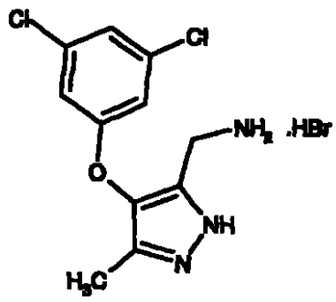
Trifluoroacetic acid (1ml) was added to a stirred solution of the pyrazole of Example 141 (122mg, 0.24mmol) in dichloromethane (2ml) at room temperature under nitrogen. The reaction was stirred for 3 hours and the mixture was concentrated under reduced pressure. The residue was dissolved in dichloromethane (50ml) and the resulting solution was washed with 1M aqueous potassium carbonate solution (30ml), dried over magnesium sulphate, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with dichloromethane:methanol:ammonia (90:9:1, by volume) to provide the title compound (64mg) as a colourless oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.15 (t, 3H), 1.95 (s, 3H), 2.45 (q, 2H), 2.69 (t, 2H), 3.20 (t, 2H), 3.27 (m, 2H), 3.65 (s, 2H), 4.15 (t, 2H), 6.31 (s, 1H), 6.81 (s, 2H), 7.02 (s, 1H).

LRMS (thermospray): m/z [MH^+] 414.

EXAMPLE 109

[4-(3,5-Dichlorophenoxy)-3-methyl-1*H*-pyrazol-5-yl]methanamine hydrobromide

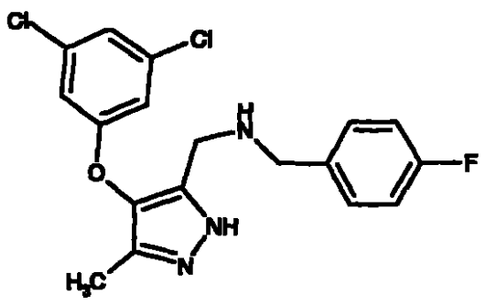


The bromide of Preparation 8 (500mg, 1.30mmol) was added portionwise to a saturated solution of ammonia in isopropanol (50ml) at 0°C. The reaction was stirred for 2 hours and allowed to slowly warm to room temperature. The mixture was concentrated under reduced pressure and the resulting solid was triturated with diethyl ether to provide the title compound (340mg) as a white solid.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 2.38 (s, 3H), 4.78 (s, 2H), 6.88 (s, 2H), 7.19 (s, 1H).
LRMS (thermospray): m/z [MH^+] 272.

EXAMPLE 110

N-[[4-(3,5-Dichlorophenoxy)-3-methyl-1*H*-pyrazol-5-yl]methyl]-*N*-(4-fluorobenzyl)amine



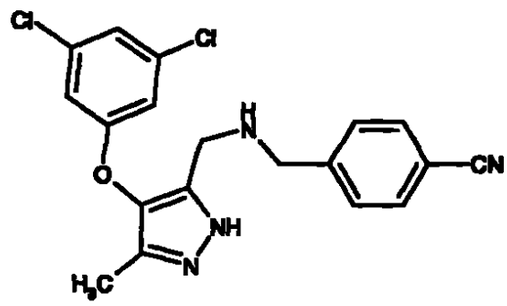
Sodium triacetoxyborohydride (36mg, 0.160mmol) was added in one portion to a stirred solution of the pyrazole of Example 109 (150mg, 0.400mmol), 4-fluorobenzaldehyde (11mg, 0.080mmol) and acetic acid (3 drops) in dichloromethane (15ml) at room temperature under nitrogen. The reaction was stirred for 3 hours and then concentrated under reduced pressure. The crude

product was purified by flash chromatography on silica gel eluting with dichloromethane:methanol:ammonia (90:9:1, by volume) to provide the title compound (6mg) as a colourless oil.

^{1}H-NMR (300MHz, $CDCl_3$): δ = 2.17 (s, 3H), 3.67 (s, 2H), 3.73 (s, 2H), 6.81 (s, 2H), 6.99 (s, 2H), 7.02 (s, 1H), 7.22 (s, 2H).
LRMS (electrospray): m/z [M-H$^+$] 378.

EXAMPLE 111

4-[({[4-(3,5-Dichlorophenoxy)-3-methyl-1*H*-pyrazol-5-yl]methyl}amino)methyl]benzonitrile

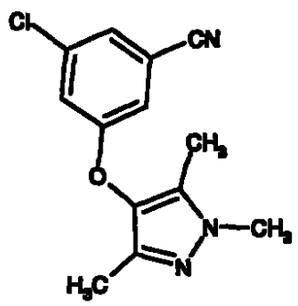


Sodium triacetoxyborohydride (216mg, 1.09mmol) was added in one portion to a stirred solution of the pyrazole of Example 109 (300mg, 0.850mmol), 4-cyanobenzaldehyde (111mg, 0.850mmol) and acetic acid (3 drops) in dichloromethane (25ml) at room temperature under nitrogen. The reaction was stirred for 14 hours and then washed with 1M aqueous sodium carbonate solution (2x10ml) and brine (10ml), dried over magnesium sulphate, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with dichloromethane:methanol:ammonia (95:4:1, by volume) to provide the title compound (10mg) as a colourless oil.

^{1}H-NMR (300MHz, $CDCl_3$): δ = 2.16 (s, 3H), 3.70 (s, 2H), 3.85 (s, 2H), 6.78 (s, 2H), 7.01 (s, 2H), 7.35 (d, 2H), 7.58 (d, 2H).
LRMS (electrospray): m/z [MH$^+$] 387.

EXAMPLE 112

3-Chloro-5-[(1,3,5-trimethyl-1*H*-pyrazol-4-yl)oxy]benzonitrile

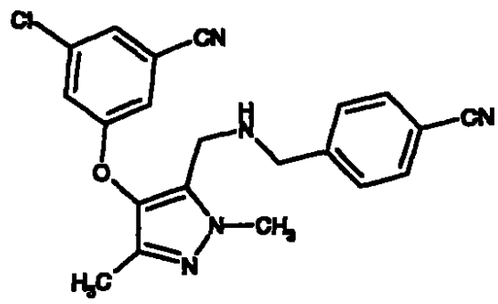


Methyl hydrazine (250mg, 5.17mol) was added to a stirred solution of the β-diketone of Preparation 16 (1.00g, 3.97mmol) in glacial acetic acid (10ml) and the resulting solution was stirred at room temperature for 2 days. The mixture was concentrated under reduced pressure and the resulting orange oil was purified by flash column chromatography on silica gel eluting with pentane:ethyl acetate (50:50, by volume) to provide the title compound (500mg) as a white solid, m.p. 114-116°C.

^{1}H-NMR (300MHz, $CDCl_3$): δ = 1.85 (s, 3H), 1.87 (s, 3H), 3.61 (s, 3H), 6.88 (s, 1H), 6.98 (s, 1H), 7.11 (s, 1H).
LRMS (thermospray): m/z [MH^+] 262.
Microanalysis: Found: C, 59.48; H, 4.60; N, 15.88. $C_{13}H_{12}N_3OCl$ requires C, 59.66; H, 4.62; N, 16.06%.

EXAMPLE 113

3-Chloro-5-[(5-[[(4-cyanobenzyl)amino]methyl]-1,3-dimethyl-1*H*-pyrazol-4-yl)oxy]benzonitrile

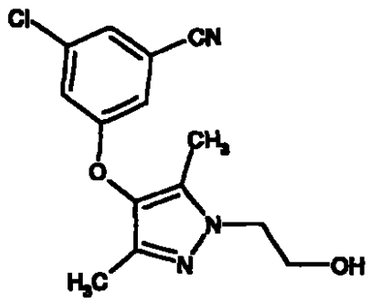


4-Cyanobenzylamine (155mg, 1.17mmol) was added in one portion to a stirred solution of the bromide of Example 144 (100mg, 0.300mmol) in isopropanol (10ml) at room temperature. The mixture was heated at 50°C for 1 hour, cooled to room temperature and concentrated under reduced pressure to leave a yellow oil. The crude product was purified by flash column chromatography on silica gel eluting with dichloromethane:methanol:ammonia (95:4:1, by volume) to provide the title compound (97mg) as a colourless oil.

^{1}H-NMR (300MHz, $CDCl_3$): δ = 2.03 (s, 3H), 3.66 (s, 2H), 3.79 (s, 2H), 3.84 (s, 3H), 7.02 (s, 1H), 7.13 (s, 1H), 7.31 (s, 1H), 7.37 (d, 2H), 7.58 (d, 2H).
LRMS (thermospray): m/z [MH^+] 392.

EXAMPLE 114

3-Chloro-5-[[1-(2-hydroxyethyl)-3,5-dimethyl-1*H*-pyrazol-4-yl]oxy]benzonitrile

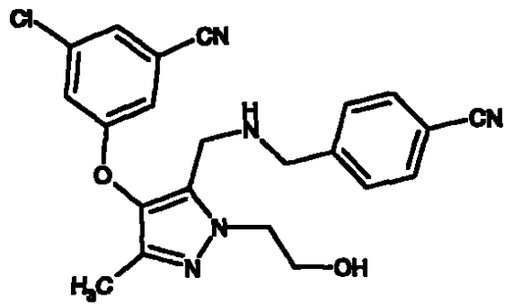


2-Hydroxyethyl hydrazine (1.80g, 24.0mol) was added to a stirred solution of the β-diketone of Preparation 16 (5.80g, 23.0mmol) in glacial acetic acid (30ml) and the resulting solution was stirred at room temperature for 2 days. The mixture was concentrated under reduced pressure and the resulting brown oil was purified by flash column chromatography on silica gel eluting with pentane:ethyl acetate (50:50, by volume) to provide the title compound (4.80g) as a yellow solid, m.p. 114-116°C.

^{1}H-NMR (300MHz, $CDCl_3$): δ = 2.04 (s, 3H), 2.12 (s, 3H), 3.24 (s, 1H), 4.08 (m, 4H), 7.03 (s, 1H), 7.15 (s, 1H), 7.28 (s, 1H).
LRMS (thermospray): m/z [MH^+] 292.
Microanalysis: Found: C, 57.40; H, 4.86; N, 14.14. $C_{14}H_{14}N_3O_2Cl$ requires C, 57.69; H, 4.84; N, 14.40%.

EXAMPLE 115

3-Chloro-5-[[5-[[(4-cyanobenzyl)amino]methyl]-1-(2-hydroxyethyl)-3-methyl-1*H*-pyrazol-4-yl]oxy]benzonitrile

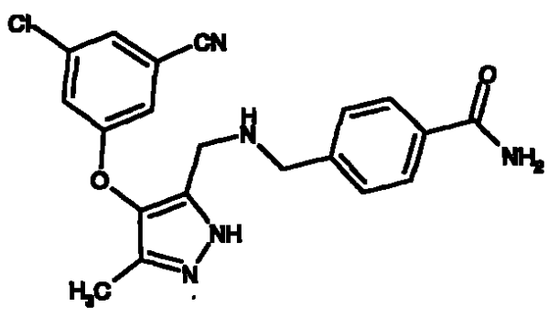


4-Cyanobenzylamine (131mg, 0.910mmol) was added to a stirred solution of the pyrazole of Preparation 30 (120mg, 0.240mmol) in *N*-methylpyrrolidine (10ml) and the resulting solution was heated at 60°C for 3 hours. The mixture was concentrated under reduced pressure and the resulting brown oil was dissolved in acetic acid (10ml) and heated at 40°C for 6 hours. The mixture was concentrated under reduced pressure and the crude product was purified by flash column chromatography on silica gel eluting with dichloromethane:methanol:ammonia (95:4:1, by volume) to provide the title compound (5mg) as a white solid.

^{1}H-NMR (300MHz, $CDCl_3$): δ = 2.05 (s, 3H), 3.04 (s, 2H), 3.91 (s, 2H), 3.99 (t, 2H), 4.32 (m, 2H), 7.06 (s, 1H), 7.11 (s, 1H), 7.33 (s, 1H), 7.46 (d, 2H), 7.62 (d, 2H).
LRMS (thermospray): m/z [MNa^+] 444.

EXAMPLE 116

4-[([[4-(3-Chloro-5-cyanophenoxy)-3-methyl-1*H*-pyrazol-5-yl]methyl]amino)methyl]benzamide

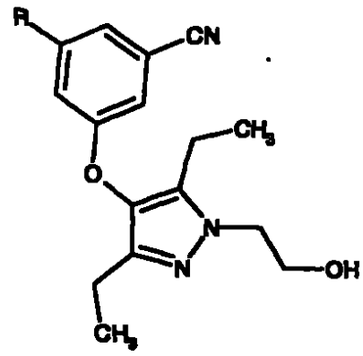


The amine of Preparation 55 (150mg, 0.800mmol) was added to a stirred solution of the pyrazole of Preparation 18 (100mg, 0.270mmol) and triethylamine (81mg, 0.800mmol) in isopropanol (10ml) and *N,N*-dimethylformamide (5ml) and the resulting solution was heated at 80°C for 3 hours. The mixture was concentrated under reduced pressure and the resulting brown oil was dissolved in ethyl acetate (20ml). The solution was washed with 1M aqueous sodium carbonate solution (2x10ml) and brine (10ml), dried over magnesium sulphate, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with dichloromethane:methanol:ammonia (90:9:1, by volume) to provide the title compound (5mg) as a colourless oil.

^{1}H-NMR (300MHz, $CDCl_3$): δ = 2.16 (s, 3H), 3.68 (s, 2H), 3.82 (s, 2H), 7.05 (s, 1H), 7.13 (s, 1H), 7.28 (s, 1H), 7.32 (d, 2H), 7.76 (d, 2H).
LRMS (electrospray): m/z [MH^+] 396.

EXAMPLES 117 TO 120

The compounds of the following tabulated Examples of the general formula:

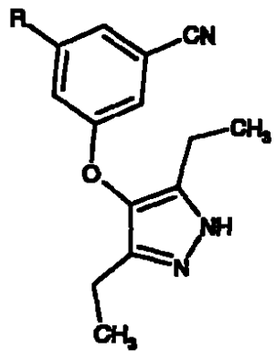


were prepared by a similar method to that of Example 114 using the appropriate diketone starting material and 2-hydroxyethylhydrazine.

Example No (Diketone No)	R	LRMS	Analytical Data
117 (Preparation 43)	F	m/z [MH$^+$] 303 (thermospray)	^{1}H-NMR (300MHz, $CDCl_3$) δ = 1 10 (m, 6H), 2 39 (q, 2H), 2.49 (q, 2H), 4 04 (m, 4H), 6 85 (dd, 1H), 6 99 (s, 1H), 7 00 (dd, 1H) Microanalysis Found C, 62 96, H, 5 94, N, 13 75 $C_{16}H_{18}N_3O_2F$ requires C, 63 35, H, 5 98, N, 13 85%
118 (Preparation 44)	Me	m/z [MH$^+$] 300 (electrospray)	^{1}H-NMR (400MHz, $CDCl_3$) δ = 1 09 (t,3H), 1 12 (t, 3H), 2 34 (s, 3H), 2 39 (q, 2H), 2 50 (q, 2H), 3 70 (s, 1H), 4 60 (m, 4H), 6 91 (s, 1H), 6 97 (s, 1H), 7 10 (s, 1H)
119 (Preparation 45)	CN	m/z [MH$^+$] 311 (electrospray)	^{1}H-NMR (400MHz, $CDCl_3$) δ = 1 13 (m, 6H), 2 40 (q, 2H), 2 53 (q, 2H), 3 53 (m, 1H), 4 11 (m, 4H), 7 40 (s, 2H), 7 58 (s, 1H) Microanalysis Found C, 65 64, H, 5 84, N, 18 05 $C_{17}H_{18}N_4O_2$ requires C, 65 79, H, 5 85, N, 18 05% m p 120-121°C
120 (Preparation 46)	Cl	m/z [MH$^+$] 320 (thermospray)	^{1}H-NMR (400MHz, $CDCl_3$) δ = 1 08 (m, 6H), 2 39 (q, 2H), 2 50 (q, 2H), 4 01 (m, 2H), 4 08 (m, 2H), 7 03 (s, 1H), 7 13 (s, 1H), 7.24 (s, 1H) Microanalysis Found C, 59 67, H, 5 71, N, 12 99 $C_{16}H_{18}N_3O_2Cl$ requires C, 60 09, H, 5 67, N, 13 14%

EXAMPLES 121 TO 124

The compounds of the following tabulated Examples of the general formula:

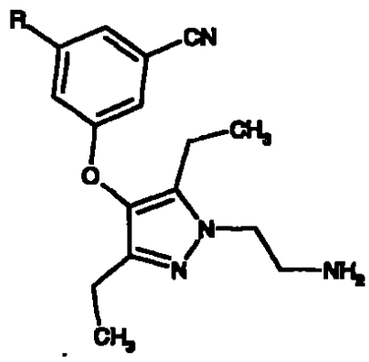


were prepared by a similar method to that of Example 76 using the appropriate diketone starting material and hydrazine.

Example No (Diketone No)	R	LRMS	Analytical Data
121 (Preparation 43)	F	m/z [MH^+] 260 (thermospray)	^{1}H-NMR (400MHz, $CDCl_3$) δ = 1 18 (t, 6H), 2 47 (q, 4H), 6 85 (dd, 1H), 6 98 (s, 1H), 7 01 (dd, 1H)
122 (Preparation 45)	CN	m/z [MH^+] 267 (thermospray)	^{1}H-NMR (400MHz, $CDCl_3$) δ = 1 20 (6H, m), 2.47 (q, 4H), 7 39 (s, 2H), 7 59 (s, 1H)
123 (Preparation 44)	Me	m/z [MH^+] 256 (electrospray)	^{1}H-NMR (400MHz, $CDCl_3$) δ = 1 17 (t, 6H), 2 34 (s, 3H), 2 48 (q, 4H), 6 92 (s, 1H), 6 96 (s, 1H), 7 10 (s, 1H)
124 (Preparation 46)	Cl	m/z [MH^+] 276 (thermospray)	^{1}H-NMR (400MHz, $CDCl_3$) δ = 1 18 (t, 6H), 2 49 (q, 4H), 7 07 (s, 1H), 7 13 (s, 1H), 7 27 (s, 1H)

EXAMPLES 125 TO 128

The compounds of the following tabulated Examples of the general formula:

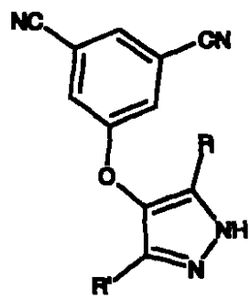


were prepared by a similar method to that of Example 13 using the appropriate pyrazole starting material and chloroethylamine hydrochloride.

Example No (Starting pyrazole No)	R	LRMS	Analytical Data
125 (Example 123)	Me	m/z [MH^+] 299 (electrospray)	^{1}H-NMR (400MHz, $CDCl_3$) δ = 1 10 (m, 6H), 2 34 (s, 3H), 2 39 (q, 2H), 2 43 (q, 2H), 3 17 (t, 2H), 4 04 (t, 2H), 6 91 (s, 1H), 6 96 (s, 1H), 7 09 (s, 1H)
126 (Example 124)	Cl	m/z [MH^+] 319 (thermospray)	^{1}H-NMR (400MHz, $CDCl_3$) δ = 1 09 (m, 6H), 2.40 (q, 2H), 2 51 (q, 2H), 3 15 (m, 2H), 4 02 (m, 2H), 7 04 (s, 1H), 7 12 (s, 1H), 7 28 (s, 1H)
127 (Example 122)	CN	m/z [MH^+] 310 (thermospray)	^{1}H-NMR (400MHz, $CDCl_3$) δ = 1 09 (m, 6H), 2 38 (q, 2H), 2 50 (q, 2H), 3 15 (m, 2H), 4 03 (m, 2H), 7 39 (s, 2H), 7 57 (s, 1H)
128 (Example 121)	F	m/z [MH^+] 303 (thermospray)	^{1}H-NMR (400MHz, $CDCl_3$) δ = 1 06 (m, 6H), 2 37 (q, 2H), 2 48 (q, 2H), 3 13 (t, 2H), 4 03 (t, 2H), 6 84 (d, 1H), 6 94 (s, 1H), 6 97 (d, 1H)

EXAMPLES 129 TO 131

The compounds of the following tabulated Examples of the general formula:

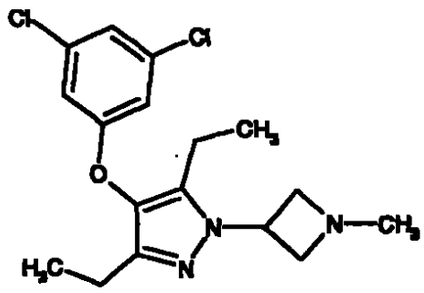


were prepared by a similar method to that of Example 76 using the appropriate diketone starting material and hydrazine.

Example No (Diketone No)	R	R'	LRMS	Analytical Data
129 (Preparation 52)	cycloPr	Et	m/z [MH^+] 279 (electrospray)	^{1}H-NMR (400MHz, $CDCl_3$) 0 73 (m, 2H), 0 81 (m, 2H), 1 16 (t, 3H), 1 58 (m, 1H), 2 46 (q, 2H), 7 42 (s, 2H), 7 58 (s, 1H) m p 136-141°C
130 (Preparation 53)	tBu	Me	m/z [MH^+] 281 (electrospray)	^{1}H-NMR (300MHz, $CDCl_3$) 1 21 (s, 9H), 1 94 (s, 3H), 7 34 (s, 2H), 7 56 (s, 1H) Microanalysis Found C, 68 18, H, 5 74, N, 19 72 $C_{16}H_{16}N_4O$ requires C, 68 55, H, 5 75, N, 19 99% m p 61-63°C
131 (Preparation 54)	iPr	Et	m/z [MH^+] 281 (electrospray)	^{1}H-NMR (400MHz, $CDCl_3$) 1 15 (m, 9H), 2.41 (q, 2H), 2 82 (m, 1H), 7 36 (s, 2H), 7 58 (s, 1H) m p 136-141°C

EXAMPLE 132

4-(3,5-Dichlorophenoxy)-3,5-diethyl-1-(1-methyl-3-azetidinyl)-1*H*-pyrazole

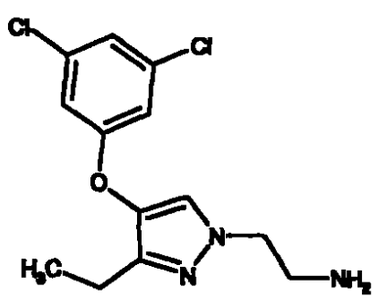


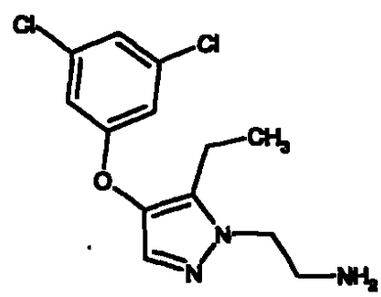
Paraformaldehyde (30mg, 0.330mmol) was added in one portion to a stirred solution of the pyrazole of Example 51 (120mg, 0.330mmol) in formic acid (2ml) at room temperature. The mixture was heated at 100°C for 5 hours, cooled to room temperature and concentrated under reduced pressure to leave a colourless oil. The oil was dissolved in ethyl acetate (50ml) and the resulting solution was washed with saturated aqueous sodium hydrogencarbonate (20ml), water (20ml) and brine (20ml), dried over magnesium sulphate, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel eluting with dichloromethane:methanol:ammonia (95:4:1, by volume) to provide the title compound (85mg) as a colourless oil.

^{1}H-NMR (300MHz, $CDCl_3$): δ = 1.08 (t, 3H), 1.16 (t, 3H), 2.49 (m, 7H), 3.63 (m, 2H), 3.81 (m, 2H), 4.79 (m, 1H), 6.79 (s, 2H), 7.00 (s, 1H).
LRMS (thermospray): m/z [MH^+] 354.

EXAMPLES 133-134

2-[4-(3,5-Dichlorophenoxy)-3-ethyl-1*H*-pyrazol-1-yl]ethylamine (Example 133) and
2-[4-(3,5-Dichlorophenoxy)-5-ethyl-1*H*-pyrazol-1-yl]ethylamine (Example 134)



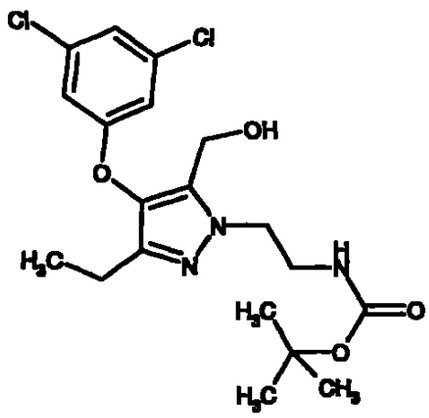


A mixture of the pyrazole (1.03g, 4.00mmol) of Example 42 and chloroethylamine hydrochloride (510mg, 4.40mmol) was stirred and heated at 150°C for 24 hours. After cooling the mixture was partitioned between 1M aqueous potassium carbonate solution (30ml) and dichloromethane (30ml). The organic layer was washed with brine (30ml), dried over magnesium sulphate, filtered and concentrated under reduced pressure. The resulting brown oil was purified by flash chromatography on silica gel eluting with dichloromethane:methanol:ammonia (93:6:1, by volume) to afford the title compounds (768mg) in a 85:15 ratio of regioisomers as a colourless oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.16 (major, t, 3H), 1.16 (minor, t, 3H), 2.48 (major, q, 2H), 2.60 (minor, q, 2H), 3.13 (major, t, 2H), 3.19 (minor, t, 2H), 4.10 (major, t, 2H), 4.10 (minor, t, 2H), 6.85 (major, s, 2H), 6.85 (minor, s, 2H), 7.02 (major, s, 1H), 7.02 (minor, s, 1H), 7.27 (major, s, 1H), 7.31 (minor, s, 1H).
LRMS (thermospray): m/z [MH^+] 300.

EXAMPLE 135

tert-Butyl 2-[4-(3,5-dichlorophenoxy)-3-ethyl-5-(hydroxymethyl)-1*H*-pyrazol-1-yl]ethylcarbamate



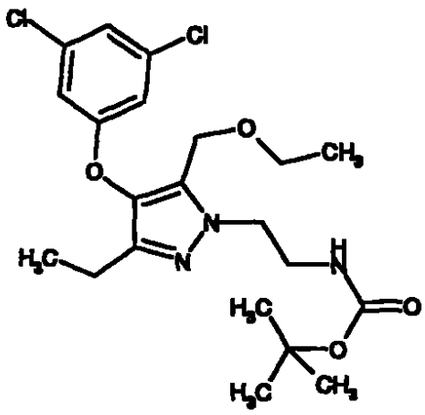
A solution of the pyrazole of Example 97 (1.98g, 6.00mmol) in concentrated hydrochloric acid (50ml) was heated under reflux for 20 hours. The reaction was cooled to room temperature and concentrated under reduced pressure. The residue was dissolved in dioxane (80ml) and water (60ml), di-t-butyldicarbonate (1.44g, 6.60mmol) and sodium hydrogencarbonate (1.26g, 15.0mmol) were added and the

reaction was stirred at room temperature for 3 days. The reaction was concentrated under reduced pressure. A solution of the residue in dichloromethane (300ml) was washed with 2M aqueous hydrochloric acid (100ml), dried over magnesium sulphate, filtered and concentrated under reduced pressure. A solution of the crude product in tetrahydrofuran (50ml) was cooled to -40°C under nitrogen and triethylamine (0.79ml, 5.68mmol) and isopropylchloroformate (5.68ml of a 1.0M solution in toluene, 5.68mmol) were added dropwise. The reaction was stirred at -40°C for 40 minutes and then warmed to 0°C. Sodium borohydride (537mg, 14.2mmol) was added in one portion and then water (3 drops) was added and the reaction was stirred at 0°C for 1 hour and at room temperature for 14 hours. The mixture was concentrated under reduced pressure and a solution of the residue in dichloromethane (100ml) was washed with water (100ml), dried over magnesium sulphate, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with dichloromethane:methanol (97:3, by volume) to provide the title compound (1.37g) as a white foam.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.10 (t, 3H), 1.37 (s, 9H), 2.40 (q, 2H), 3.00 (s, 1H), 3.56 (m, 2H), 4.20 (t, 2H), 4.48 (d, 2H), 5.00 (m, 1H), 6.80 (s, 2H), 6.97 (s, 1H).
LRMS (thermospray): m/z [MH^+] 430.

EXAMPLE 136

tert-Butyl 2-[4-(3,5-dichlorophenoxy)-5-(ethoxymethyl)-3-ethyl-1*H*-pyrazol-1-yl]ethylcarbamate



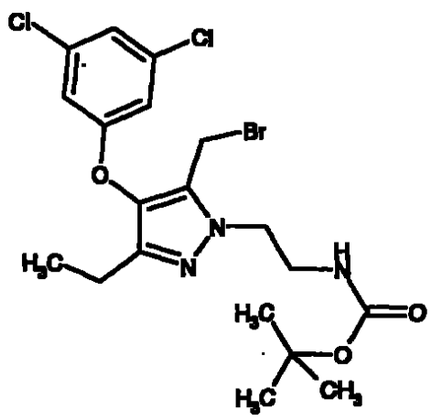
Silver(I)oxide (210mg, 0.900mmol) was added in one portion to a stirred solution of the alcohol of Example 135 (129mg, 0.300mmol) in ethyl iodide (1.75ml) at room

temperature under nitrogen. The reaction was heated at 40°C for 1 day and then cooled to room temperature. The mixture was filtered and the residual solid was washed with dichloromethane (10ml). The filtrate was concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with dichloromethane:methanol (99:1, by volume) to provide the title compound (60mg) as a colourless oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.15 (m, 6H), 1.44 (s, 9H), 2.45 (q, 2H), 3.45 (q, 2H), 3.58 (m, 2H), 4.18 (m, 2H), 4.29 (s, 2H), 5.26 (m, 1H), 6.92 (s, 2H), 7.00 (s, 1H).
LRMS (electrospray): m/z [MNa^+] 480.

EXAMPLE 137

tert-Butyl 2-[5-(bromomethyl)-4-(3,5-dichlorophenoxy)-3-ethyl-1*H*-pyrazol-1-yl]ethylcarbamate

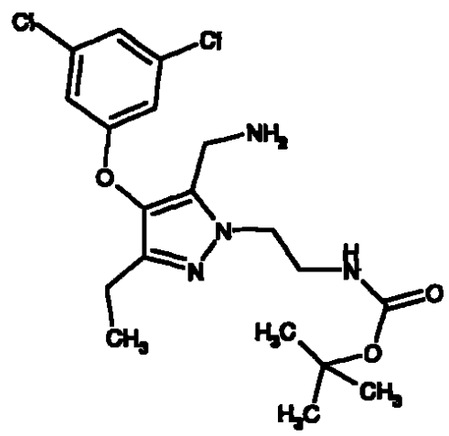


Bromine (160µl, 3.12mmol) was added dropwise to a stirred solution of triphenylphosphine (820mg, 3.12mmol) and imidazole (213mg, 3.12mmol) in dichloromethane (15ml) at room temperature under nitrogen. A solution of the alcohol of Example 135 (1.12g, 2.60mmol) in dichloromethane (5ml) was then added to the reaction. The reaction was stirred at room temperature for 2 hours, diluted with dichloromethane (50ml), washed with brine (20ml), dried over magnesium sulphate, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with dichloromethane:methanol (98:2, by volume) to provide the title compound (969mg) as a white foam.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.10 (t, 3H), 1.40 (s, 9H), 2.40 (q, 2H), 3.60 (m, 2H), 4.18 (t, 2H), 4.27 (s, 2H), 4.95 (s, 1H), 6.82 (s, 2H), 7.00 (s, 1H).
LRMS (electrospray): m/z [MH^+] 494.
Microanalysis: Found: C, 46.22; H, 4.89; N, 8.44. $C_{19}H_{24}BrCl_2N_3O_3$ requires C, 46.27; H, 4.90; N, 8.52%.

EXAMPLE 138

tert-Butyl 2-[5-(aminomethyl)-4-(3,5-dichlorophenoxy)-3-ethyl-1*H*-pyrazol-1-yl]ethylcarbamate

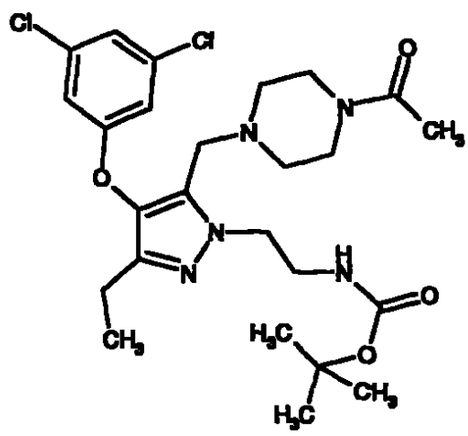


The bromide of Example 137 (444mg, 0.900mmol) was added to a saturated solution of ammonia in isopropanol (25ml) and diisopropylethylamine (173µl, 1.00mmol) at room temperature. The reaction was stirred for 5 hours and then concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with dichloromethane:methanol (95:5, by volume) to provide the title compound (359mg) as a white solid, m.p. 112-114°C.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.11 (t, 3H), 1.40 (s, 9H), 2.40 (q, 2H), 3.55 (m, 2H), 3.73 (s, 2H), 4.18 (t, 2H), 5.60 (s, 1H), 6.77 (s, 2H), 6.98 (s, 1H).
LRMS (thermospray): m/z [MH^+] 429.

EXAMPLE 139

tert-Butyl 2-[5-[(4-acetyl-1-piperazinyl)methyl]-4-(3,5-dichlorophenoxy)-3-ethyl-1*H*-pyrazol-1-yl]ethylcarbamate

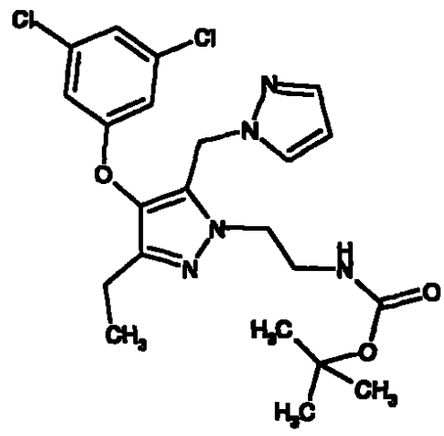


N-Acetylpiperazine (42mg, 0.330mmol) in *N,N*-dimethylformamide (1ml) was added to a stirred solution of the bromide of Example 137 (148mg, 0.300mmol) and diisopropylethylamine (57µL, 0.330mmol) in *N,N*-dimethylformamide (2ml) at room temperature. The reaction was stirred for 5 hours and the mixture was concentrated under reduced pressure. A solution of the residue in dichloromethane (30ml) was washed with 1M aqueous potassium carbonate solution (10ml), dried over magnesium sulphate, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with dichloromethane:methanol (98:2, by volume) to provide the title compound (150mg) as a colourless oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.15 (t, 3H), 1.42 (s, 9H), 2.06 (s, 3H), 2.44 (m, 6H), 3.32 (s, 2H), 3.47 (m, 2H), 3.60 (m, 2H), 3.65 (m, 2H), 4.23 (m, 2H), 5.89 (s, 1H), 6.76 (s, 2H), 7.02 (s, 1H).
LRMS (thermospray): m/z [MH^+] 540.

EXAMPLE 140

tert-Butyl 2-[4-(3,5-dichlorophenoxy)-3-ethyl-5-(1*H*-pyrazol-1-ylmethyl)-1*H*-pyrazol-1-yl]ethylcarbamate

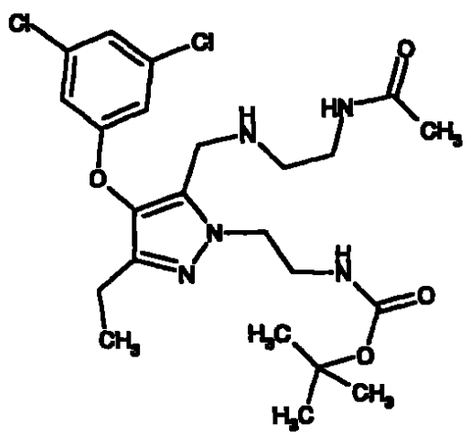


Pyrazole (23mg, 0.330mmol) was added in one portion to a stirred solution of the bromide of Example 137 (148mg, 0.300mmol) and sodium hydride (60% dispersion in oil, 13.2mg, 0.330mmol) in *N,N*-dimethylformamide (2ml) at room temperature under nitrogen. The reaction was stirred for 5 hours, quenched with water (1.00ml) and concentrated under reduced pressure. The residue was dissolved in dichloromethane (30ml) and the resulting solution was washed with 1M aqueous potassium carbonate solution (10ml), dried over magnesium sulphate, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with dichloromethane:methanol (98:2, by volume) to provide the title compound (125mg) as a colourless oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.13 (t, 3H), 1.44 (s, 9H), 2.42 (q, 2H), 3.52 (m, 2H), 4.26 (t, 2H), 5.18 (s, 2H), 5.48 (s, 1H), 6.16 (s, 1H), 6.73 (s, 2H), 7.00 (s, 1H), 7.18 (s, 1H), 7.45 (s, 1H).
LRMS (thermospray): m/z [MH^+] 480.

EXAMPLE 141

tert-Butyl 2-[5-({[2-(acetylamino)ethyl]amino}methyl)-4-(3,5-dichlorophenoxy)-3-ethyl-1*H*-pyrazol-1-yl]ethylcarbamate

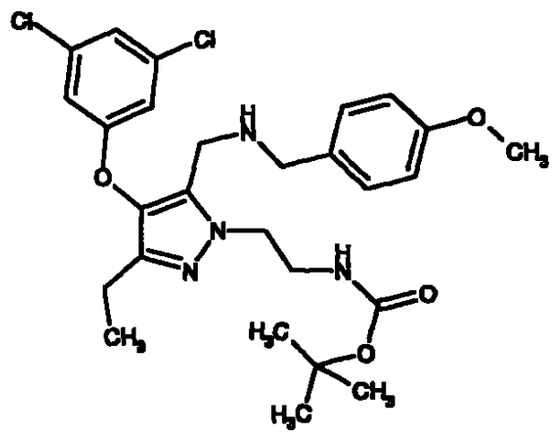


N-Acetylethylenediamine (153mg, 1.50mmol) in isopropanol (1ml) was added to a stirred solution of the bromide of Example 137 (148mg, 0.300mmol) and diisopropylethylamine (57µl, 0.330mmol) in isopropanol (2ml) at room temperature. The reaction was stirred for 5 hours and the mixture was concentrated under reduced pressure. A solution of the residue in dichloromethane (50ml) was washed with 1M aqueous potassium carbonate solution (20ml), dried over magnesium sulphate, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with dichloromethane:methanol (90:10, by volume) then dichloromethane:methanol:ammonia (90:9:1, by volume) to provide the title compound (122mg) as a colourless oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.13 (t, 3H), 1.42 (s, 9H), 1.94 (d, 3H), 2.44 (q, 2H), 2.74 (m, 2H), 3.35 (m, 2H), 3.58 (m, 4H), 4.19 (m, 2H), 5.68 (s, 1H), 6.77 (s, 2H), 7.00 (s, 1H), 7.65 (s, 1H).
LRMS (thermospray): m/z [MH^+] 514.

EXAMPLE 142

tert-Butyl 2-(4-(3,5-dichlorophenoxy)-3-ethyl-5-[[(4-methoxybenzyl)amino]methyl]-1*H*-pyrazol-1-yl)ethylcarbamate



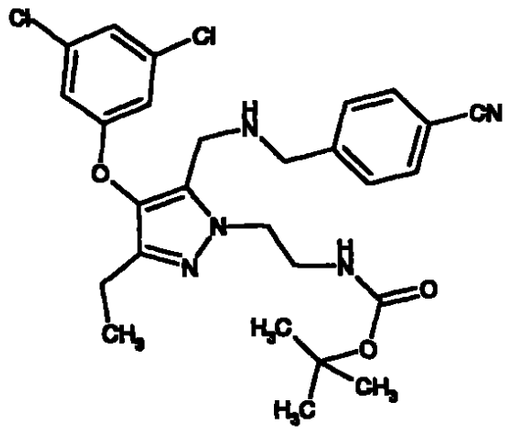
4-Methoxybenzaldehyde (46µl, 0.380mmol), the amine of Example 138 (172mg, 0.400mmol) and magnesium sulphate (200mg) were stirred in dichloromethane (4ml) at room temperature for 4 days. The mixture was filtered and the filtrate was concentrated under reduced pressure to leave a yellow oil. The oil was dissolved in methanol (4ml) and sodium borohydride (18mg, 0.480mmol) was added with vigorous stirring. Once the addition was complete the reaction was stirred for 4 hours and then water (2ml) was added. The mixture was concentrated under reduced pressure and the residue was dissolved in dichloromethane (50ml). The resulting solution was washed with 1M aqueous potassium carbonate solution (20ml), dried over magnesium sulphate, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with dichloromethane:methanol (99:1, by volume) and then dichloromethane:methanol (95:5, by volume) to provide the title compound (142mg) as a colourless oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.10 (t, 3H), 1.40 (s, 9H), 2.42 (m, 2H), 3.55 (m, 5H), 3.66 (s, 2H), 3.77 (s, 2H), 4.15 (m, 2H), 6.11 (s, 1H), 6.74 (s, 2H), 6.80 (d, 2H), 7.00 (s, 1H), 7.11 (d, 2H).

LRMS (thermospray): m/z [MH^+] 549.

EXAMPLE 143

tert-Butyl 2-[5-[[(4-cyanobenzyl)amino]methyl]-4-(3,5-dichlorophenoxy)-3-ethyl-1*H*-pyrazol-1-yl]ethylcarbamate



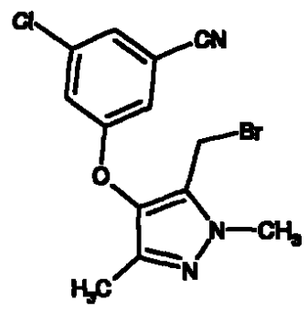
A mixture of 4-cyanobenzaldehyde (50mg, 0.380mmol), the amine of Example 138 (172mg, 0.400mmol), magnesium sulphate (200mg) and dichloromethane (4ml) was stirred at room temperature for 4 days. The mixture was filtered and the filtrate was concentrated under reduced pressure to leave a yellow oil. The oil was dissolved in methanol (4ml) and sodium borohydride (18mg, 0.480mmol) was added with vigorous stirring. Once the addition was complete the reaction was stirred for 4 hours and then water (2ml) was added. The mixture was concentrated under reduced pressure and the residue was dissolved in dichloromethane (50ml). The resulting solution was washed with 1M aqueous potassium carbonate solution (20ml), dried over magnesium sulphate, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with dichloromethane:methanol (99:1, by volume) then dichloromethane:methanol (95:5, by volume) to provide the title compound (120mg) as a colourless oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.10 (t, 3H), 1.35 (s, 9H), 2.40 (q, 2H), 3.55 (m, 2H), 3.58 (s, 2H), 3.76 (s, 2H), 4.16 (m, 2H), 5.45 (s, 1H), 6.73 (s, 2H), 6.98 (s, 1H), 7.32 (d, 2H), 7.55 (d, 2H).

LRMS (thermospray): m/z [MH^+] 544.

EXAMPLE 144

3-[[5-(Bromomethyl)-1,3-dimethyl-1*H*-pyrazol-4-yl]oxy]-5-chlorobenzonitrile

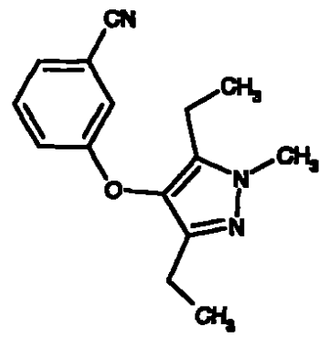


N-Bromosuccinimide (340mg, 1.90mmol) was added to a stirred solution of the pyrazole of Example 112 (500mg, 1.90mmol) in carbon tetrachloride (10ml) and azobisisobutyronitrile (20mg) at room temperature under nitrogen. The reaction was heated under reflux for 1 hour, cooled to room temperature and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel eluting with pentane:ethyl acetate (80:20, by volume) to provide the title compound (340mg) as a white solid, m.p. 76-78°C.

^{1}H-NMR (300MHz, $CDCl_3$): δ = 2.03 (s, 3H), 3.45 (s, 3H), 4.32 (s, 2H), 7.12 (s, 1H), 7.19 (s, 1H), 7.34 (s, 1H).
LRMS (thermospray): m/z [MH^+] 342.

EXAMPLE 145

3-[(3,5-Diethyl-1-methyl-1*H*-pyrazol-4-yl)oxy]benzonitrile

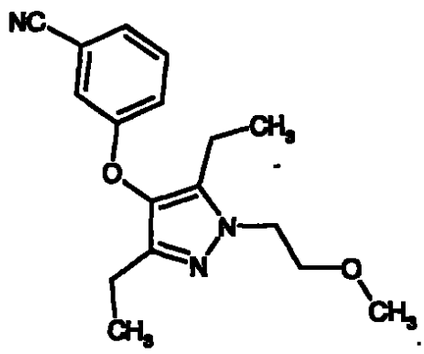


Sodium hydride (60% dispersion in oil, 22mg, 0.53mmol) was added to a solution of the pyrazole from Example 60 (100mg, 0.41mmol) and methyl iodide (34µl, 0.53mmol) in dimethylformamide (1.5ml) at 0°C under nitrogen. The reaction was allowed to warm to room temperature and was stirred for 4 hours. The reaction was quenched with water and the solvent was removed under reduced pressure. The residue was partitioned between ethyl acetate (20ml) and water (10ml) and the organic phase was washed with water (2x10ml), dried over magnesium sulphate and concentrated under reduced pressure. The residual oil was purified by flash chromatography on silica gel eluting with a solvent gradient of 100% pentane changing to 100% ethyl acetate and finally ethyl acetate:methanol (10:1, by volume) to provide the title compound (65mg) as a colourless oil.

^{1}H NMR (400MHz, $CDCl_3$): δ = 1.09 (t, 3H), 1.12 (t, 3H), 2.41 (q, 2H), 2.50 (q, 2H), 3.77 (s, 3H), 7.12-7.38 (m, 4H).
LRMS (electrospray) : m/z [MH^+] 256, [MNa^+] 278.
Microanalysis: Found C, 70.15; H, 6.78; N, 16.42. $C_{15}H_{15}N_3O.0.08H_2O$ requires C, 70.17; H, 6.74; N, 16.37%.

EXAMPLE 146

3-[[3,5-Diethyl-1-(2-methoxyethyl)-1*H*-pyrazol-4-yl]oxy]benzonitrile



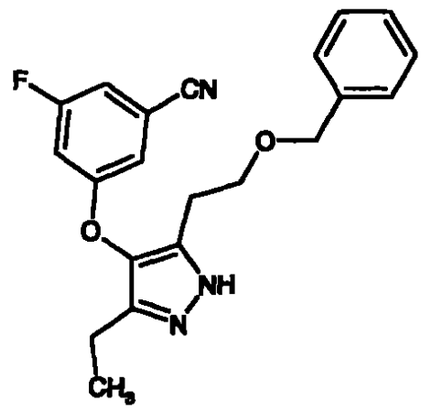
Sodium hydride (60% dispersion in oil, 22mg, 0.54mmol) was added to a solution of the pyrazole from Example 60 (100mg, 0.41mmol) and 1-bromo-2-methoxy-ethane (51µl, 0.54mmol) in dimethylformamide (1.5ml) at 0°C under nitrogen. The reaction was allowed to warm to room temperature and was stirred for 4 hours. The reaction was quenched with water and the solvent was removed under reduced pressure. The residue was partitioned between ethyl acetate (20ml) and water (10ml) and the

organic phase was washed with water (2x10ml), dried over magnesium sulphate and concentrated under reduced pressure. The residual oil was purified by flash chromatography on silica gel eluting with a solvent gradient of 100% pentane changing to 100% ethyl acetate and finally ethyl acetate:methanol (90:10, by volume) to provide the title compound (66mg) as a colourless oil.

^{1}H NMR (400MHz, $CDCl_3$): δ = 1.09 (t, 3H), 1.12 (t, 3H), 2.42 (q, 2H), 2.54 (q, 2H), 3.34 (s, 3H), 3.75 (t, 2H), 4.16 (t, 2H), 7.11-7.38 (m, 4H).
LRMS (electrospray) : m/z [MH^+] 300, [MNa^+] 322.
Microanalysis: Found C, 68.21; H, 7.07; N, 14.04. $C_{17}H_{21}N_3O_2$ requires C, 67.85; H, 7.12; N, 14.09%.

EXAMPLE 147

3-({5-[2-(Benzyloxy)ethyl]-3-ethyl-1*H*-pyrazol-4-yl}oxy)-5-fluorobenzonitrile



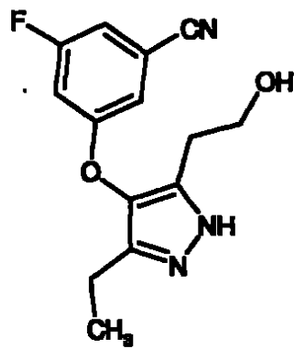
Hydrazine hydrate (390µl, 8.00mmol) was added to a solution of the enol from Preparation 60 (2.47g, 6.69mmol) in acetic acid (5ml) under nitrogen at room temperature. After stirring for 18 hours, the mixture was concentrated under reduced pressure and purified by flash chromatography on silica gel eluting with pentane:ethyl acetate (70:30 changing to 50:50, by volume) to provide the title compound (5.8g) as a yellow oil.

^{1}H NMR (400MHz, $CDCl_3$): δ = 1.13 (t, 3H), 2.41 (q, 2H), 2.67 (t, 2H), 3.62 (t, 2H), 4.48 (s, 2H), 6.79 (m, 1H), 6.98 (m, 2H), 7.24 (m, 5H).
LRMS (electrospray) : m/z [$M-H^+$] 364.

Microanalysis: Found C, 66.96; H, 5.62; N, 11.25. $C_{21}H_{20}N_3O_2F.0.60H_2O$ requires C, 67.04; H, 5.68; N, 11.17%.

EXAMPLE 148

3-[[3-Ethyl-5-(2-hydroxyethyl)-1*H*-pyrazol-4-yl]oxy]-5-fluorobenzonitrile

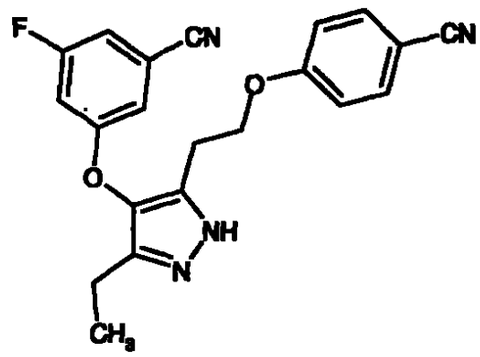


Iron(III)chloride (9.30g, 57.5mmol) was added to a solution of the pyrazole from Example 147 (2.10g, 5.75mmol) in dichloromethane (90ml) under nitrogen at room temperature. After stirring for 20 minutes the mixture was diluted with dichloromethane (50ml), washed with water (100ml) then saturated aqueous sodium ethylenediaminetetraacetate solution (70ml), dried over magnesium sulphate and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with dichloromethane:methanol (98:2 changing to 95:5, by volume) to provide the title compound (1.2g) as a brown oil which solidified on standing.

^{1}H NMR (400MHz, $CDCl_3$): δ = 1.16 (t, 3H), 2.44 (q, 2H), 2.63 (t, 2H), 3.82 (t, 2H), 6.82 (m, 1H), 6.98 (m, 2H).
LRMS (electrospray) : m/z [MH^+] 276.
Microanalysis: Found C, 60.69; H, 5.12; N, 15.08. $C_{14}H_{14}N_3O_2F$ requires C, 61.08; H, 5.13; N, 15.26%.

EXAMPLE 149

3-({5-[2-(4-Cyanophenoxy)ethyl]-3-ethyl-1*H*-pyrazol-4-yl}oxy)-5-fluorobenzonitrile

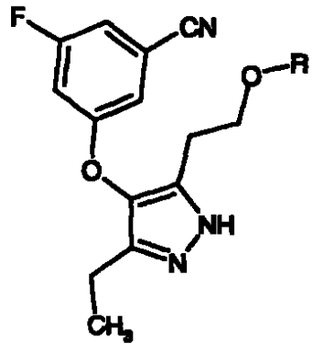


4-Hydroxy-benzonitrile (49mg, 0.41mmol), triphenylphosphine (106mg, 0.41mmol) and diethylazodicarboxylate (65µl, 0.41mmol) were added sequentially to a solution of the alcohol from Example 148 (74mg, 0.27mmol) in tetrahydrofuran (2ml) under nitrogen at 0°C. The reaction was allowed to warm to room temperature and was stirred for 18 hours. The mixture was concentrated under reduced pressure and purified by flash chromatography on silica gel eluting with toluene:ethyl acetate (75:25, by volume) to provide the title compound (50mg) as a yellow oil.

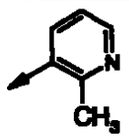
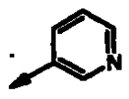
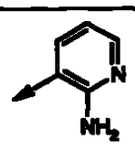
^{1}H NMR (400MHz, $CDCl_3$): δ = 1.18 (t, 3H), 2.49 (q, 2H), 2.98 (t, 2H), 4.21 (t, 2H), 6.82 (m, 3H), 6.99 (m, 2H), 7.56 (m, 2H).
LRMS (electrospray) : m/z [MH^+] 377.

EXAMPLES 150-152

The preparations of the following tabulated Examples of the general formula



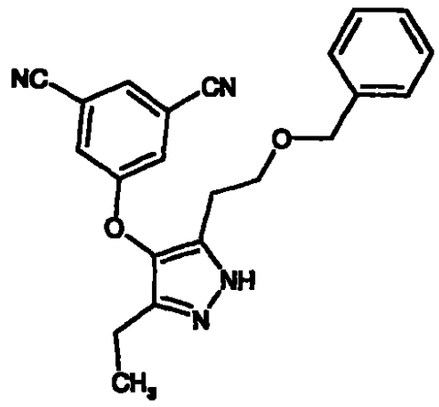
were performed by a similar method to that of Example 149 using the appropriate aryl alcohol as the starting material.

Example No.	Starting Material Example No.	R	Analytical Data
150[1]	148[sic]		^{1}H NMR (400MHz, $CDCl_3$): δ = 1.18 (t, 3H), 2.42 (s, 3H), 2.52 (q, 2H), 2.99 (t, 2H), 4.18 (t, 2H), 6.83 (m, 1H), 6.99 (m, 4H), 8.04 (m, 1H). LRMS (thermospray) : m/z [MH^+] 367.
151[1]	148		^{1}H NMR (400MHz, $CDCl_3$): δ = 1.19 (t, 3H), 2.50 (q, 2H), 2.98 (t, 2H), 4.22 (t, 2H), 6.85 (m, 1H), 6.99 (m, 2H), 7.12 (m, 1H), 7.18 (m, 1H), 8.22 (m, 2H). LRMS (thermospray) : m/z [MH^+] 353.
152[1]	148		^{1}H NMR (400MHz, $CDCl_3$): δ = 1.20 (t, 3H), 2.53 (q, 2H), 2.98 (t, 2H), 4.19 (t, 2H), 4.85 (brs, 2H), 6.58 (m, 1H), 6.83 (m, 2H), 6.99 (m, 2H), 7.63 (d, 1H). LRMS (thermospray) : m/z [MH^+] 368.

[1] These compounds were purified on silica gel eluting with a solvent gradient of cyclohexane:ethyl acetate (75:25 then 66:34 then 50:50, by volume) changing to ethyl acetate and finally ethyl acetate:methanol (90:10, by volume).

EXAMPLE 153

5-({5-[2-(benzyloxy)ethyl]-3-ethyl-1*H*-pyrazol-4-yl}oxy)isophthalonitrile

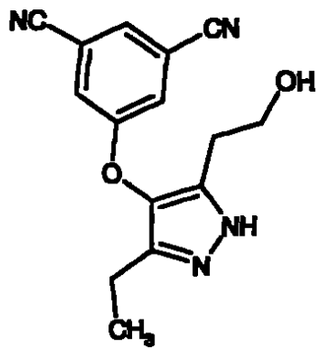


Hydrazine hydrate (177µl, 3.66mmol) was added to a solution of the crude enol from Preparation 61 (917mg, 2.40mmol) in acetic acid (10ml) under nitrogen at room temperature. After stirring for 18 hours, the mixture was concentrated under reduced pressure and purified by flash chromatography on silica gel eluting with pentane:cyclohexane (75:25, by volume) changing to toluene:ethyl acetate (50:50, by volume) to give the product which was further purified by preparative HPLC using a Develosil combi-rp C30 50x4.6mm 3µm column eluting with a solvent gradient of 5:95 0.1% aqueous trifluoroacetic acid in water:acetonitrile to provide the title compound (5mg) as a colourless oil.

^{1}H NMR (400MHz, $CDCl_3$): δ = 1.18 (t, 3H), 2.44 (q, 2H), 2.77 (t, 2H), 3.63 (t, 2H), 4.52 (s, 2H), 7.30 (m, 7H), 7.55 (s, 1H).
LRMS (electrospray) : m/z [MH^+] 231, [MNa^+] 253.

EXAMPLE 154

5-[3-Ethyl-5-(2-hydroxyethyl)-1*H*-pyrazol-4-yloxy]isophthalonitrile

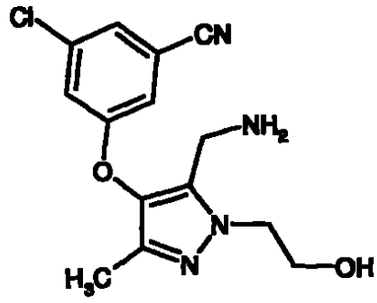


Iron(III)Chloride (217mg, 1.30mmol) was added to a solution of the pyrazole from Example 153 (50mg, 0.13mmol) in dichloromethane (5ml) under nitrogen at room temperature. After stirring for 30 minutes the mixture was diluted with dichloromethane (20ml), washed with water (100ml) then saturated aqueous sodium ethylenediaminetetraacetate solution (20ml), dried over magnesium sulphate and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with dichloromethane:methanol (98:2 changing to 95:5, by volume) to provide the title compound (20mg) as a white solid.

^{1}H NMR (400MHz, $CDCl_3$): δ = 1.19 (t, 3H), 2.51 (q, 2H), 2.69 (t, 2H), 3.88 (t, 2H), 7.40 (s, 2H), 7.59 (s, 1H).
LRMS (electrospray) : m/z [MH^+] 283.

EXAMPLE 155

3-[5-(Aminomethyl)-1-(2-hydroxyethyl)-3-methyl-1*H*-pyrazol-4-yloxy]-5-chlorobenzonitrile

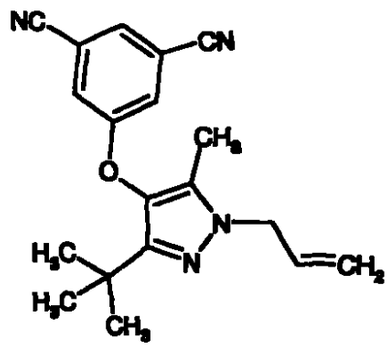


The protected alcohol from Preparation 31 (100mg, 0.23mmol) and tert-butyl-ammonium fluoride (360µl of a 1M solution in tetrahydrofuran, 0.36mmol) were stirred in dichloromethane (5ml) at room temperature under nitrogen for 3 hours. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in methanol (2ml) and purified on a BondElut® SCX polymer supported sulphonic acid column washing with methanol (2x3ml) to remove impurities and 2N aqueous ammonia to remove the product. This procedure was repeated twice to provide the title compound (40mg) as a colourless oil.

^{1}H NMR (400MHz, CD_3OD): δ = 1.99 (s, 3H), 3.85 (t, 2H), 4.02 (s, 2H), 4.32 (t, 2H), 7.22 (s, 1H), 7.28 (s, 1H), 7.47 (s, 1H).
LRMS (thermospray) : m/z [MH^+] 309.
Microanalysis: Found C, 53.32; H, 5.17; N, 16.38. $C_{14}H_{15}ClN_4O_2.0.85CH_3OH$ requires C, 53.40; H, 5.55; N, 16.77%.

EXAMPLE 158

5-[(1-Allyl-3-*tert*-butyl-5-methyl-1*H*-pyrazol-4-yl)oxy]isophthalonitrile



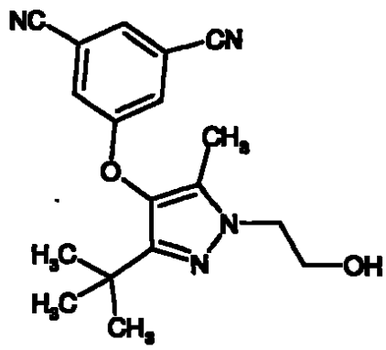
Sodium hydride (60% dispersion in oil, 120mg, 3.15mmol) was added to a solution of the pyrazole from Example 130 (800mg, 2.80mmol) and allyl bromide (345mg, 2.80mmol) in dimethylformamide (30ml) at room temperature under nitrogen and the reaction was stirred for 3 hours. The reaction was diluted with ethyl acetate (50ml), washed with water (2x50ml) then brine (50ml) and the organic phase was concentrated under reduced preasure. The residual oil was purified by flash chromatography on silica gel eluting with a solvent gradient of pentane changing to

ethyl acetate:pentane (20:80, by volume) to provide the title compound (600mg) as a colourless oil.

^{1}H NMR (400MHz, $CDCl_3$): δ = 1.21 (s, 9H), 1.96 (s, 3H), 4.66 (s, 2H), 5.04 (d, 1H), 5.24 (d, 1H), 5.98 (m, 1H), 7.37 (s, 2H), 7.57 (s, 1H).
LRMS (thermospray) : m/z [MH^+] 322.
Microanalysis: Found C, 70.79; H, 6.29; N, 17.11. $C_{18}H_{20}N_4O.0.05CH_2Cl_2$ requires C, 70.48; H, 6.24; N, 17.26%.

EXAMPLE 157

5-[[3-*tert*-Butyl-1-(2-hydroxyethyl)-5-methyl-1*H*-pyrazol-4-yl]oxy]isophthalonitrile



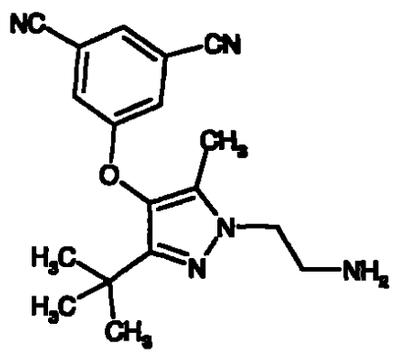
Sodium periodate (1.00g, 4.60mmol), osmium tetroxide (1.5% solution in tert-butanol, 190mg, 0.02mmol) and the pyrazole from Example 156 (600mg, 1.86mmol) were dissolved in acetone (9ml) and water (3ml) under nitrogen at room temperature, and the reaction was stirred for 5 hours. The acetone was removed under reduced pressure and the residue was extracted with ethyl acetate (30ml). The organic phase was washed with water (2x30ml) then brine (30ml), dried over magnesium sulphate and concentrated under reduced pressure. The crude aldehyde was then dissolved in methanol (15ml) and sodium borohydride (84mg, 2.22mmol) was added portionwise at room temperature under nitrogen. The reaction was stirred for 3 hours and the solvent was removed under reduced pressure. The residue was partitioned between ethyl acetate (10ml) and water (10ml) and the organic phase was washed with water (2x10ml) then brine (10ml), dried over magnesium sulphate and concentrated under reduced pressure. The residual oil was purified by flash chromatography on silica gel eluting with a solvent

gradient of pentane changing to ethyl acetate:pentane (50:50, by volume) to provide the title compound (250mg) as a colourless oil.

^{1}H NMR (400MHz, $CDCl_3$): δ = 1.17 (s, 9H), 1.98 (s, 3H), 3.67 (s, 1H), 4.04 (m, 4H), 7.35 (s, 2H), 7.54 (s, 1H).
LRMS (thermospray) : m/z [MH^+] 325.
Microanalysis: Found C, 64.30; H, 6.10; N, 16.35. $C_{18}H_{20}N_4O_2.0.20CH_2Cl_2$ requires C, 64.04; H, 6.02; N, 16.41%.

EXAMPLE 158

5-{[1-(2-Aminoethyl)-3-*tert*-butyl-5-methyl-1*H*-pyrazol-4-yl]oxy}isophthalonitrile



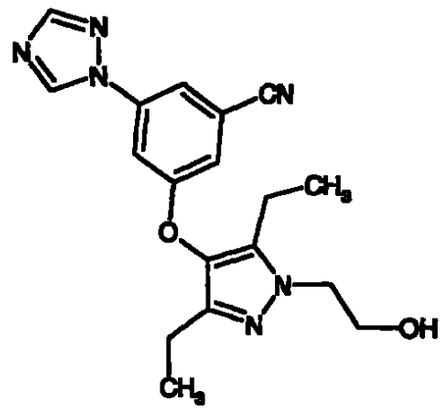
Diphenylphosphorylazide (305mg, 1.10mmol) was dissolved in tetrahydrofuran (5ml) and added to a solution of the pyrazole from Example 157 (180mg, 0.55mmol), triphenylphosphine (291mg, 1.10mmol) and diethylazodicarboxylate (193mg, 1.10mmol) in tetrahydrofuran (20ml) under nitrogen at room temperature. The reaction was stirred for 18 hours then triphenylphosphine (291mg, 1.10mmol) was added, and the reaction was stirred for a further 18 hours. Water (180µl, 10.0mmol) was then added and the reaction was stirred for 64 hours. The solvent was removed under reduced pressure and the residual white paste was purified by flash chromatography on silica gel eluting with dichloromethane:methanol:0.88 ammonia (95:4.5:0.5, by volume) to provide the title compound (55mg) as a colourless oil.

^{1}H NMR (300MHz, $CDCl_3$): δ = 1.22 (s, 9H), 1.78 (s, 2H), 2.03 (s, 3H), 3.18 (t, 2H), 4.05 (m, 2H), 7.38 (s, 2H), 7.58 (s, 1H).
LRMS (thermospray) : m/z [MH^+] 324.

Microanalysis: Found C, 64.46; H, 6.48; N, 20.47. $C_{18}H_{21}N_5O.0.20CH_2Cl_2$ requires C, 64.22; H, 6.34; N, 20.57%.

EXAMPLE 159

3-[3,5-Diethyl-1-(2-hydroxyethyl)-1*H*-pyrazol-4-yloxy]-5-(1*H*-1,2,4-triazol-1-yl)benzonitrile



Cesium carbonate (179mg, 0.55mmol) was added to a solution of 1H[1,2,4]triazole (38mg, 0.55mmol) in dimethylsulfoxide (1ml) under nitrogen at room temperature and the reaction was stirred for 10 minutes. The aryl fluoride from Preparation 62 (210mg, 0.5mmol) dissolved in dimethylsulfoxide (1ml) was then added and the reaction was heated to 100°C for 18 hours. After cooling to room temperature the reaction was diluted with water (15ml) and extracted with ethyl acetate (25ml). The organic phase was washed with brine (15ml), dried over magnesium sulphate, concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel eluting with a solvent gradient of dichloromethane:methanol (98:2 changing to 90:10, by volume) to provide the title compound (67.5mg) as a white solid, m.p. 122-124°C.

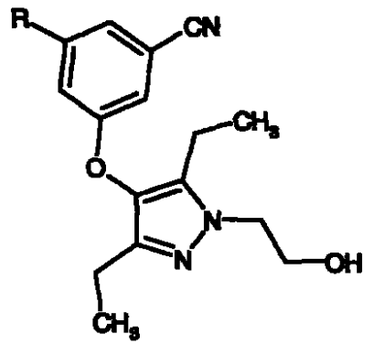
^{1}H NMR (400MHz, $CDCl_3$): δ = 1.10 (m, 6H), 2.39 (q, 2H), 2.51 (q, 2H), 3.61 (brs, 1H), 4.04 (m, 2H), 4.07 (m, 2H), 7.10 (s, 1H), 7.52 (s, 1H), 7.60 (s, 1H), 8.07 (s, 1H), 8.54 (s, 1H).

LRMS (thermospray) : m/z [MH^+] 353.

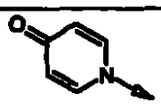
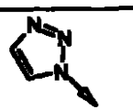
Microanalysis: Found C, 60.69; H, 5.83; N, 22.98. $C_{18}H_{20}N_5O_2.0.08CH_2Cl_2$ requires C, 60.46; H, 5.66; N, 23.40%.

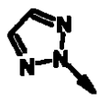
EXAMPLES 160-162

The preparation of the following tabulated Examples of the general formula



were performed by a similar method to that of Example 159 using the appropriate heterocycle as the starting material.

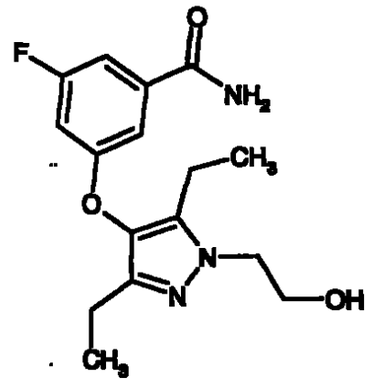
Example No. (Starting Material Preparation No)	R	Analytical Data
160 (62)		^{1}H NMR (400MHz, $CDCl_3$): δ = 1.10 (m, 6H), 2.39 (q, 2H), 2.52 (q, 2H), 3.62 (brs, 1H), 4.02 (t, 2H), 4.08 (t, 2H), 6.44 (d, 2H), 7.14 (s, 1H), 7.16 (s, 1H), 7.25 (s, 1H), 7.49 (d, 2H). m.p. 169-170°C. LRMS (thermospray) : m/z [MH^+] 379. Microanalysis: Found C, 65.68; H, 5.98; N, 14.31. $C_{21}H_{22}N_4O_3.0.09CH_2Cl_2$ requires C, 65.61; H, 5.79; N, 14.51%.
161[1] (62)		^{1}H NMR (400MHz, $CDCl_3$): δ = 1.10 (m, 6H), 2.40 (q, 2H), 2.51 (q, 2H), 3.56 (t, 1H), 4.04 (m, 2H), 4.07 (m, 2H), 7.20 (s, 1H), 7.65 (s, 2H), 7.85 (s, 1H), 7.98 (s, 1H). LRMS (thermospray) : m/z [MH^+] 353. HRMS: [MH^+] 353.1722. $C_{18}H_{20}N_6O_2$ requires 353.1720.

162[1] (62)		^{1}H NMR (400MHz, $CDCl_3$): δ = 1.10 (m, 6H), 2.41 (q, 2H), 2.51 (q, 2H), 3.62 (t, 1H), 4.04 (m, 2H), 4.07 (m, 2H), 7.08 (s, 1H), 7.80 (s, 2H), 7.87 (s, 1H), 8.02 (s, 1H). LRMS (thermospray) : m/z [MH^+] 353. HRMS: [MH^+] 353.1719. $C_{18}H_{20}N_6O_2$ requires 353.1720.

[1] Both of these compounds were isolated from a single reaction starting from 1,2,3-triazole with Example 161 being the most polar.

EXAMPLE 163

3-[(3,5-Diethyl-1-(2-hydroxyethyl)-1*H*-pyrazol-4-yl)oxy]-5-fluorobenzamide



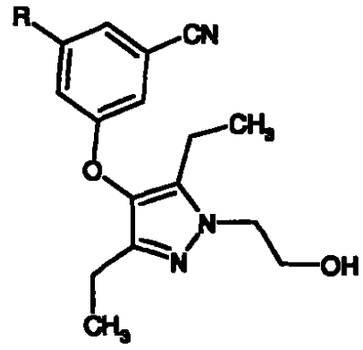
The protected alcohol from Preparation 64 (432mg, 1.07mmol) and p-toluene-sulphonic acid (30.3mg, 0.11mmol) were dissolved in methanol (4ml) and stirred under nitrogen at room temperature for 18 hours. The solvent was removed under reduced pressure and the residue was partitioned between saturated aqueous sodium bicarbonate solution (20ml) and dichloromethane (20ml). The aqueous phase was extracted with dichloromethane (10ml) and the combined organic extracts were dried over magnesium sulphate, concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel eluting with a solvent gradient of dichloromethane:methanol (100:0 changing to 93:7, by volume) to provide the title compound (241mg) as a white foam.

^{1}H NMR (400MHz, $CDCl_3$): δ = 1.10 (m, 6H), 2.39 (q, 2H), 2.49 (q, 2H), 3.68 (brs, 1H), 4.04 (m, 4H), 5.59 (brs, 1H), 5.88 (brs, 1H), 6.71 (d, 1H), 7.11 (m, 2H).
LRMS (thermospray) : m/z [MH^+] 322.

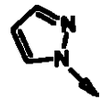
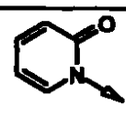
Microanalysis: Found C, 57.91; H, 6.32; N, 12.56. $C_{16}H_{20}FN_3O_3.0.13CH_2Cl_2.0.12H_2O$ requires C, 57.91; H, 6.18; N, 12.56%.

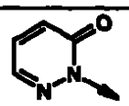
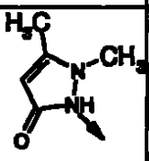
EXAMPLES 164-167

The preparation of the following tabulated Examples of the general formula



were performed by a similar method to that of Example 163 using the appropriate protected alcohol as the starting material.

Example No. (Starting Material Preparation No.)	R	Analytical Data
164[1] (65)		^{1}H NMR (400MHz, $CDCl_3$): δ = 1.13 (m, 6H), 2.44 (q, 2H), 2.54 (q, 2H), 3.65 (brs, 1H), 4.07 (t, 2H), 4.11 (t, 2H), 6.51 (s, 1H), 7.00 (s, 1H), 7.56 (s, 1H), 7.63 (s, 1H), 7.74 (s, 1H), 7.90 (s, 1H). LRMS (electrospray) : m/z [MH^+] 352, [MNa^+] 374. HRMS: [MH^+] Found 352.1770. $C_{16}H_{22}N_5O_2$ requires 352.1768.
165[1] (66)		^{1}H NMR (400MHz, $CDCl_3$): δ = 1.10 (m, 6H), 2.40(q, 2H), 2.50 (q, 2H), , 4.00 (t, 2H), 4.06 (t, 2H), 6.24 (t, 1H), 6.60 (d, 1H), 7.18 (d, 2H), 7.24 (d, 1H), 7.30 (s, 1H), 7.38 (t, 1H). LRMS (electrospray) : m/z [MH^+] 379, [MNa^+] 401. HRMS: [MH^+] Found 379.1766. $C_{21}H_{23}N_4O_3$ requires 379.1765 [MNa^+] Found 401.1585. $C_{21}H_{22}N_4O_3Na$ requires 401.1584.

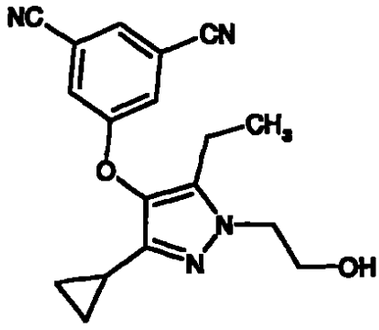
166[1] (67)		^{1}H NMR (400MHz, $CDCl_3$): δ = 1.10 (m, 6H), 2.41 (q, 2H), 2.51 (q, 2H), 4.01 (t, 2H), 4.06 (t, 2H), 7.07 (d, 1H), 7.13 (s, 1H), 7.22 (m, 1H), 7.52 (s, 1H), 7.65 (s, 1H), 7.88 (s, 1H). LRMS (electrospray) : m/z [MH^+] 380, [MNa^+] 402. HRMS: [MH^+] Found 380.1722. $C_{20}H_{22}N_5O_3$ requires 380.1717.
167[2] (68)		^{1}H NMR (400MHz, $CDCl_3$): δ = 1.11 (m, 6H), 2.27 (s, 3H), 2.41 (q, 2H), 2.50 (q, 2H), 3.70 (s, 3H), 4.04 (t, 1H), 4.08 (t, 2H), 5.64 (s, 1H), 6.81 (s, 1H), 6.91 (s, 1H), 6.99 (s, 1H). LRMS (electrospray) : m/z [MH^+] 396, [MNa^+] 418. HRMS: [MH^+] Found 396.2027. $C_{21}H_{25}N_5O_3$ requires 396.2030.

[1] The eluent used for flash column chromatography purification of these compounds was dichloromethane:methanol (99:1 changing to 80:20, by volume).

[2] The eluent used for flash column chromatography purification of this compound was dichloromethane:methanol (99:1 changing to 98:2, by volume).

EXAMPLE 168

5-[[3-Cyclopropyl-5-ethyl-1-(2-hydroxyethyl)-1*H*-pyrazol-4-yl]oxy]isophthalonitrile

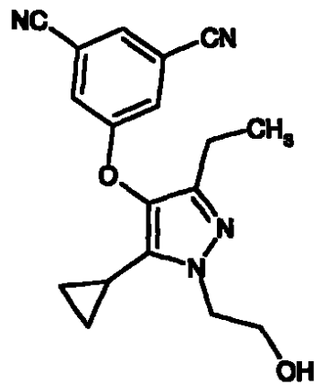


and

EXAMPLE 169

5-[[5-Cyclopropyl-3-ethyl-1-(2-hydroxyethyl)-1*H*-pyrazol-4-yl]oxy]isophthalonitrile

134



Potassium carbonate (91mg, 0.66mmol) and 2-(2-bromoethoxy)-tetrahydropyran (91µl, 0.61mmol) were sequentially added to a solution of the pyrazole from Example 129 (152mg, 0.55mmol) dissolved in dimethylformamide (4ml) and the reaction was heated to 35°C under nitrogen for 5 hours. Starting material still remained, so the temperature was increased to 80°C and the reaction was stirred for a further 18 hours. The reaction was cooled to room temperature, sodium hydride (60% dispersion in oil, 24mg, 0.60mmol) was added and the reaction was stirred at room temperature for 1hour. The mixture was diluted with water (50ml) and extracted with ethyl acetate (2x50ml). The combined organic extracts were washed with brine (30ml), dried over magnesium sulphate, concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel eluting with pentane:cyclohexane (75:25, by volume) to provide a mixture of regioisomers (239mg). The regioisomers (239mg, 0.55mmol) and p-toluenesulphonic acid (10mg, 0.05mmol) were dissolved in methanol (5ml) and stirred under nitrogen at room temperature for 18 hours. The solvent was removed under reduced pressure and the residue was partitioned between saturated aqueous sodium bicarbonate solution (20ml) and dichloromethane (30ml). The organic phase was dried over magnesium sulphate, concentrated under reduced pressure and the residual oil was purified by flash chromatography on silica gel eluting with toluene:ethyl acetate (50:50, by volume) to yield two products as colourless oils.

Least Polar Fraction (Example 168) – 34mg

^{1}H NMR (400MHz, $CDCl_3$): δ = 0.76 (m, 4H), 1.05 (t, 3H), 1.45 (m, 1H), 2.48 (q, 2H), 3.39 (brs, 1H), 4.02 (m, 4H), 7.39 (s, 2H), 7.56 (s, 1H).

LRMS (electrospray) : m/z [M-H$^+$] 321.

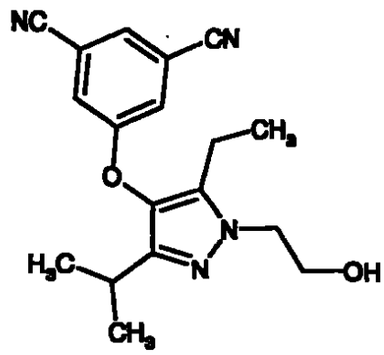
Most Polar Fraction (Example 169) – 9mg

^{1}H NMR (400MHz, $CDCl_3$): δ = 0.62 (m, 2H), 0.78 (m, 2H), 1.18 (t, 3H), 1.46 (m, 1H), 2.38 (q, 2H), 3.42 (brs, 1H), 4.02 (m, 2H), 4.21 (t, 2H), 7.38 (s, 2H), 7.57 (s, 1H).

LRMS (electrospray) : m/z [MH^+] 323, [MH] 321.

EXAMPLE 170

5-[[5-Ethyl-1-(2-hydroxyethyl)-3-isopropyl-1*H*-pyrazol-4-yl]oxy]isophthalonitrile



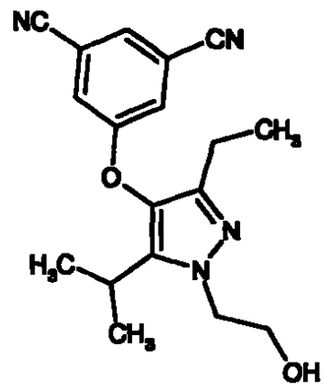
2-(2-Bromoethoxy)-tetrahydropyran (91µl, 0.60mmol) was added to a solution of the pyrazole from Example 131 (153mg, 0.55mmol) dissolved in dimethylformamide (4ml) at room temperature under nitrogen, then sodium hydride (60% dispersion in oil, 24mg, 0.60mmol) was added and the reaction was stirred at room temperature for 3 hours. The mixture was diluted with water (50ml) and extracted with ethyl acetate (2x50ml). The combined organic extracts were washed with brine (30ml), dried over magnesium sulphate, concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel eluting with toluene:ethyl acetate (85:15, by volume) to provide the separated isomers as colourless oils (83mg of isomer 1, 55mg of isomer 2).

The least polar isomer (isomer 1) (83mg, 0.20mmol) and p-toluene-sulphonic acid (4mg, 0.02mmol) were dissolved in methanol (5ml) and stirred under nitrogen at room temperature for 18 hours. The solvent was removed under reduced pressure and the residue was partitioned between water (30ml) and dichloromethane (30ml).The aqueous phase was extracted with dichloromethane (20ml) and the combined organic extracts were dried over magnesium sulphate, concentrated under reduced pressure and the residual oil was purified by flash chromatography on silica gel eluting with toluene:ethyl acetate (66:34, by volume) to provide the title compound (39mg) as an oil.

^{1}H NMR (400MHz, $CDCl_3$): δ = 1.05 (t, 3H), 1.14 (d, 6H), 2.44 (q, 2H), 2.68 (sept, 1H), 3.77 (brs, 1H), 4.06 (m, 4H), 7.38 (s, 2H), 7.58 (s, 1H).
LRMS (electrospray) : m/z [MH^+] 325.

EXAMPLE 171

5-[[3-Ethyl-1-(2-hydroxyethyl)-5-isopropyl-1*H*-pyrazol-4-yl]oxy]isophthalonitrile

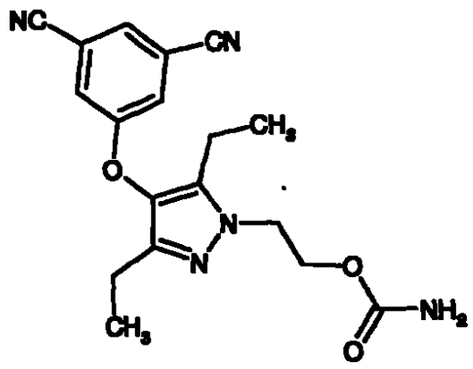


The most polar isomer (isomer 2) from Example 170 (55mg, 0.13mmol) and p-toluene-sulphonic acid (3mg, 0.01mmol) were dissolved in methanol (5ml) and stirred under nitrogen at room temperature for 18 hours. The solvent was removed under reduced pressure and the residue was partitioned between water (30ml) and dichloromethane (30ml). The aqueous phase was extracted with dichloromethane (20ml) and the combined organic extracts were dried over magnesium sulphate, concentrated under reduced pressure and the residual oil was purified by flash chromatography on silica gel eluting with toluene:ethyl acetate 66:33, by volume) to provide the title compound (39mg) as a white solid.

^{1}H NMR (400MHz, $CDCl_3$): δ = 1.08 (t, 3H), 1.13 (d, 6H), 2.49 (q, 2H), 2.97 (sept, 1H), 3.59 (t, 1H), 4.06 (m, 4H), 7.37 (s, 2H), 7.57 (s, 1H).
LRMS (electrospray) : m/z [MH^+] 325.

EXAMPLE 172

2-[4-(3,5-Dicyanophenoxy)-3,5-diethyl-1*H*-pyrazol-1-yl]ethyl carbamate

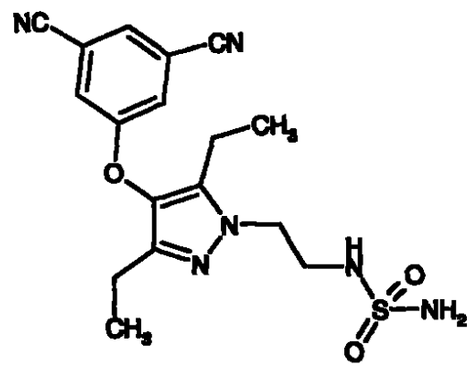


Trichloroacetyl-isocyanate (46µl, 0.38mmol) was added to a solution of the alcohol from Example 119 (100mg, 0.32mmol) dissolved in dichloromethane (3.2ml) under nitrogen at 0°C. After stirring for 2 hours the dichloromethane was removed under reduced pressure and methanol (1.6ml), water (1.6ml) and potassium carbonate (134mg, 0.96mmol) were added and the reaction was stirred for a further 2 hours. The methanol was removed under reduced pressure and the residue was extracted with dichloromethane (3x10ml). The combined organic extracts were dried over magnesium sulphate, concentrated under reduced pressure and the residual solid was purified by flash chromatography on silica gel eluting with dichloromethane:methanol (98:2, by volume) to provide the title compound (60mg) as a white solid.

^{1}H NMR (400MHz, $CDCl_3$): δ = 1.10 (m, 6H), 2.39 (q, 2H), 2.48 (q, 2H), 4.26 (m, 2H), 4.44 (m, 2H), 4.62 (brs, 2H), 7.41 (s, 2H), 7.58 (s, 1H).
LRMS (thermospray) : m/z [MH^+] 354.
Microanalysis: Found C, 60.00; H, 5.55; N, 19.82. $C_{18}H_{19}N_5O_3$.0.23EtOAc requires C, 60.30; H, 5.67; N, 18.58%.

EXAMPLE 173

N-[2-[4-(3,5-Dicyanophenoxy)-3,5-diethyl-1*H*-pyrazol-1-yl]ethyl]sulfamide

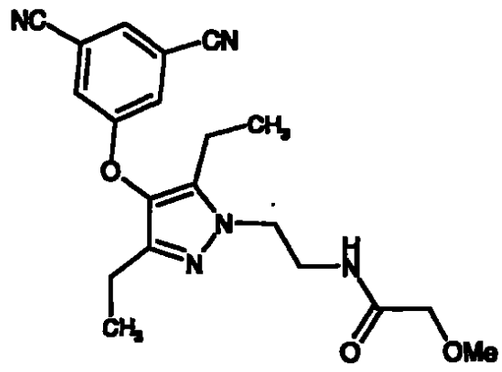


Sulfamide (31mg, 0.32mmol) was added to a solution of the amine from Example 127 (100mg, 0.32mmol) dissolved in dioxan (0.5ml) under nitrogen at room temperature. The reaction was heated to 100°C for 18 hours, cooled to room temperature and partitioned between ethyl acetate (15ml) and water (15ml). The organic phase was dried over magnesium sulphate, concentrated under reduced pressure and the residual brown oil was purified by flash chromatography on silica gel eluting with dichloromethane:methanol:0.88 ammonia (95:5:0.5, by volume) to provide the title compound (25mg) as a white solid.

^{1}H NMR (400MHz, $CDCl_3$): δ = 1.12 (m, 6H), 2.39 (q, 2H), 2.51 (q, 2H), 3.61 (m, 2H), 4.20 (m, 2H), 4.78 (s, 2H), 5.42 (s, 1H), 7.40 (s, 2H), 7.59 (s, 1H).
Microanalysis: Found C, 50.33; H, 5.07; N, 20.60. $C_{17}H_{20}N_6O_3S.0.95H_2O$ requires C, 50.35; H, 5.44; N, 20.72%.

EXAMPLE 174

N-[2-[4-(3,5-Dicyanophenoxy)-3,5-diethyl-1*H*-pyrazol-1-yl]ethyl]-2-methoxyacetamide



The amine from Example 127 (100mg, 0.32mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (68mg, 0.35mmol) and *N,N*-dimethylaminopyridine (43mg, 0.35mmol) were added to a solution of 1-methoxyacetic acid (27µl, 0.35mmol) dissolved in dichloromethane (10ml) under nitrogen at room temperature. The reaction was stirred for 18 hours, concentrated under reduced pressure and the residual yellow oil was purified by flash chromatography on silica gel eluting with dichloromethane:methanol:0.88 ammonia (95:5:0.5, by volume) to provide the title compound (32mg) as a colourless oil.

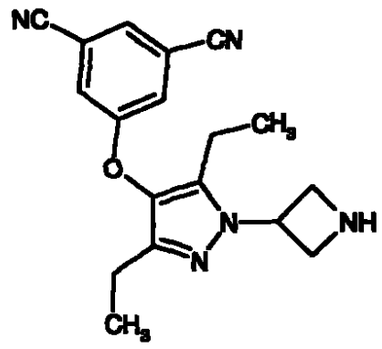
^{1}H NMR (400MHz, $CDCl_3$): δ = 1.11 (t, 3H), 1.16 (t, 3H), 2.38 (q, 2H), 2.47 (q, 2H), 3.41 (s, 3H), 3.77 (dd, 2H), 3.89 (s, 2H), 4.15 (m, 2H), 7.19 (brs, 1H), 7.40 (s, 2H), 7.59 (s, 1H).

LRMS (thermospray) : m/z [MH^+] 382.

Microanalysis: Found C, 61.26; H, 6.18; N, 17.59. $C_{20}H_{23}N_5O_3.0.60H_2O$ requires C, 61.24; H, 6.22; N, 17.85%.

EXAMPLE 175

5-[(1-(3-Azetidinyl)-3,5-diethyl-1*H*-pyrazol-4-yl)oxy]isophthalonitrile



The protected amine from Preparation 69 (178mg, 0.42mmol) was dissolved in 4M hydrochloric acid in dioxan solution (1ml) and dioxan (1ml) and the reaction was stirred at room temperature for 18 hours. The solvent was removed under reduced pressure and the residue was partitioned between dichloromethane (20ml) and saturated aqueous sodium bicarbonate solution (20ml). The organic phase was dried over magnesium sulphate, concentrated under reduced pressure and purified by flash chromatography on silica gel eluting with a solvent gradient of dichloromethane:methanol:0.88 ammonia (100:0:0 then 98:2:0 then 95:5:0 then 95:5:0.5 then 90:10:1 then 80:20:1, by volume) to provide the title compound (33mg) as a white solid.

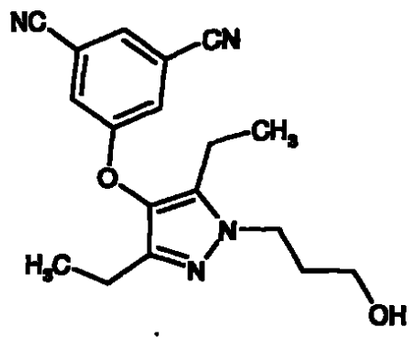
^{1}H NMR (400MHz, $CDCl_3$): δ = 1.05 (t, 3H), 1.11 (t, 3H), 2.44 (m, 4H), 3.85 (m, 2H), 4.38 (m, 2H), 5.05 (m, 1H), 7.37 (s, 2H), 7.56 (s, 1H).

LRMS (electrospray) : m/z [MH^+] 322.

Microanalysis: Found C, 65.87; H, 5.94; N, 20.98. $C_{18}H_{19}N_5O.0.38H_2O$ requires C, 65.87; H, 6.07; N, 21.04%.

EXAMPLE 176

5-[(3,5-Diethyl-1-(3-hydroxypropyl)-1*H*-pyrazol-4-yl)oxy]isophthalonitrile

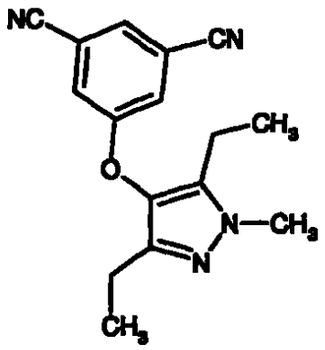


The protected alcohol from Preparation 70 (215mg, 0.53mmol) and p-toluene-sulphonic acid (10mg, 0.05mmol) were dissolved in methanol (2ml) and stirred under nitrogen at room temperature for 18 hours. The solvent was removed under reduced pressure and the residue was partitioned between water (10ml) and dichloromethane (10ml). The organic phase was dried over magnesium sulphate and concentrated under reduced pressure to provide the title compound (148mg) as a pale yellow solid, m.p. 93-95°C.

^{1}H NMR (400MHz, $CDCl_3$): δ = 1.11 (m, 6H), 2.04 (tt, 2H), 2.37 (q, 2H), 2.53 (q, 2H), 3.06 (t, 1H), 3.69 (dt, 2H), 4.18 (t, 2H), 7.38 (s, 2H), 7.58 (s, 1H).
LRMS (electrospray) : m/z [MH^+] 325, [MNa^+] 347.
Microanalysis: Found C, 66.27; H, 6.27; N, 17.00. $C_{18}H_{20}N_4O_2$ requires C, 66.28; H, 6.24; N, 17.18%.

EXAMPLE 177

5-[(3,5-Diethyl-1-methyl-1*H*-pyrazol-4-yl)oxy]isophthalonitrile

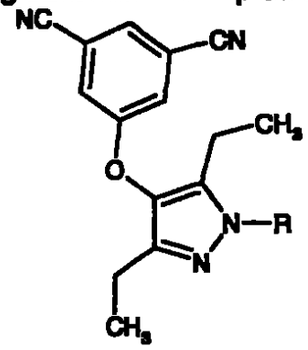


Sodium hydride (60% dispersion in oil, 33mg, 0.82mmol) was added to a solution of the pyrazole from Example 122 (200mg, 0.75mmol) in dimethylformamide (3ml) at 0°C under nitrogen and the reaction was stirred for 10 minutes. Methyl iodide (117mg, 0.82mmol) was added and the reaction was stirred at room temperature for 18 hours. The reaction was quenched with water (0.2ml) and concentrated under reduced pressure. The residue was partitioned between dichloromethane (5ml) and water (5ml) and the organic phase was isolated using a 5µM Whatman PTFE fritted cartridge, then concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with a solvent gradient of ethyl acetate:pentane (20:80, by volume) changing to ethyl acetate:methanol (90:10, by volume) then dichloromethane:methanol:0.88 ammonia (90:10:1 then 80:20:1, by volume) to provide the title compound (170mg) as a yellow solid.

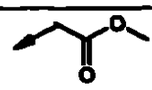
^{1}H NMR (400MHz, $CDCl_3$): δ = 1.10 (m, 6H), 2.39 (q, 2H), 2.49 (q, 2H), 3.80 (s, 3H), 7.40 (s, 2H), 7.56 (s, 1H).
LRMS (electrospray) : m/z [MH^+] 281.
Microanalysis: Found C, 68.41; H, 5.71; N, 19.93. $C_{16}H_{16}N_4O$ requires C, 68.55; H, 5.75; N, 19.99%.

EXAMPLES 178-180

The preparation of the following tabulated Examples of the general formula



were performed by a similar method to that of Example 177 using the appropriate alkyl halide as the starting material.

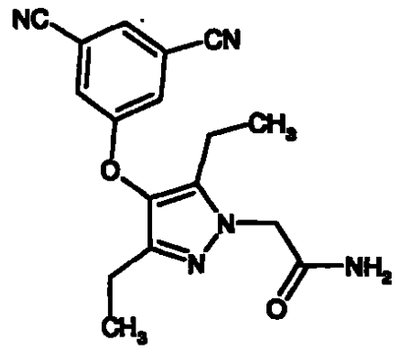
Example No. (Starting Material Example No.)	R	Analytical Data
178 (122)		^{1}H NMR (400MHz, $CDCl_3$): δ = 1.08 (t, 3H), 1.12 (t, 3H), 2.40 (q, 2H), 2.54 (q, 2H), 3.34 (s, 3H), 3.75 (t, 2H), 4.17 (t, 2H), 7.38 (s, 2H), 7.56 (s, 1H). LRMS (electrospray) : m/z [MH^+] 325, [MNa^+] 347. Microanalysis: Found C, 65.73; H, 6.17; N, 17.08. $C_{18}H_{20}N_4O_3.0.25H_2O$ requires C, 65.74; H, 6.28; N, 17.04%.
179[1,2] (122)		^{1}H NMR (400MHz, $CDCl_3$): δ = 1.10 (m, 6H), 1.98 (tt, 2H), 2.38 (q, 2H), 2.51 (q, 2H), 2.76 (t, 2H), 4.09 (t, 2H), 7.38 (s, 2H), 7.57 (s, 1H). LRMS (electrospray) : m/z [MH^+] 324. Microanalysis: Found C, 64.86; H, 6.51; N, 20.79. $C_{18}H_{21}N_5O.0.57H_2O$ requires C, 64.79; H, 6.69; N, 20.99%.
180[3] (122)		^{1}H NMR (400MHz, $CDCl_3$): δ = 1.09 (t, 3H), 1.14 (t, 3H), 2.41 (q, 2H), 2.47 (q, 2H), 3.79 (s, 3H), 4.82 (s, 2H), 7.40 (s, 2H), 7.57 (s, 1H). LRMS (electrospray) : m/z [MH^+] 339. Microanalysis: Found C, 63.58; H, 5.35; N, 16.35. $C_{18}H_{18}N_4O_3.0.10H_2O$ requires C, 63.56; H, 5.39; N, 16.47%.

[1] The two reagents were heated together as a melt at 160°C for 24 hours, and the reaction was worked up by partitioning between dichloromethane and saturated sodium bicarbonate solution, extracting the organic phase with 2M aqueous hydrochloric acid and basifying the aqueous phase with sodium carbonate. After extraction with dichloromethane the organic phase was dried and concentrated to give the crude product.

[2] The eluent used for flash column chromatography purification of this compound was dichloromethane:methanol:0.88 ammonia (95:5:0.5 changing to 80:20:1, by volume).
[3] The eluent used for flash column chromatography purification of this compound was pentane:ethyl acetate (75:25 changing to 66:34 then 50:50, by volume).
[4] The hydrochloride salt of the starting alkyl halide was used.

EXAMPLE 181

2-[4-(3,5-Dicyanophenoxy)-3,5-diethyl-1*H*-pyrazol-1-yl]acetamide

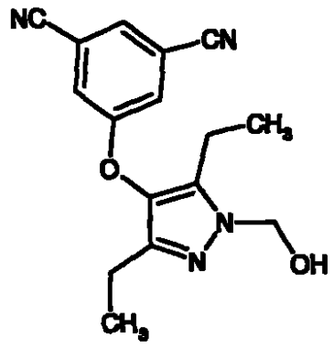


The ester from Example 180 (200mg, 0.59mmol) was dissolved in 2M methanolic ammonia solution (5ml) and the reaction was stirred under nitrogen at 75°C for 18 hours. The mixture was concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel eluting with a solvent gradient of dichloromethane:methanol:0.88 ammonia (95:5:0.5, by volume) to provide the title compound (6mg).

^{1}H NMR (400MHz, $CDCl_3$): δ = 1.10 (t, 3H), 1.15 (t, 3H), 2.44 (q, 2H), 2.54 (q, 2H), 4.69 (s, 2H), 5.55 (brs, 1H), 6.22 (brs, 1H), 7.38 (s, 2H), 7.59 (s, 1H).
LRMS (electrospray) : m/z [M-H$^+$] 322.
Microanalysis: Found C, 68.41; H, 5.71; N, 19.93. $C_{18}H_{18}N_4O$ requires C, 68.55; H, 5.75; N, 19.99%.

EXAMPLE 182

5-[(3,5-Diethyl-1-(hydroxymethyl)-1*H*-pyrazol-4-yl)oxy]isophthalonitrile



Formaldehyde (37% solution in water, 253µl, 3.14mmol) was added to a solution of the pyrazole from Example 122 (440mg, 1.65mmol) in ethanol (5ml) and the reaction was stirred at 80°C for 18 hours. After cooling to room temperature the solvent was removed under reduced pressure and the residual yellow solid was partitioned between ethyl acetate (15ml) and water (10ml) and the organic phase was removed. The aqueous phase was washed with ethyl acetate (2x15ml) and the combined organic extracts were dried over magnesium sulphate and concentrated under reduced pressure to provide the title compound (490mg) as a white solid.

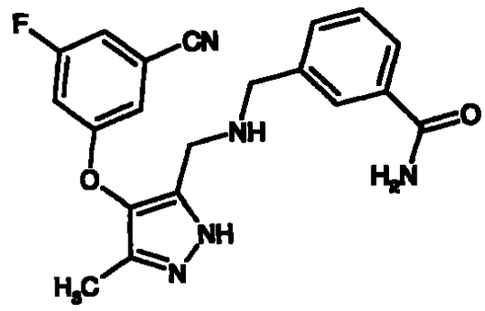
^{1}H NMR (400MHz, $CDCl_3$): δ = 1.13 (t, 3H), 1.14 (t, 3H), 2.39 (q, 2H), 2.61 (q, 2H), 5.49 (s, 2H), 5.68 (brs, 1H), 7.40 (s, 2H), 7.56 (s, 1H).

LRMS (thermospray) : m/z [MH^+] 267.

Microanalysis: Found C, 64.28; H, 5.52; N, 18.47. $C_{16}H_{16}N_4O_2.0.15H_2O$ requires C, 64.27; H, 5.49; N, 18.24%.

EXAMPLE 183

3-[({[4-(3-cyano-5-fluorophenoxy)-3-methyl-1*H*-pyrazol-5-yl]methyl}amino)methyl]benzamide

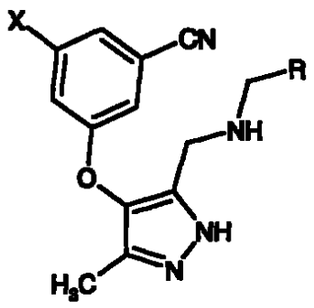


The pyrazole from Preparation 75 (320mg, 0.91mmol) and the amine from Preparation 80 (680mg, 4.61mmol) were refluxed in isopropanol (5ml) for 1.5 hours. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel eluting with dichloromethane:methanol:0.88 ammonia (95:5:0.5, by volume) to give the product which was further purified by preparative HPLC using a Develosil combi-rp C30 50x4.6mm 3μm column eluting with a solvent gradient of 5:95 0.1% aqueous trifluoroacetic acid in acetonitrile:acetonitrile (0-6min 95:5 changing to 50:50; 6-7min 50:50; 7-7.1min 50:50 changing to 5:95; 7.1-8min 5:95) to provide the title compound (38mg).

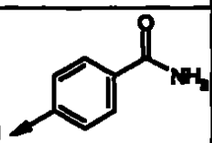
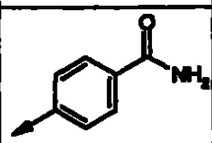
^{1}H NMR (400MHz, CD_3OD): δ = 2.14 (s, 3H), 4.10 (s, 2H), 4.34 (s, 2H), 7.03 (m, 1H), 7.10 (s, 1H), 7.25 (m, 1H), 7.54 (t, 1H), 7.64 (d, 1H), 7.92 (d, 1H), 7.97 (s, 1H).
LRMS (electrospray) : m/z [MH^+] 380.
Microanalysis: Found C, 51.32; H, 3.91; N, 13.69. $C_{20}H_{18}N_5O_2F.1.00CF_3CO_2H1.10H_2O$ requires C, 51.49; H, 4.16; N, 13.65%.

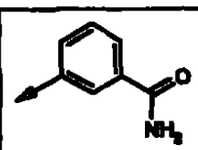
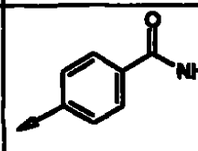
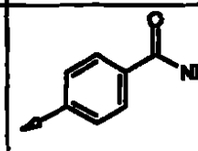
EXAMPLES 184-188

The preparation of the following tabulated Examples of the general formula



were performed by a similar method to that of Example 183 using as the starting materials the appropriate pyrazole (P) and amine (A).

Ex. no.	P prep. no.	A prep. no.	X	R	Analytical Data
184[1]	75	55	F		^{1}H NMR (400MHz, $CDCl_3$): δ = 2.09 (s, 3H), 3.65 (s, 2H), 3.79 (s, 2H), 6.80 (d, 1H), 6.93 (s, 1H), 6.97 (d, 1H), 7.31 (d, 2H), 7.72 (d, 2H). LRMS (thermospray) : m/z [MH^+] 380.
185[1]	76	55	CN		m.p. 114-116°C ^{1}H NMR (400MHz, $CDCl_3$): δ = 2.08 (s, 3H), 3.62 (s, 2H), 3.77 (s, 2H), 7.34 (d, 2H), 7.55 (s, 1H), 7.77 (d, 2H), 7.79 (s, 1H). LRMS (thermospray) : m/z [MH^+] 387.

186[1]	18	80	Cl		m.p. 98-101°C ^{1}H NMR (400MHz, $CDCl_3$): δ = 2.04 (s, 3H), 3.62 (s, 2H), 3.74 (s, 2H), 6.97 (s, 1H), 7.07 (s, 1H), 7.20 (s, 1H), 7.22 (d, 1H), 7.29 (t, 1H), 7.62 (s, 1H), 7.81 (s, 1H). LRMS (thermospray) : m/z [MH^+] 396. Microanalysis: Found C, 56.98; H, 4.58; N, 17.69. $C_{20}H_{18}ClN_5O_2.0.40CH_2Cl_2$ requires C, 57.01; H, 4.41; N, 16.29%.
187[1, 2,3]	77	55	Me		^{1}H NMR (400MHz, $CDCl_3$): δ = 2.10 (s, 3H), 2.30 (s, 3H), 3.65 (s, 2H), 3.80 (s, 2H), 6.85 (s, 1H), 6.95 (s, 1H), 7.10 (s, 1H), 7.30 (d, 2H), 7.70 (d, 2H). LRMS (electrospray) : m/z [MH^+] 376, [$M-H^+$] 374. Microanalysis: Found C, 65.59; H, 5.65; N, 18.19. $C_{21}H_{21}N_5O_2.0.50H_2O$ requires C, 65.51; H, 5.77; N, 18.22%.
188[4]	78	55	H		^{1}H NMR (400MHz, CD_3OD): δ = 2.15 (s, 3H), 4.10 (s, 2H), 7.20 (m, 2H), 7.40 (m, 1H), 7.50 (m, 1H), 7.55 (d, 2H), 7.90 (d, 2H). Microanalysis: Found C, 53.51; H, 4.13; N, 13.59. $C_{20}H_{19}N_5O_2$. 1.25 TFA requires C, 53.63; H, 4.05; N, 13.90%.

[1] No preparative HPLC was required for purification of this compound.

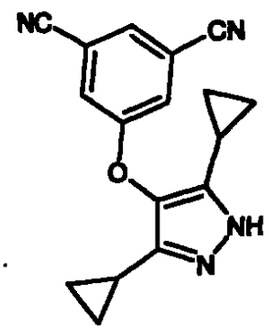
[2] The eluent used for flash column chromatography purification of this compound was dichloromethane:methanol:0.88 ammonia (95:5:0.5 changing to 90:10:1, by volume).

[3] The product was triturated with dichloromethane containing a trace of methanol – a solid crystallised out which was an impurity. This was filtered off and the filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography eluting with dichloromethane:methanol:0.88 ammonia (90:10:1, by volume) to give the title compound.

[4] The column used for preparative HPLC was a LUNA C18 10µm 150x21.2mm.

EXAMPLE 189

5-[(3,5-Dicyclopropyl-1*H*-pyrazol-4-yl)oxy]isophthalonitrile



Hydrazine hydrate (133µl, 2.75mmol) was added to a solution of the diketone from Preparation 82 (735mg, 2.50mmol) in acetic acid (25ml) under nitrogen at room temperature. After stirring for 64 hours, the mixture was concentrated under reduced pressure and the residue was partitioned between dichloromethane (25ml) and saturated aqueous sodium bicarbonate solution (25ml). The organic phase was dried over magnesium sulphate, concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel eluting with dichloromethane:methanol (98:2 changing to 96:4, by volume) to provide the title compound (473mg) as a white solid, m.p. 168-170°C.

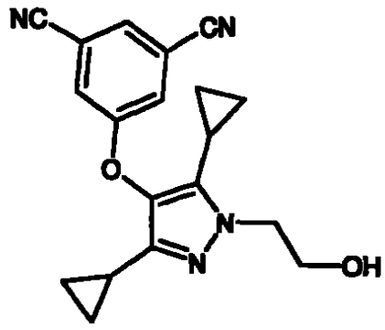
^{1}H NMR (400MHz, $CDCl_3$): δ = 0.77 (m, 4H), 0.85 (m, 4H), 1.59 (m, 2H), 7.44 (s, 2H), 7.59 (s, 1H).

LRMS (thermospray) : m/z [MH^+] 291.

Microanalysis: Found C, 69.90; H, 4.85; N, 19.18. $C_{17}H_{14}N_4O.0.10H_2O$ requires C, 69.90; H, 4.90; N, 19.18%.

EXAMPLE 190

5-[(3,5-Dicyclopropyl-1-(2-hydroxyethyl)-1*H*-pyrazol-4-yl)oxy]isophthalonitrile

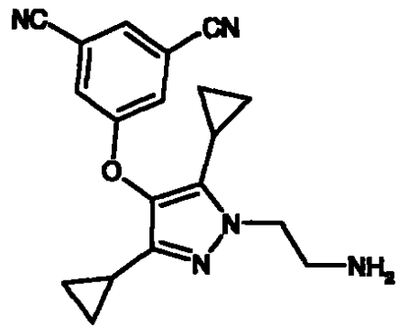


2-Hydroxyethylhydrazine (84mg, 1.10mmol) was added to a solution of the diketone from Preparation 82 (294mg, 1.00mmol) in acetic acid (10ml) under nitrogen at room temperature. After stirring for 64 hours, the mixture was concentrated under reduced pressure and the residue was partitioned between dichloromethane (25ml) and saturated aqueous sodium bicarbonate solution (25ml). The organic phase was dried over magnesium sulphate, concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel eluting with dichloromethane:methanol (99:1 changing to 95:5, by volume) to provide the title compound (137mg) as a white solid, m.p. 115-117°C.

^{1}H NMR (400MHz, $CDCl_3$): δ = 0.67 (m, 2H), 0.80 (m, 4H), 0.85 (m, 2H), 1.52 (m, 2H), 3.39 (brs, 1H), 4.05 (m, 2H), 4.22 (t, 2H), 7.42 (s, 2H), 7.58 (s, 1H).
LRMS (thermospray) : m/z [MH^+] 355.
Microanalysis: Found C, 67.63; H, 5.55; N, 16.35. $C_{19}H_{18}N_4O_2.0.17H_2O$ requires C, 67.63; H, 5.48; N, 16.60%.

EXAMPLE 191

5-[[1-(2-Aminoethyl)-3,5-dicyclopropyl-1*H*-pyrazol-4-yl]oxy]isophthalonitrile

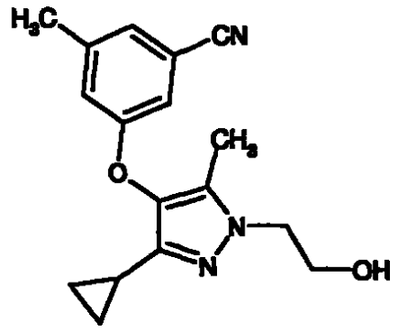


2-Chloroethylamine hydrochloride (192mg, 1.65mmol) and the pyrazole from Example 189 (440mg, 1.50mmol) were heated as a melt at 160°C for 18 hours and the residue was partitioned between dichloromethane (25ml) and 10% aqueous potassium carbonate solution (25ml). The organic phase was dried over magnesium sulphate, concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel eluting with dichloromethane:methanol:0.88 ammonia (95:5:0 changing to 95:5:0.5, by volume) to provide the title compound (9.2mg) as a white solid, m.p. 175-177°C.

^{1}H NMR (400MHz, $CDCl_3$): δ = 0.70 (m, 2H), 0.79 (m, 4H), 0.88 (m, 2H), 1.57 (m, 1H), 1.66 (m, 1H), 3.46 (t, 2H), 4.41 (t, 2H), 7.62 (s, 2H), 7.58 (s, 1H).

EXAMPLE 192

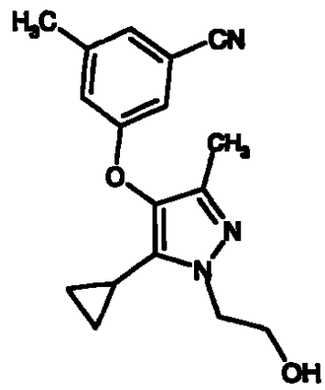
3-[[3-cyclopropyl-1-(2-hydroxyethyl)-5-methyl-1*H*-pyrazol-4-yl]oxy]-5-methylbenzonitrile



and

EXAMPLE 193

3-[5-cyclopropyl-1-(2-hydroxyethyl)-3-methyl-1*H*-pyrazol-4-yloxy]-5-methylbenzonitrile



2-Hydroxy-ethyl-hydrazine (326µl, 4.80mmol) was added to a solution of the diketone from Preparation 86 (1.00g, 4.37mmol) in acetic acid (10ml) under nitrogen at room temperature. After stirring for 18 hours, the mixture was concentrated under reduced pressure and the residual orange oil was purified by flash chromatography on silica gel eluting with ethyl acetate:pentane (50:50 changing to 100:0, by volume) to provide two pale yellow oils.

Least Polar Fraction (Example 192) – 419mg

^{1}H NMR (400MHz, $CDCl_3$): δ = 0.69 (m, 2H), 0.82 (m, 2H), 1.54 (m, 1H), 2.00 (s, 3H), 2.35 (s, 3H), 3.46 (brs, 1H), 4.05 (t, 2H), 4.22 (t, 2H), 6.88 (s, 1H), 6.94 (s, 1H), 7.08 (s, 1H).

LRMS (thermospray) : m/z [MH^+] 298.

Microanalysis: Found C, 68.29; H, 6.51; N, 13.92. $C_{17}H_{19}N_3O_2$ requires C, 68.67; H, 6.44; N, 14.13%.

Most Polar Fraction (Example 193) – 201mg

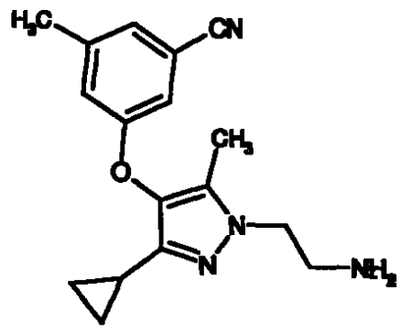
^{1}H NMR (400MHz, $CDCl_3$): δ = 0.75 (m, 4H), 1.58 (m, 1H), 2.07 (s, 3H), 2.35 (s, 3H), 3.45 (brs, 1H), 4.00 (m, 4H), 6.92 (s, 1H), 7.00 (s, 1H), 7.10 (s, 1H).

LRMS (thermospray) : m/z [MH^+] 298.

Microanalysis: Found C, 68.44; H, 6.49; N, 13.95. $C_{17}H_{19}N_3O_2$ requires C, 68.67; H, 6.44; N, 14.13%.

EXAMPLE 194

3-[3-Cyclopropyl-1-(2-amino-ethyl)-5-methyl-1H-pyrazol-4-yloxy]-5-methyl-benzonitrile

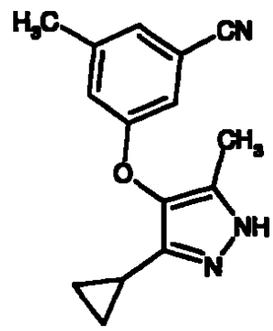


The alcohol from Example 192 (140mg, 0.47mmol), triphenylphosphine (309mg, 1.18mmol) and phthalimide (174mg, 1.18mmol) were dissolved in tetrahydrofuran (9ml) at 0°C under nitrogen and diisopropylazodicarboxylate (232µl, 1.18mmol) dissolved in tetrahydrofuran (2ml) was added over 10 minutes. The reaction was allowed to warm to room temperature and was stirred for 18 hours. The solvent was removed under reduced pressure, the residue was dissoved in ethanol (11ml) and hydrazine hydrate (114µl, 2.35mmol) was added. The thick white slurry was stirred for 18h at room temperature under nitrogen, methanol (10ml) was added and the mixture was filtered. The filtrate was concentrated under reduced pressure and the residue was dissolved in dichloromethane (20ml). The organic phase was extracted with 2M aqueous hydrochloric acid (20ml) and the aqueous phase was washed with dichloromethane (5x10ml), basified with 1M aqueous sodium hydroxide and extracted with dichloromethane (50ml). The organic phase was dried over magnesium sulphate and concentrated under reduced pressure to provide the title compound (135mg) as a yellow oil.

^{1}H NMR (400MHz, $CDCl_3$): δ = 0.70 (m, 4H), 1.56 (m, 1H), 2.06 (s, 3H), 2.30 (s, 3H), 3.10 (t, 2H), 3.97 (t, 2H), 6.87 (s, 1H), 6.92 (s, 1H), 7.05 (s, 1H).
LRMS (electrospray) : m/z [MH^+] 297.
Microanalysis: Found C, 63.81; H, 6.51; N, 17.30. $C_{17}H_{20}N_4O.0.36CH_2Cl_2$ requires C, 63.78; H, 6.39; N, 17.14%.

EXAMPLE 195

3-[(3-Cyclopropyl-5-methyl-1*H*-pyrazol-4-yl)oxy]-5-methylbenzonitrile

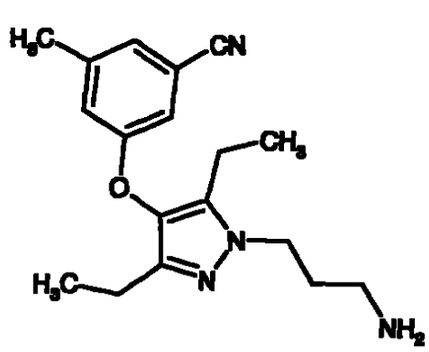


Hydrazine hydrate (31µl, 0.64mmol) was added to a solution of the diketone from Preparation 86 (150mg, 0.58mmol) in acetic acid (1.3ml) under nitrogen at room temperature. After stirring for 24 hours, the mixture was concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel eluting with pentane:ethyl acetate (60:40 changing to 40:60, by volume) to provide the title compound (140mg).

^{1}H NMR (400MHz, $CDCl_3$): δ = 0.60 (m, 4H), 1.69 (m, 1H), 2.09 (s, 3H), 2.34 (s, 3H), 6.95 (s, 1H), 6.99 (s, 1H), 7.10 (s, 1H).
LRMS (thermospray) : m/z [MH^+] 254.
Microanalysis: Found C, 68.35; H, 6.13; N, 15.10. $C_{15}H_{15}N_3O.0.29EtOAc$ requires C, 68.72; H, 6.32; N, 14.88%.

EXAMPLE 196

3-[[1-(3-Aminopropyl)-3,5-diethyl-1*H*-pyrazol-4-yl]oxy]-5-methylbenzonitrile

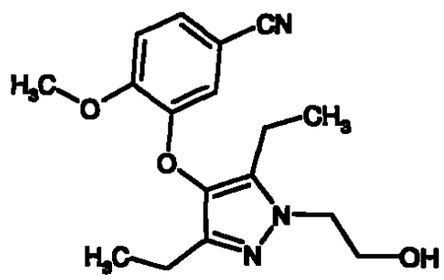


3-Chloropropylamine hydrochloride (62mg, 0.48mmol) and the pyrazole from Example 123 (113mg, 0.44mmol) were heated as a melt at 150°C for 18 hours. After cooling the residue was purified by flash chromatography on silica gel eluting with dichloromethane:methanol:0.88 ammonia (98:2:0 changing to 95:5:0.5, by volume). An impurity remained so the oil was dissolved in acetone (3ml) and (L)-tartaric acid (54mg, 0.44mmol) was added, the mixture was heated to effect dissolution and cooled. The resultant precipitate was isolated by filtration washing with acetone (10ml) to provide the title compound (127mg) as a white solid which was the tartrate salt.

^{1}H NMR (400MHz, CD_3OD): δ = 1.05 (m, 6H), 2.07 (m, 2H), 2.37 (q, 2H), 2.53 (s, 3H), 2.57 (q, 2H), 2.99 (t, 2H), 4.15 (t, 2H), 4.38 (s, 2H), 6.89 (s, 1H), 7.01 (s, 1H), 7.19 (s, 1H).
LRMS (thermospray) : m/z [MH^+] 313.
Microanalysis: Found C, 56.81; H, 6.57; N, 12.06. $C_{22}H_{30}N_4O_7$ requires C, 57.13; H, 6.54; N, 12.11%.

EXAMPLE 197

3-[(3,5-Diethyl-1-(2-hydroxyethyl)-1*H*-pyrazol-4-yl)oxy]-4-methoxybenzonitrile



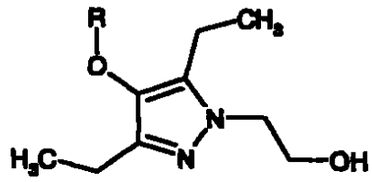
Cesium carbonate (700mg, 2.14mmol) was added to a stirred solution of 2-methoxy-5-cyanophenol (285mg, 2.15mmol) and the dione of Preparation 2 (348mg, 2.15mmol) in acetone (20ml) at room temperature. The reaction was heated at 50°C for 3 hours and then cooled to room temperature. The mixture was concentrated under reduced pressure, dissolved in dichloromethane (5ml) and washed with water (5ml). The organic phase was isolated using a 5µM Whatman PTFE fritted cartridge, then concentrated under reduced pressure. The residue was dissolved in acetic acid (5.4ml) and 2-hydroxy-ethyl-hydrazine (160µl, 2.15mmol) added under nitrogen at

room temperature. After stirring for 18 hours, the mixture was concentrated under reduced pressure and the residual orange oil was purified by flash chromatography on silica gel eluting with a solvent gradient of ethyl acetate:pentane (25:75 changing to 50:50, by volume) to provide the title compound (182mg).

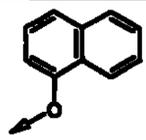
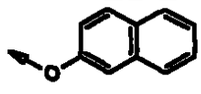
^{1}H NMR (400MHz, $CDCl_3$): δ = 1.10 (m, 6H), 2.39 (q, 2H), 2.51 (q, 2H), 3.71 (brs, 1H), 4.00 (s, 3H), 4.08 (m, 2H), 4.09 (m, 2H), 6.89 (s, 1H), 6.99 (d, 1H), 7.32 (d, 1H).
LRMS (thermospray) : m/z [MH^+] 316.
Microanalysis: Found C, 64.57; H, 6.73; N, 13.15. $C_{17}H_{21}N_3O_3$ requires C, 64.74; H, 6.71; N, 13.32%.

Examples 198-199

The preparation of the following tabulated Examples of the general formula



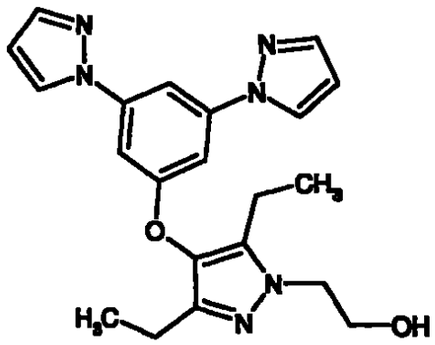
were performed by a similar method to that of Example 197 using the β-diketone of Preparation 2 and the appropriate aryl alcohol as the starting materials.

Example No.	R	Analytical Data
198		^{1}H NMR (400MHz, $CDCl_3$): δ = 1.04 (m, 6H), 2.42 (q, 2H), 2.51 (q, 2H), 4.07 (m, 2H), 4.12 (m, 2H), 6.60 (d, 1H), 7.25 (t, 1H), 7.49 (d, 1H), 7.53 (m, 2H), 7.82 (m, 1H), 8.41 (m, 1H). LRMS (thermospray) : m/z [MH^+] 311.
199		^{1}H NMR (400MHz, $CDCl_3$): δ = 1.19 (m, 6H), 2.48 (q, 2H), 2.51 (q, 2H), 4.03 (m, 2H), 4.10 (m, 2H), 7.06 (s, 1H), 7.22 (m, 1H), 7.38 (t, 1H), 7.42 (m, 1H), 7.69 (d, 1H), 7.79 (s, 1H), 7.80 (s, 1H). LRMS (thermospray) : m/z [MH^+] 311. Microanalysis: Found C, 72.16; H, 7.20; N, 8.95. $C_{19}H_{22}N_2O_2$.0.10EtOAc requires C, 72.45; H, 7.19;

		N, 8.63%.

EXAMPLE 200

2-[4-[3,5-Di(1*H*-pyrazol-1-yl)phenoxy]-3,5-diethyl-1*H*-pyrazol-1-yl]ethanol

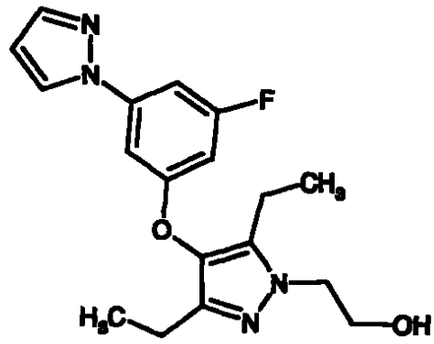


The protected alcohol from Preparation 88 (254mg, 0.53mmol) and p-toluene-sulphonic acid (10mg, 0.05mmol) were dissolved in methanol (4ml) and stirred under nitrogen at room temperature for 18 hours. The solvent was removed under reduced pressure and the residue was partitioned between saturated aqueous sodium bicarbonate solution (20ml) and dichloromethane (20ml). The aqueous phase was extracted with dichloromethane (10ml) and the combined organic extracts were dried over magnesium sulphate, concentrated under reduced pressure and purified by flash chromatography on silica gel eluting with a solvent gradient of dichloromethane:methanol (100:0 changing to 93:7, by volume) to provide the title compound (56mg) as a white solid, m.p. 108-110°C.

^{1}H NMR (400MHz, $CDCl_3$): δ = 1.11 (m, 6H), 2.46 (q, 2H), 2.53 (q, 2H), 4.01 (t, 2H), 4.07 (t, 2H), 6.44 (s, 2H), 7.16 (s, 2H), 7.68 (s, 3H), 7.92 (s, 2H).
LRMS (electrospray) : m/z [MH^+] 393, [MNa^+] 415.
Microanalysis: Found C, 63.62; H, 6.11; N, 21.11. $C_{21}H_{24}N_8O_2.0.06CH_2Cl_2$ requires C, 63.63; H, 6.12; N, 21.14%.

EXAMPLE 201

2-[3,5-Diethyl-4-[3-fluoro-5-(1*H*-pyrazol-1-yl)phenoxy]-1*H*-pyrazol-1-yl]ethanol



The protected alcohol from Preparation 89 (38.6mg, 0.09mmol) and p-toluene-sulphonic acid (3.5mg, 0.01mmol) were dissolved in methanol (1ml) and stirred under nitrogen at room temperature for 18 hours. The solvent was removed under reduced pressure and the residue was partitioned between 10% aqueous potassium carbonate solution (4ml) and dichloromethane (4ml). The aqueous phase was extracted with dichloromethane (10ml) and the combined organic extracts were dried over magnesium sulphate, concentrated under reduced pressure and purified by flash chromatography on silica gel eluting with a solvent gradient of dichloromethane:methanol (99:1 changing to 98:2, by volume) to provide the title compound (23mg) as a white solid, m.p. 120-122°C.

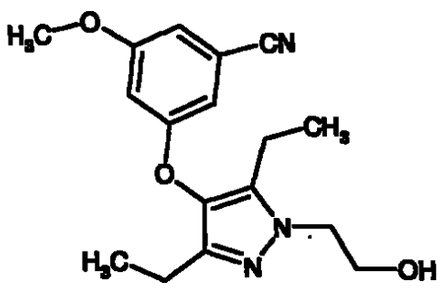
^{1}H NMR (400MHz, $CDCl_3$): δ = 1.14 (m, 6H), 2.46 (q, 2H), 2.55 (q, 2H), 4.06 (m, 2H), 4.09 (m, 2H), 6.47 (s, 1H), 6.49 (s, 1H), 7.09 (s, 1H), 7.12 (s, 1H), 7.71 (s, 1H), 7.86 (s, 1H).

LRMS (electrospray) : m/z [MNa^+] 367.

HRMS: [MH^+] Found 345.1717. $C_{18}H_{22}FN_4O_2$ requires 345.1722.

EXAMPLE 202

3-[(3,5-Diethyl-1-(2-hydroxyethyl)-1*H*-pyrazol-4-yl)oxy]-5-methoxybenzonitrile

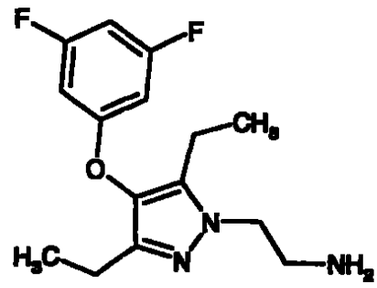


The protected alcohol from Preparation 90 (400mg, 1.00mmol) and p-toluene-sulphonic acid (19mg, 0.10mmol) were dissolved in methanol (10ml) and stirred under nitrogen at room temperature for 18 hours. The solvent was removed under reduced pressure and the residue was partitioned between saturated aqueous sodium bicarbonate solution (20ml) and dichloromethane (20ml). The aqueous phase was extracted with dichloromethane (40ml) and the combined organic extracts were dried over magnesium sulphate, concentrated under reduced pressure and purified by flash chromatography on a silica gel eluting with dichloromethane:methanol (97:3, by volume) to provide the title compound (174mg) as an oil.

^{1}H NMR (400MHz, $CDCl_3$): δ = 1.09 (m, 6H), 2.40 (q, 2H), 2.49 (q, 2H), 3.78 (s, 3H), 4.04 (m, 2H), 4.08 (m, 2H), 6.66 (s, 1H), 6.71 (s, 1H), 6.79 (s, 1H).
LRMS (electrospray) : m/z [MH^+] 316.
Microanalysis: Found C, 63.63; H, 6.76; N, 13.06. $C_{17}H_{21}N_3O_3.0.08CH_2Cl_2$ requires C, 63.68; H, 6.68; N, 13.04%.

EXAMPLE 203

2-[4-(3,5-Difluorophenoxy)-3,5-diethyl-1*H*-pyrazol-1-yl]ethylamine



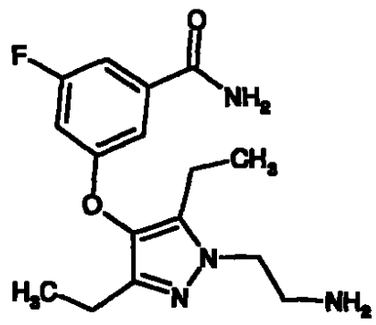
The alcohol from Example 38 (371mg, 1.25mmol), triphenylphosphine (984mg, 3.75mmol) and phthalimide (552mg, 3.75mmol) were dissolved in tetrahydrofuran (20ml) at 0°C under nitrogen and diisopropylazodicarboxylate (738µl, 3.75mmol) dissolved in tetrahydrofuran (2ml) was added over 10 minutes. The reaction was allowed to warm to room temperature and was stirred for 18 hours. The solvent was removed under reduced pressure, the residue was dissolved in ethanol (25ml) and hydrazine hydrate (303µl, 6.25mmol) was added. The slurry was stirred for 4 hours at 45°C under nitrogen, concentrated under reduced pressure and the residue was dissolved in methanol. The solution was then passed through an SCX column eluting with methanol to remove impurities, then 2M methanolic ammonia solution to elute the product. The product was then purified by flash chromatography on alumina eluting with dichloromethane:methanol:0.88 ammonia (90:10:1, by volume) to provide the title compound (212mg) as an oil.

^{1}H NMR (400MHz, $CDCl_3$): δ = 1.12 (m, 6H), 2.43 (q, 2H), 2.54 (q, 2H), 3.21 (t, 2H), 4.07 (t, 2H), 6.43 (m, 3H).

Microanalysis: Found C, 59.78; H, 6.50; N, 14.35. $C_{15}H_{19}F_2N_3O.0.26H_2O$ requires C, 60.05; H, 6.56; N, 14.01%.

EXAMPLE 204

3-[[1-(2-Aminoethyl)-3,5-diethyl-1*H*-pyrazol-4-yl]oxy]-5-fluorobenzamide

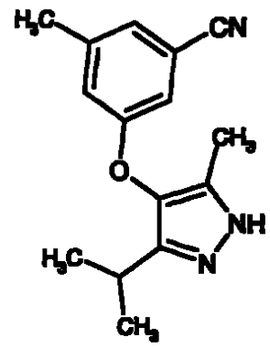


The alcohol from Example 163 (142mg, 0.44mmol), triphenylphosphine (346mg, 1.32mmol) and phthalimide (194mg, 1.32mmol) were dissolved in tetrahydrofuran (8ml) at 0°C under nitrogen and diisopropylazodicarboxylate (260µl, 1.32mmol) dissolved in tetrahydrofuran (1ml) was added over 10 minutes. The reaction was allowed to warm to room temperature and was stirred for 18 hours. The solvent was removed under reduced pressure, the residue was dissolved in ethanol (9ml) and hydrazine hydrate (107µl, 2.2mmol) was added. The slurry was stirred for 4 hours at 45°C under nitrogen, concentrated under reduced pressure and the residue was dissolved in methanol. The solution was then passed through a polymer supported sulphonic acid column eluting with methanol to remove impurities, then 2M methanolic ammonia solution to elute the product. The product was then purified by flash chromatography on alumina eluting with dichloromethane:methanol:0.88 ammonia (90:10:1, by volume) to provide the title compound (60mg) as an oil.

^{1}H NMR (400MHz, $CDCl_3$): δ = 1.11 (m, 6H), 2.43 (q, 2H), 2.53 (q, 2H), 3.17 (t, 2H), 4.05 (t, 2H), 6.01 (brs, 1H), 6.25 (brs, 1H), 6.75 (d, 1H), 7.16 (m, 2H).
HRMS: [MH^+] Found 321.1718. $C_{16}H_{21}FN_4O_2$ requires 321.1722.

EXAMPLE 205

3-[(3-Isopropyl-5-methyl-1*H*-pyrazol-4-yl)oxy]-5-methylbenzonitrile

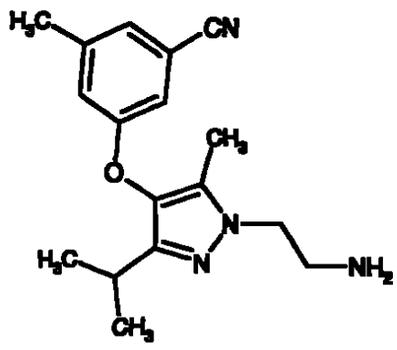


Hydrazine hydrate (100µl, 2.10mmol) was added to a solution of the diketone from Preparation 91 (544mg, 2.10mmol) in acetic acid (10ml) under nitrogen at room temperature. After stirring for 64 hours, the mixture was concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel eluting with pentane:ethyl acetate (66:34, by volume) to provide the title compound (308mg) as a pale yellow oil.

^{1}H NMR (400MHz, $CDCl_3$): δ = 1.22 (d, 6H), 2.09 (s, 3H), 2.56 (s, 3H), 2.84 (m, 1H), 6.91 (s, 1H), 6.94 (s, 1H), 7.11 (s, 1H).
LRMS (thermospray) : m/z [MH^+] 256.

EXAMPLE 206

3-[[1-(2-Aminoethyl)-3-isopropyl-5-methyl-1*H*-pyrazol-4-yl]oxy]-5-methylbenzonitrile

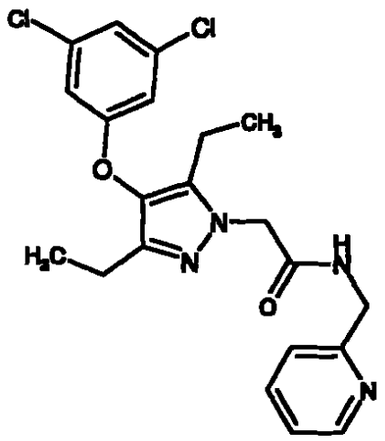


The pyrazole from Example 205 (70mg, 0.27mmol) and 2-chloroethylamine hydrochloride (38mg, 0.33mmol) were heated as a melt at 150°C for 18 hours. The residue was cooled and purified by flash chromatography on silica gel eluting with dichloromethane:methanol:0.88 ammonia (95:5:0.5, by volume) to give the title compound (25mg).

^{1}H NMR (400MHz, $CDCl_3$): δ = 1.18 (m, 6H), 2.06 (s, 3H), 2.35 (s, 3H), 2.79 (m, 1H), 3.19 (m, 2H), 4.04 (m, 2H), 6.89 (s, 1H), 6.97 (s, 1H), 7.12 (s, 1H).
LRMS (electrospray) : m/z [MH^+] 300.

EXAMPLE 207

2-[4-(3,5-Dichlorophenoxy)-3,5-diethyl-1*H*-pyrazol-1-yl]-*N*-(2-pyridinylmethyl)acetamide



Standard solutions: The acid of Preparation 4 (800mg, 2.33mmol), *1H*-benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (822mg, 3.50mmol) and diisopropylethylamine (603mg, 4.66mmol) were separately dissolved in *N,N*-dimethylformamide (3x13ml). 2-(Methylamino)pyridine (3mg, 0.029mmol) was treated with the standard solutions of the acid and coupling reagents (3x170µl) in a 96 well plate and the mixture was shaken for 14 hours at room temperature. The solvent was removed under reduced pressure and the mixture dissolved in dimethylsulphoxide (500µl) and purified by HPLC (Magellen C_8(2) 150x10mm column; a gradient mobile phase was used, 5:95 (by volume) to 95:5 (by volume) acetonitrile:(0.1% trifluoroacetic acid in water).
Retention time: 5.69 minutes.

LRMS (electrospray) : m/z [MH^+] 434.

EXAMPLE 208

[4-(3,5-Dichlorophenoxy)-3-methyl-1*H*-pyrazol-5-yl]acetonitrile

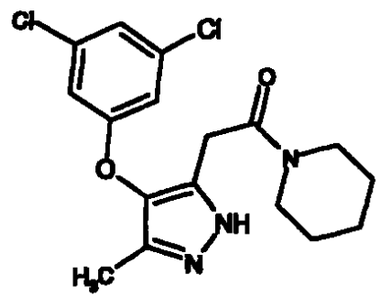


The pyrazole of Preparation 8 (1.00g, 2.60mmol) in tetrahydrofuran (10ml) was added in one portion to a solution of sodium cyanide (284mg, 5.20mmol) in water (10ml) at room temperature. The reaction was heated at 80°C for 14 hours and cooled to room temperature. The solvent was removed under reduced pressure and the resulting brown solid was dissolved in dichloromethane (50ml) and water (50ml). The organic layer was separated, washed with water (50ml), brine (30ml), dried over magnesium sulphate, filtered and the solvent removed under reduced pressure to give a brown solid. The product was purified by flash chromatography on silica gel eluting with pentane:ethyl acetate (50:50, by volume) to give the title compound as a yellow solid (500mg), m.p. 150-152°C.

^{1}H NMR (400MHz, $CDCl_3$): δ = 2.17 (s, 3H), 3.56 (s, 2H), 6.77 (s, 2H), 7.02 (s, 1H).
LRMS (thermospray) : m/z [MH^+] 282.

EXAMPLE 209

1-[[4-(3,5-Dichlorophenoxy)-3-methyl-1*H*-pyrazol-5-yl]acetyl]piperidine



Standard solutions: The acid of Preparation 92 (680mg, 2.16mmol) and *1H*-benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (761mg, 3.23mmol) were separately dissolved in *N,N*-dimethylacetamide:triethylamine (96:4) (2x17ml).

Piperidine (3mg, 0.031mmol) was treated with the standard solutions of the acid and coupling reagents (250µl of each) in a 96 well plate and the mixture was shaken for 14 hours at 80°C. The solvent was removed under reduced pressure and the mixture dissolved in dimethylsulphoxide (500µl) and purified by HPLC (Magellen C_{18}(2) 150x10mm column; a gradient mobile phase was used, 5:95 (by volume) to 95:5 (by volume) acetonitrile:(0.1% trifluoroacetic acid in water).

Retention time: 4.7 minutes.

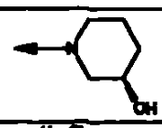
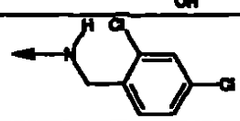
LRMS (electrospray) : m/z [MH^+] 368.

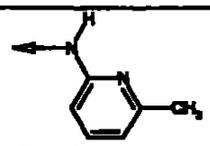
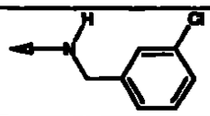
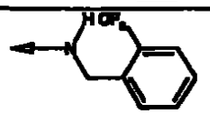
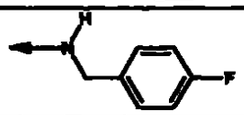
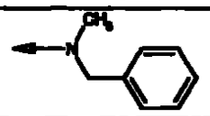
EXAMPLES 210-217

The compounds of the following tabulated Examples of the general formula:



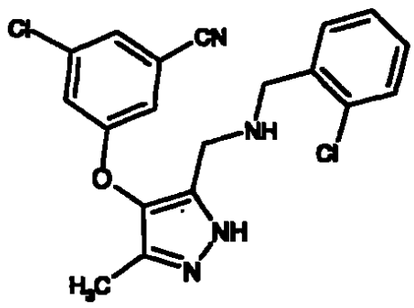
were performed by a similar method to that of Example 209 using the appropriate amine.

Example No.	X	HPLC retention times / min	LRMS (electrospray) m/z [MH^+]
210		3.9	384
211		5.5	459

212		5.4	476
213		5.3	458
214		5.1	424
215		5.3	458
216		4.9	408
217		5.2	404

EXAMPLE 218

3-chloro-5-[(5-[[(2-chlorobenzyl)amino]methyl]-3-methyl-1*H*-pyrazol-4-yl)oxy]benzonitrile



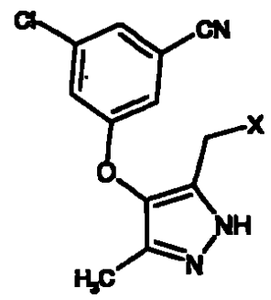
Standard solutions: The bromide of Preparation 18 (850mg, 2.30mmol) was dissolved in *N*-methylpyrolidinone (43ml).

2-Chlorobenzylamine (19mg, 0.13mmol) in a 96 well plate was treated with the solution of the bromide of Preparation 18 (500µl) and the mixture was shaken for 14 hours at 80°C. The solvent was removed under reduced pressure and the mixture dissolved in dimethylsulphoxide (500µl) and purified by HPLC (Magellen C_8(2)

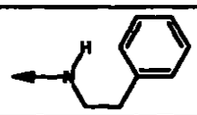
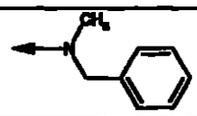
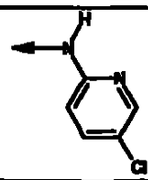
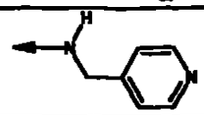
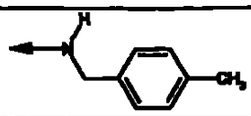
150x10mm column; a gradient mobile phase was used, 5:95 (by volume) to 95:5 (by volume) acetonitrile:(0.1% trifluoroacetic acid in water).
Retention time: 5.3 minutes.
LRMS (electrospray) : m/z [MH^+] 386.

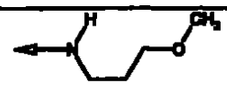
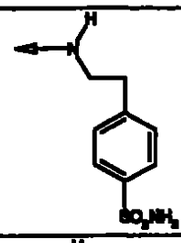
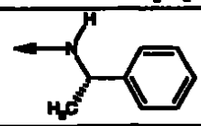
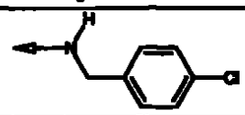
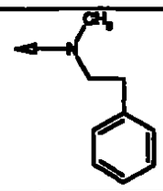
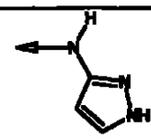
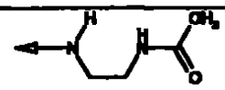
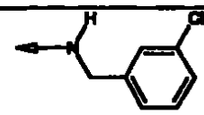
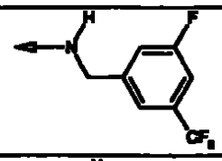
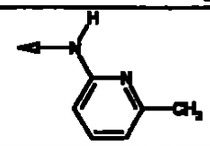
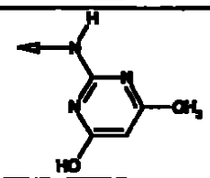
EXAMPLES 219-249

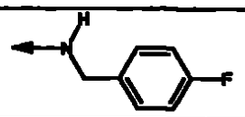
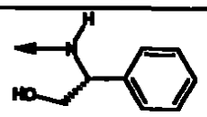
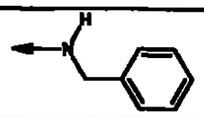
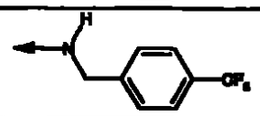
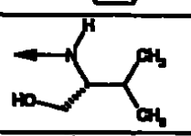
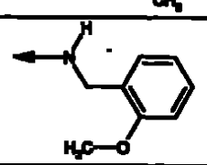
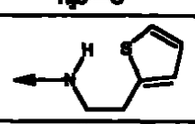
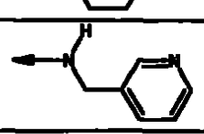
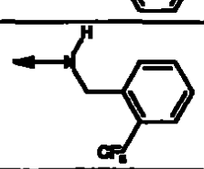
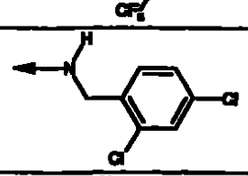
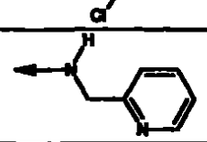
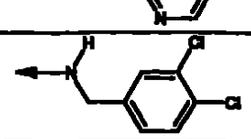
The compounds of the following tabulated Examples of the general formula:

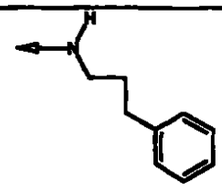
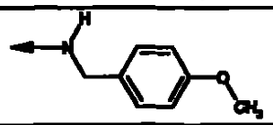


were performed by a similar method to that of Example 218 using the appropriate amine.

Example No.	X	HPLC retention times / min	LRMS (electrospray) m/z [MH^+]
219		4.2	367
220		4.1	366
221		3.8	374
222		3.2	353
223		4.2	366

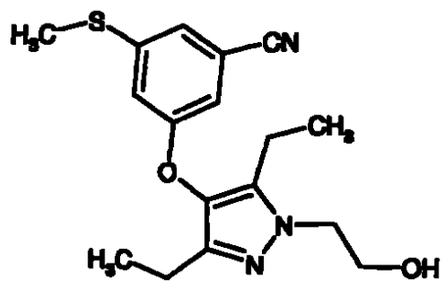
224		3.7	334
225		3.7	445
226		4.1	366
227		4.3	387
228		4.2	380
229		3.6	328
230		3.5	347
231		4.3	387
232		4.5	438
233		3.8	353
234		3.7	370

235		4.1	370
236		4.1	396
237		4.1	352
238		4.1	382
239		4.4	420
240		4.0	362
241		4.1	382
242		4.2	372
243		3.2	353
244		4.2	420
245		4.4	421
246		3.7	353
247		4.4	421

248		4.1	382
249		4.1	382

EXAMPLE 250

3-{[3,5-Diethyl-1-(2-hydroxyethyl)-1*H*-pyrazol-4-yl]oxy}-5-(methylsulfanyl)benzonitrile

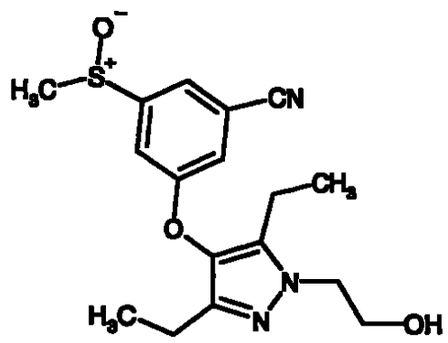


The protected alcohol from Preparation 93 (687mg, 1.65mmol) and p-toluene-sulphonic acid (32mg, 0.17mmol) were dissolved in methanol (16ml) and stirred under nitrogen at room temperature. After 4 hours a second portion of p-toluene-sulphonic acid (32mg, 0.17mmol) was added. After 18 hours the solvent was removed under reduced pressure and the residue was partitioned between saturated aqueous sodium bicarbonate solution (20ml) and dichloromethane (20ml). The aqueous phase was extracted with dichloromethane (40ml) and the combined organic extracts were dried over magnesium sulphate, concentrated under reduced pressure and purified by flash chromatography on silica gel eluting with dichloromethane:methanol (97:3, by volume) to provide the title compound (487mg) as a white solid. m.p. 72 °C.

^{1}H NMR (400MHz, $CDCl_3$): δ = 1.14 (m, 6H), 2.44 (q, 2H), 2.49 (s, 3H), 2.53 (q, 3H), 4.08 (m, 2H), 4.14 (m, 2H), 6.84 (s, 1H), 7.00 (s, 1H), 7.10 (s, 1H).
LRMS (electrospray) : m/z [MH^+] 332.
Microanalysis: Found C, 61.36; H, 6.43; N, 12.55. $C_{17}H_{21}N_3O_2S$ requires C, 61.61; H, 6.39; N, 12.68%.

EXAMPLE 251

3-[3,5-Diethyl-1-(2-hydroxyethyl)-1*H*-pyrazol-4-yl]oxy}-5-(methylsulfinyl)benzonitrile

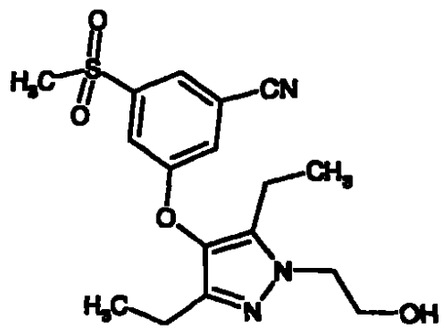


Wet alumina was prepared by adding water (1ml) to Brockman grade I alumina (5g). T a stirred solution of the sulphide from Example 250 (134mg, 0.40mmol) in dichloromethane (2ml) was added of wet alumina (400mg) followed by Oxone® (123mg, 0.4mmol) and the mixture was heated at reflux. After 1 hour a second portion of oxone (123mg, 0.40mmol) was added and the mixture was heated for a further 2 hours. After cooling to room temperature the reaction mixture was filtered and the resulting solids were washed with dichloromethane (20ml). The filtrate was concentrated and was purified by flash chromatography on silica gel eluting with dichloromethane:methanol (a gradient from 99:1 to 90:10, by volume) to provide the title compound (92mg) as an oil.

^{1}H NMR (400MHz, $CDCl_3$): δ = 1.12 (m, 6H), 2.44 (q, 2H), 2.53 (q, 2H), 2.73 (s, 3H), 4.06 (m, 2H), 4.18 (m, 2H), 7.24 (s, 1H), 7.45 (s, 1H), 7.49 (s, 1H).
LRMS (electrospray) : m/z [M+Na^+] 370.

EXAMPLE 252

3-[3,5-Diethyl-1-(2-hydroxyethyl)-1*H*-pyrazol-4-yloxy]-5-(methylsulfonyl)benzonitrile



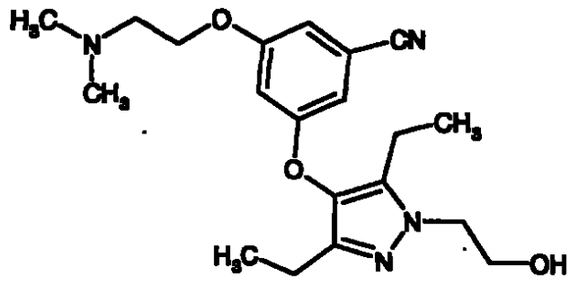
To a stirred solution of the sulphide from Example 250 (133mg, 0.4mmol) in dichloromethane (2ml) at –78°C was added a solution of meta-chloroperoxybenzoic acid (138mg of 50% by weight mixture, 0.4mmol) in dichloromethane (2ml). The cooling bath was removed and the solution was stirred at room temperature for 4 hours. The mixture was quenched by addition of saturated aqueous sodium bicarbonate solution (6ml) and extracted with dichloromethane (3x5ml). The combined organic components were dried over magnesium sulphate and concentrated. Analysis of the ^{1}H NMR (400MHz, $CDCl_3$) suggested a mixture of the desired product and the sulphoxide from Example 251. The crude product mixture was dissolved in dichloromethane (2ml), cooled to –78°C and to this was added meta-chloroperoxybenzoic acid (138mg of 50% by weight mixture, 0.4mmol) in dichloromethane (2ml). The cooling bath was removed and the mixture was stirred at room temperature for 1 hour. The mixture was quenched by addition of saturated aqueous sodium bicarbonate solution (6ml) and extracted with dichloromethane (3x5ml). The combined organic components were dried over magnesium sulphate and concentrated. The crude product mixture was purified by flash chromatography on a silica gel eluting with dichloromethane:methanol (98:2, by volume) to provide the title compound contaminated with meta-chloroperoxybenzoic acid. To a solution of this crude product in dichloromethane at –78°C was added dimethylsulphoxide (30µl, 0.4mmol). The cooling bath was removed and the mixture was stirred at room temperature for 15 minutes. The mixture was quenched by addition of 10% aqueous potassium carbonate solution (10ml) and the dichloromethane was evaporated. The remaining aqueous mixture was then extracted with diethyl ether (2x10ml) and ethyl acetate (10ml). The organic components were combined, dried over magnesium

sulphate and concentrated to give the crude product mixture which was purified by flash chromatography on a silica gel eluting with dichloromethane:methanol (98:2, by volume) to provide the title compound (26mg) as a white solid. m.p. 133 °C.

^{1}H NMR (400MHz, $CDCl_3$): δ = 1.10 (m, 6H), 2.39 (q, 2H), 2.51 (q, 2H), 3.06 (s, 3H), 4.05 (m, 2H), 4.10 (m, 2H), 7.39 (s, 1H), 7.67 (s, 1H), 7.84 (s, 1H).
LRMS (electrospray) : m/z [$M+Na^+$] 385.
HRMS: [MH^+] 364.1329. $C_{18}H_{20}N_6O_2$ requires 364.1326.

EXAMPLE 253

3-[[3,5-Diethyl-1-(2-hydroxyethyl)-1*H*-pyrazol-4-yl]oxy]-5-[2-(dimethylamino)ethoxy]benzonitrile



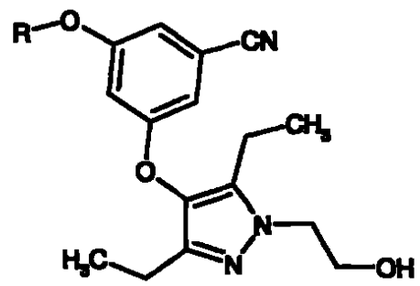
To a stirred solution of the protected alcohol from Preparation 94 (180mg, 0.39mmol) in methanol (4ml) was added para-toluenesulphonic acid (89mg, 0.47mmol). After 18 hours at room temperature the solvent was evaporated under reduced pressure and the residue was partitioned between dichloromethane (5ml) and 10% aqueous potassium carbonate solution (5ml). The aqueous phase was separated and extracted with a dichloromethane (3ml). The organic components were combined, dried over magnesium sulphate and concentrated under reduced pressure. The crude product mixture was purified by flash chromatography on silica gel eluting with dichloromethane:methanol (95:5, by volume) followed by dichloromethane:methanol:ammonia (80:20:1, by volume) to provide the title compound (63mg) as an oil.

^{1}H NMR (400MHz, $CDCl_3$): δ =1.13 (m, 6H), 2.43 (m, 8H), 2.52 (q, 2H), 2.85 (m, 2H), 3.81 (broad s, 1H), 4.08 (m, 6H), 6.70 (s, 1H), 6.78 (s, 1H), 6.81 (s, 1H).
LRMS (APCI) : m/z [MH^+] 373.

HRMS: [MH^+] 373.2234. $C_{20}H_{29}N_4O_3$ requires 373.2234.

EXAMPLES 254-256

The compounds of the following tabulated Examples of the general formula:



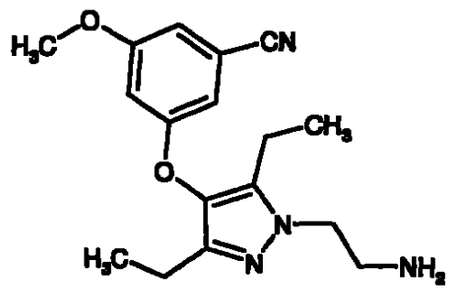
were performed by a similar method to that of Example 253 using as starting material the appropriate protected alcohol (PA) from Preparations 95-97.

Example No.	PA prep No.	R	Analytical Data
254	95	CH_2CH_2NHMe	^1H NMR (400MHz, $CDCl_3$): δ = 1.13 (m, 6H), 2.42 (q, 2H), 2.53 (q, 2H), 2.59 (s, 3H), 3.12 (t, 2H), 4.05 (m, 2H), 4.09 (m, 2H), 4.16 (t, 2H), 6.75 (s, 1H), 6.81 (s, 1H), 6.82 (s, 1H). LRMS (APCI): m/z [MH^+] 359 HRMS: [MH^+] 359.2083. $C_{19}H_{27}N_4O_3$ requires 359.2078.
255	96	CH_2CONH_2	^1H NMR (400MHz, $CDCl_3$): δ = 1.11 (m, 6H), 2.41 (q, 2H), 2.52 (q, 2H), 4.05 (t, 2H), 4.09 (t, 2H), 4.46 (s, 2H), 5.74 (broad s, 1H), 6.42 (broad s, 1H), 6.69 (s, 1H), 6.85 (s, 2H). LRMS (APCI): m/z 359 (MH^+)

256	97	$CH_2CH_2OCH_3$	^1H NMR (400MHz, $CDCl_3$): δ = 1.12 (m, 6H), 2.42 (q, 2H), 2.51 (q, 2H), 3.44 (s, 3H), 3.73 (t, 2H), 4.09 (m, 6H), 6.71 (s, 1H), 6.77 (s, 1H), 6.83 (s, 1H). LRMS (electrospray): m/z 360 (MH^+) HRMS: [MH^+] 360.1920. $C_{19}H_{26}N_3O_4$ requires 360.1918.

EXAMPLE 257

3-[[1-(2-Aminoethyl)-3,5-diethyl-1*H*-pyrazol-4-yl]oxy]-5-methoxybenzonitrile

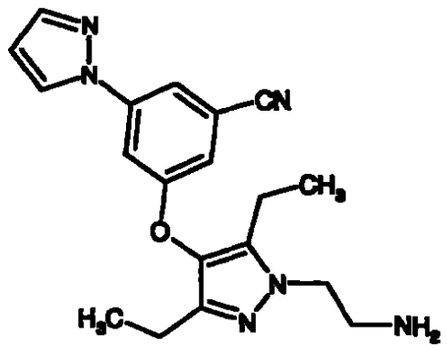


The alcohol from Example 202 (87mg, 0.28mmol), triphenylphosphine (220mg, 0.84mmol) and phthalimide (124mg, 0.84mmol) were dissolved in tetrahydrofuran (5ml) at 0°C under nitrogen and diisopropylazodicarboxylate (165µl, 0.84mmol) dissolved in tetrahydrofuran (1ml) was added dropwise. The reaction was allowed to warm to room temperature and was stirred for 18 hours. The solvent was removed under reduced pressure, the residue was dissolved in ethanol (6ml) and hydrazine hydrate (68µl, 1.40mmol) was added. The slurry was stirred for 48 hours at room temperature under nitrogen, concentrated under reduced pressure and the residue was dissolved in methanol. The solution was then passed through an SCX column eluting with methanol to remove impurities, then 2M ammonia in methanol solution to elute the product. The product was then purified by flash chromatography on silica gel eluting with dichloromethane:methanol (95:5) then dichloromethane:methanol:0.88 ammonia (90:10:1, by volume) to provide the title compound (67mg) as an oil.

^{1}H NMR (400MHz, $CDCl_3$): δ = 1.13 (m, 6H), 2.19 (broad s, 2H), 2.43 (q, 2H), 2.54 (q, 2H), 3.19 (t, 2H), 3.60 (s, 3H), 4.06 (t, 2H), 6.68 (s, 1H), 6.73 (s, 1H), 6.80 (s, 1H).
LRMS (electrospray): m/z 315 (MH^+)
HRMS: [MH^+] 315.1819. $C_{17}H_{23}N_4O_2$ requires 315.1816.

EXAMPLE 258

3-[[1-(2-Aminoethyl)-3,5-diethyl-1*H*-pyrazol-4-yl]oxy]-5-(1*H*-pyrazol-1-yl)benzonitrile



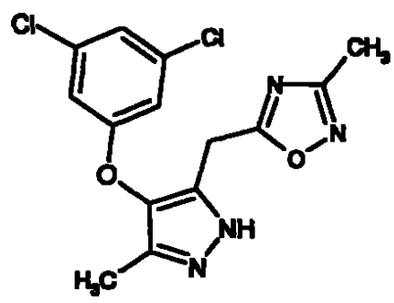
The alcohol from Example 164 (162mg, 0.46mmol), triphenylphosphine (362mg, 1.38mmol) and phthalimide (203mg, 1.38mmol) were dissolved in tetrahydrofuran (8ml) at 0°C under nitrogen and diisopropylazodicarboxylate (272µl, 1.38mmol) dissolved in tetrahydrofuran (1ml) was added dropwise. The reaction was allowed to warm to room temperature and was stirred for 18 hours. The solvent was removed under reduced pressure, the residue was dissolved in ethanol (9ml) and hydrazine hydrate (112µl, 2.3mmol) was added. The slurry was stirred for 48 hours at room temperature under nitrogen, concentrated under reduced pressure and the residue was dissolved in methanol. The solution was then passed through an SCX column eluting with methanol to remove impurities, then 2M ammonia in methanol solution to elute the product. The product was then purified by flash chromatography on silica gel eluting with dichloromethane:methanol (95:5) then dichloromethane:methanol:0.880 ammonia (90:10:1, by volume) to provide the title compound (62mg) as an oil.

^{1}H NMR (400MHz, CD_3OD): δ = 1.15 (m, 6H), 2.46 (q, 2H), 2.63 (q, 2H), 3.13 (t, 2H), 4.13 (t, 2H), 6.54 (s, 1H), 7.17 (s, 1H), 7.69 (s, 1H), 7.72 (s, 1H), 7.82 (s, 1H), 8.32 (s, 1H).

LRMS (APCI): m/z 351 (MH^+)
HRMS: [MH^+] 351.1929. $C_{19}H_{22}N_4O_2$ requires 351.1928.

EXAMPLE 259

3,5-Dichlorophenyl-3-methyl-5-[(3-methyl-1,2,4-oxadiazol-5-yl)methyl]-1*H*-pyrazol-4-yl ether

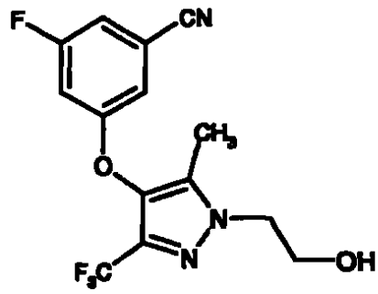


To a stirred solution of the acid (100mg, 0.33mmol) from Preparation 92 in dimethylformamide (2ml) was added carbonyldiimidazole (59mg, 0.36mmol) in one portion. After 30 minutes at room temperature (1*Z*)-*N*'-hydroxyethanimidamide (27mg, 0.36mmol) was added and the reaction mixture was stirred at room temperature for 3 hours. A second portion of carbonyldiimidazole (59mg, 0.36mmol) was added and the mixture was heated at 100°C for 12 hours. After cooling to room temperature water (30ml) was added and the mixture was extracted with ethyl acetate (3 x 20ml). The combined organic components were dried over magnesium sulphate and concentrated under reduced pressure to give a brown oil. Th crude product mixture was purified by flash chromatography on silica gel eluting with ethyl acetate:pentane (30:70, by volume) to provide the title compound (40mg) as a pale yellow oil.

^{1}H NMR (400MHz, $CDCl_3$): δ = 2.12 (s, 3H), 2.29 (s, 3H), 4.08 (s, 2H), 6.74 (s, 2H), 6.98 (s, 1H).
LRMS (electrospray): m/z 339 (MH^+)

EXAMPLE 260

3-Fluoro-5-[[1-(2-hydroxyethyl)-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl]oxy]benzonitrile

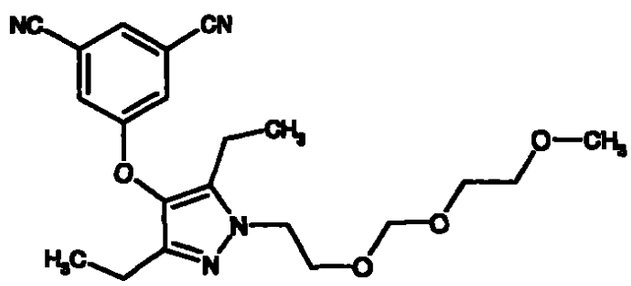


To a stirred solution of the protected alcohol (85mg, 0.21mmol) from Preparation 99 in methanol (0.5ml) was added para-toluenesulphonic acid (4mg, 0.02mmol). After 5 hours the reaction mixture was concentrated under reduced pressure, dissolved in dichloromethane (20ml), washed with saturated sodium bicarbonate solution (20ml), dried over magnesium sulphate and concentrated under reduced pressure. The crude product mixture was purified by flash chromatography on silica gel eluting with pentane:ethyl acetate (60:40 followed by 40:60, by volume) to provide the title compound (54mg) as a white solid.

^{1}H NMR (400MHz, $CDCl_3$): δ = 2.19 (s, 3H), 2.45 (t, 1H), 4.10 (m, 2H), 4.20 (m, 2H), 6.87 (d, 1H), 6.96 (s, 1H), 7.05 (d, 1H).
LRMS (APCI): m/z 330 (MH^+)
Microanalysis: Found C, 51.38; H, 3.52; N, 12.37. $C_{14}H_{11}F_4N_3O_2$ requires C, 51.07; H, 3.37; N, 12.76%.

EXAMPLE 261

5-[(3,5-Diethyl-1-[2-[(2-methoxyethoxy)methoxy]ethyl]-1*H*-pyrazol-4-yl)oxy]isophthalonitrile

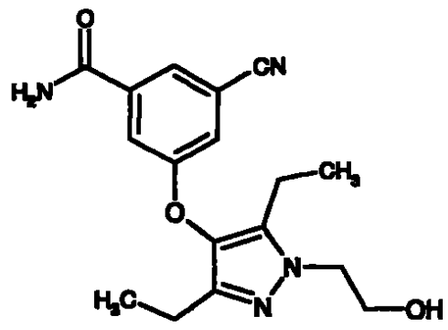


To a stirred solution of the alcohol (5.0g, 16.11mmol) from Example 119 in tetrahydrofuran (65ml) at 0°C was added 2-methoxyethoxymethylchloride (2.39ml, 20.94mmol) followed by sodium hydride (838mg of a 60% by weight dispersion in oil, 20.94mmol). After 10 minutes the reaction mixture was heated at 50°C for 18 hours. After cooling to room temperature, the mixture was diluted with saturated aqueous ammonium chloride solution dropwise (3ml). The mixture was concentrated under reduced pressure and the residue was partitioned between dichloromethane (250ml) and water (200ml). The aqueous phase was separated and extracted with dichloromethane (150ml). The organic components were combined, dried over magnesium sulphate and concentrated under reduced pressure. The crude product mixture was purified by flash chromatography on silica gel eluting with dichloromethane, followed by dichloromethane:methanol (99:1, by volume) to provide the title compound (5.38g) as a colourless oil.

^{1}H NMR (400MHz, $CDCl_3$): δ = 1.10 (m, 6H), 2.39 (q, 2H), 2.55 (q, 2H), 3.38 (s, 3H), 3.51 (m, 2H), 3.56 (m, 2H), 3.93 (t, 2H), 4.20 (t, 2H), 4.66 (s, 2H), 7.38 (s, 2H), 7.56 (s, 1H).
LRMS (APCI): m/z 399 (MH^+)
Microanalysis: Found C, 62.11; H, 6.67; N, 13.51. $C_{21}H_{26}N_4O_4$+0.43H_2O requires C, 62.09; H, 6.67; N, 13.79%.

EXAMPLE 262

3-Cyano-5-[[3,5-diethyl-1-(2-hydroxyethyl)-1*H*-pyrazol-4-yl]oxy]benzamide



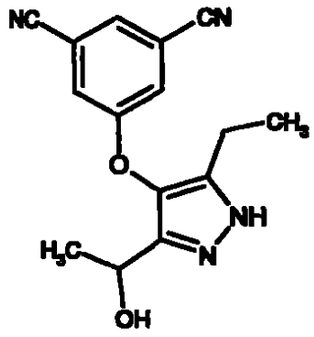
To a stirred solution of the pyrazole (80mg) from Preparation 100 in dichloromethane (4ml) was added aluminium trichloride (134mg, 1mmol). After 18 hours, ice was added, the mixture was neutralised using saturated aqueous sodium

bicarbonate solution, diluted with water (30ml) and extracted with dichloromethane (2x40ml). The organic components were combined, dried over magnesium sulphate and concentrated under reduced pressure. The crude product mixture was purified by flash chromatography on silica gel eluting with dichloromethane:methanol (95:5, by volume) to provide the title compound (27mg) as a colourless glass.

^{1}H NMR (400MHz, $CDCl_3$): δ = 1.10 (m, 6H), 2.40 (q, 2H), 2.52 (q, 2H), 4.07 (m, 4H), 7.25 (s, 1H), 7.60 (s, 1H), 7.65 (s, 1H).
LRMS (APCI): m/z 329 (MH^+)

EXAMPLE 263

5-[[5-Ethyl-3-(1-hydroxyethyl)-1*H*-pyrazol-4-yl]oxy]isophthalonitrile

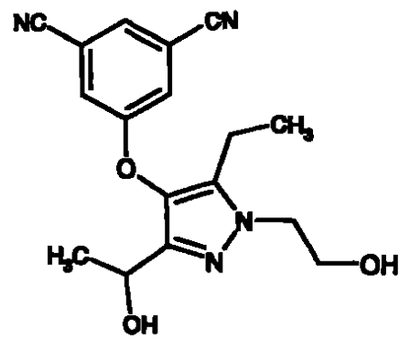


To a stirred solution of the pyrazole from Preparation 102 (219mg, 0.57mmol) in tetrahydrofuran (2.5ml) was added saturated aqueous sodium carbonate solution (0.5ml). The reaction mixture was stirred at room temperature for 4 hours and then heated at reflux for 18 hours. The reaction mixture was concentrated under reduced pressure and the residue was partitioned between dichloromethane (20ml) and water (20ml). The organic phase was dried over magnesium sulphate and concentrated under reduced pressure. The crude product mixture was purified by flash chromatography on silica gel eluting with dichloromethane:methanol (a gradient from 100:0 to 90:10, by volume) to provide the title compound (68mg) as a white solid.

^{1}H NMR (400MHz, $CDCl_3$): δ =1.21 (t, 3H), 1.51 (d, 3H), 2.54 (q, 2H), 4.89 (q, 1H), 7.25 (s, 2H), 7.43 (s, 1H).
LRMS (APCI): m/z 283 (MH^+)

EXAMPLE 264

5-[[5-Ethyl-3-(1-hydroxyethyl)-1-(2-hydroxyethyl)-1*H*-pyrazol-4-yl]oxy]isophthalonitrile

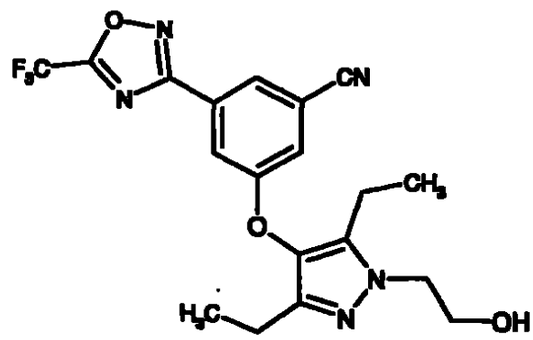


T a stirred solution of the pyrazole from Preparation 103 (80mg, 0.19mmol) in methanol (1ml) was added para-toluenesulphonic acid (4mg, 0.02mmol). After 5 hours at room temperature the reaction mixture was concentrated under reduced pressure and the residue was partitioned between dichloromethane (20ml) and water (20ml). The organic component was dried over magnesium sulphate and concentrated under reduced pressure. The crude product mixture was purified by flash chromatography on silica gel eluting with dichloromethane:methanol (a gradient from 100:0 to 95:5, by volume) to provide the title compound (44mg) white solid.

^{1}H NMR (400MHz, $CDCl_3$): δ =1.11 (t, 3H), 1.46 (d, 3H), 2.54 (q, 2H), 4.10 (q, 2H), 4.17 (q, 2H), 4.79 (q, 1H), 7.44 (s, 2H), 7.57 (s, 1H).
LRMS (APCI): m/z 327 (MH^+)

EXAMPLE 265

3-[3,5-Diethyl-1-(2-hydroxyethyl)-1*H*-pyrazol-4-yl]oxy)-5-(5-trifluoromethyl-1,2,4-oxadiazol-3-yl)benzonitrile

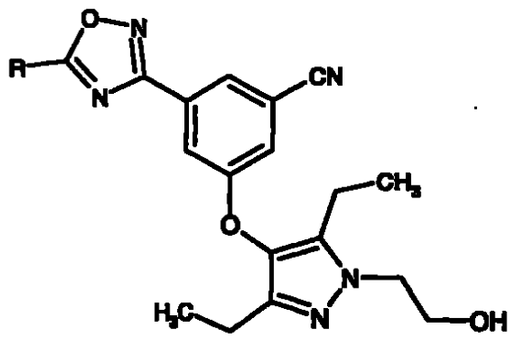


To a stirred solution of the pyrazole from Preparation 105 (235mg, 0.46mmol) in dichloromethane (2ml) was added aluminium trichloride (373mg, 2.8mmol). The reaction mixture was stirred at room temperature for 48 hours, diluted with water (6ml) and extracted with dichloromethane (6ml). The organic component was concentrated under reduced pressure and purified by flash chromatography on silica gel eluting with dichloromethane:methanol (a gradient from 99:1 to 80:20, by volume) followed by dichloromethane:methanol:0.88 ammonia (80:20:1, by volume) to provide an impure sample of the title compound (44mg) as a white solid. The product was further purified by HPLC using a Phenomonex Luna C_{18} 150x21.2mm column eluting with a solvent gradient of 5:95 0.1% aqueous trifluoroacetic acid in acetonitrile:acetonitrile (0-1min 80:20; 1-7min 80:20 changing to 0:100; 7-12min 0:100; 12-12.1min 0:100 changing to 80:20; 12.1-15min 80:20) to provide the titl compound (38mg) as a white solid.

Retention time 5.7minutes.
LRMS (electrospray): m/z 422 (MH^+)

EXAMPLES 266-268

The compounds of the following tabulated Examples of the general formula:

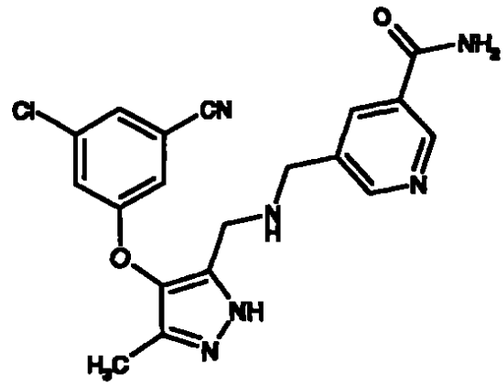


were prepared by a similar method to that of Example 265 using the appropriate protected alcohol (PA) from Preparation 106-108.

Example No.	PA prep No.	R	Analytical Data
266	106	Me	Retention time 4.8 minutes LRMS (electrospray): m/z [MH^+] 368
267	107	Et	Retention time 5.3 minutes LRMS (electrospray): m/z [MH^+] 382
268	108	^iPr	Retention time 5.7 minutes LRMS (electrospray): m/z 396 (MH^+)

EXAMPLE 269

5-[({[4-(3-Chloro-5-cyanophenoxy)-3-methyl-1*H*-pyrazol-5-yl]methyl}amino)methyl]nicotinamide

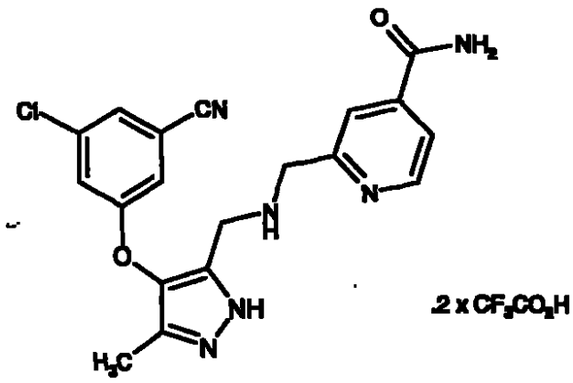


To a stirred solution of the amine from Preparation 111 (650mg, 1.70mmol) in iso-propyl alcohol (6ml) was added the pyrazole from Preparation 18 (210mg, 0.57mmol) followed by potassium carbonate (240mg, 1.70mmol). The reaction mixture was heated at reflux for 1.5 hours. After cooling to room temperature the mixture was concentrated under reduced pressure and the crude product mixture was purified by flash chromatography on silica gel eluting with dichloromethane:methanol:0.88 ammonia (95:5:0.5 then 90:10:1 then 80:20:1, by volume) which gave an impure sample of the desired product. Flash chromatography was repeated eluting with dichloromethane:methanol:0.88 ammonia (100:0:0 then 95:5:0.5 then 90:10:1, by volume) to provide the title compound (10mg) as a pale yellow solid.

^{1}H NMR (400MHz, CD_3OD): δ = 2.05 (s, 3H), 3.62 (s, 2H), 3.79 (s, 2H), 7.16 (m, 1H), 7.18 (m, 1H), 7.38 (s, 1H), 8.15 (s, 1H), 8.54 (s, 1H), 8.84 (s, 1H).
LRMS (APCI): m/z 419 ($M+Na^+$)
HRMS: [MH^+] 397.1173. $C_{18}H_{18}N_6O_2Cl$ requires 397.1175.

EXAMPLE 270

2-[({[4-(3-Chloro-5-cyanophenoxy)-3-methyl-1*H*-pyrazol-5-yl]methyl}amino)methyl]isonicotinamide



To a stirred suspension of the amine from Preparation 115 (250mg, 1.66mmol) and the pyrazole from Preparation 18 (155mg, 0.42mmol) in isopropanol (6ml) was added tetrahydofuran (2ml). The mixture was heated at reflux for 2 hours after which the reaction mixture was concentrated under reduced pressure. The crude product mixture was purified by flash chromatography on silica gel eluting with dichloromethane:methanol:0.88 ammonia (85:15:1, by volume) to provide an impure sample of the title compound. The product was further purified by HPLC using a Phenomonex Luna C_8(II) 10µM 150x21.2mm column eluting with a solvent gradient of 5:95 0.1% aqueous trifluoroacetic acid in acetonitrile:acetonitrile (0-6min 95:5 changing to 0:100; 6-10min 0:100) to provide the title compound (65mg) as an off-white solid.

Retention time: 3.40 minutes

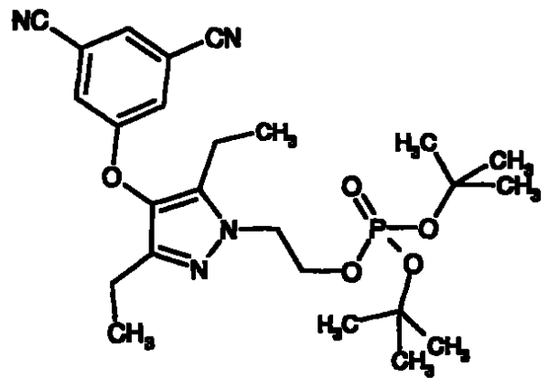
^{1}H NMR (400MHz, CD_3OD): δ = 2.14 (s, 3H), 4.21 (s, 2H), 4.50 (s, 2H), 7.19 (s, 1H), 7.27 (m, 1H), 7.43 (m, 1H), 7.48 (m, 1H), 7.78 (m, 1H), 8.68 (d, 1H)

LRMS (electrospray): m/z 397 (MH^+)

Microanalysis: Found C, 44.56; H, 3.41; N, 14.07. $C_{18}H_{17}N_5O_2Cl$+1.9.CF_3CO_2H requires C, 44.64; H, 3.11; N, 13.70%.

EXAMPLE 271

Di(*tert*-butyl) 2-[4-(3,5-dicyanophenoxy)-3,5-diethyl-1*H*-pyrazol-1-yl]ethyl phosphate

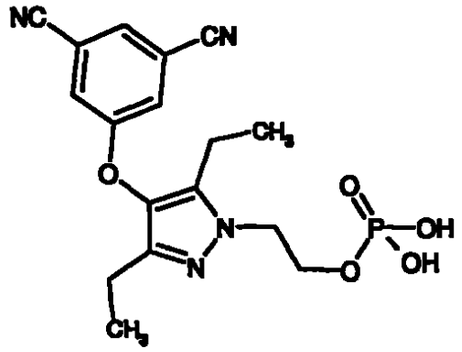


To a stirred solution of the alcohol from Example 119 (500mg, 1.60mmol) in dichloromethane (5ml) was added tetrazole (226mg, 3.20mmol) followed by di-*tert*-butyl-N,N-diisopropylphosphoramidite (1.02ml, 3.20mmol). After stirring for 4 hours at room temperature the reaction mixture was cooled to 0°C and meta-chloroperoxybenzoic acid (1.0g of 50% by weight mixture, 3mmol) was added portionwise (CARE, EXOTHERM). After 10 minutes the mixture was warmed to room temperature and was diluted with dichloromethane (50ml). The solution was washed with saturated aqueous sodium carbonate solution (20ml) and the aqueous component was separated and extracted with dichloromethane (20ml). The combined organic components were washed with brine (20ml), dried over magnesium sulphate and concentrated under reduced pressure. The crude product mixture was purified by flash chromatography on silica gel eluting with dichloromethane:methanol:0.88 ammonia (100:0:0 then 99:1:0.1 then 98:2:0.2, by volume) to provide a sample of the title compound (660mg)

^{1}H NMR (400MHz, $CDCl_3$): δ = 1.10 (m, 6H), 1.43 (s, 18H), 2.38 (q, 2H), 2.55 (q, 2H), 4.26 (m, 4H), 7.38 (s, 2H), 7.54 (s, 1H).
LRMS (electrospray): m/z 525 (MH^+)
Microanalysis: Found C, 57.77; H, 7.38; N, 10.33. $C_{25}H_{35}N_4O_5P+H_2O$ requires C, 57.68; H, 7.16; N, 10.76%.

EXAMPLE 272

2-[4-(3,5-Dicyanophenoxy)-3,5-diethyl-1*H*-pyrazol-1-yl]ethyl dihydrogen phosphate



To a stirred solution of the phosphate ester from Example 271 (250mg, 0.48mmol) in dichloromethane (10ml) at 0°C was added trifluoroacetic acid (0.5ml). The reaction mixture was allowed to warm to room temperature and after 4 hours it was concentrated under reduced pressure. The residue was purified by HPLC using a Phenomonex Luna C_8(II) 10µM 150x21.2mm column eluting with a solvent gradient of 5:95 0.1% aqueous trifluoroacetic acid in acetonitrile:acetonitrile (0-1.9min 95:5; 2-10min 90:10 changing to 30:70; 10.0-13.8min 30:70; 13.8-13.9min 30:70 changing to 95:5; 13.9-15min 95:5) to give a sample of the desired product. This sample was further purified by recrystallisation using acetonitrile/water which gave the title compound as a white solid, m.p. 198-199 °C.

Retention time: 2.31 minutes.

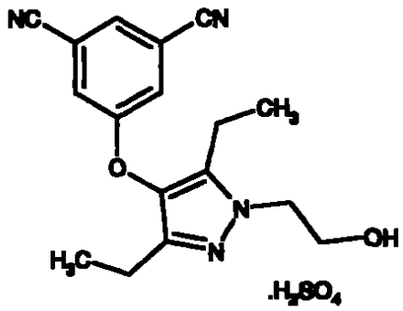
^{1}H NMR (400MHz, CD_3OD): δ = 1.09 (m, 6H), 2.35 (q, 2H), 2.61 (q, 2H), 4.28 (m, 4H), 7.55 (s, 2H), 7.79 (s, 1H).

LRMS (APCI): m/z 391 (MH^+)

Microanalysis: Found C, 50.99; H, 4.92; N, 14.06. $C_{17}H_{19}N_4O_5P+0.5H_2O$ requires C, 51.13; H, 5.05; N, 14.03%.

EXAMPLE 273

5-[(3,5-Diethyl-1-(2-hydroxyethyl)-1*H*-pyrazol-4-yl)oxy]isophthalonitrile sulfate salt

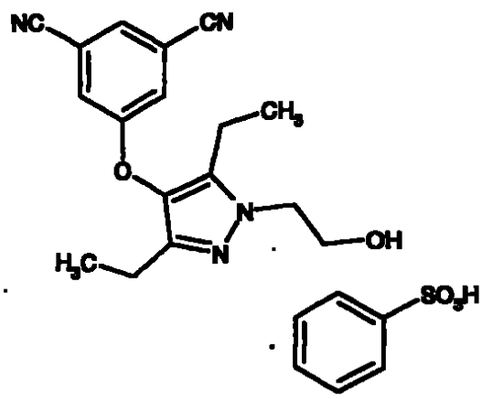


To a stirred solution of the pyrazole from Example 119 (200mg, 0.65mmol) in acetone (5ml) was added sulfuric acid (0.32ml of a 2M aqueous solution, 0.64mmol) and the mixture was stirred at room temperature and the solvent allowed to evaporate. The residue was recrystallised (toluene/acetone) to give the title compound (160mg) as a white powder, m.p. 105-110°C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.22 (m, 6H), 2.70 (m, 4H), 4.12 (bs, 1H), 4.5? (m, 2H), 4.75 (bs, 1H), 7.66 (s, 1H), 7.69 (m, 1H), 7.72 (s, 1H).
Microanalysis: Found C, 50.29; H, 4.90; N, 13.48. $C_{17}H_{18}N_4O_2.H_2SO_4$ requires C, 49.99; H, 4.93; N, 13.72%.

EXAMPLE 274

5-[(3,5-Diethyl-1-(2-hydroxyethyl)-1*H*-pyrazol-4-yl)oxy]isophthalonitrile benzenesulfonic acid salt

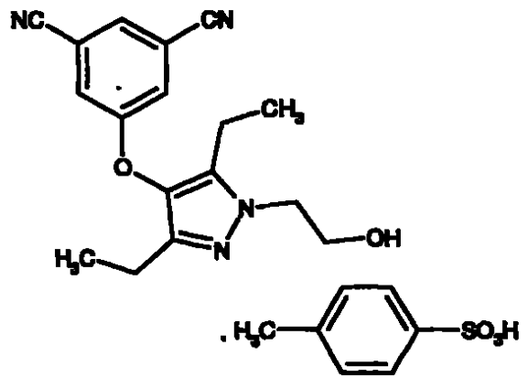


To a stirred solution of the pyrazole from Example 119 (20g, 65mmol) in acetone (200ml) was added benzenesulfonic acid (10.7g, 68mmol) and the mixture was stirred at room temperature for 10 minutes. The reaction mixture was concentrated under reduced pressure and the residue was recrystallised twice (acetone) to give the title compound (16.2g) as a white powder, m.p. 142-144°C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.05-1.08 (m, 6H), 2.59 (q, 2H), 2.68 (q, 2H), 4.04 (t, 2H), 4.54 (t, 2H), 7.35-7.42 (m, 3H), 7.55 (s, 1H), 7.64 (s, 1H), 7.86 (d, 2H).
Microanalysis: Found C, 58.86; H, 5.13; N, 11.88. $C_{23}H_{24}N_4O_5S$ requires C, 58.96; H, 5.16; N, 11.96%.

EXAMPLE 275

5-[(3,5-Diethyl-1-(2-hydroxyethyl)-1*H*-pyrazol-4-yl)oxy]isophthalonitrile tosylate salt

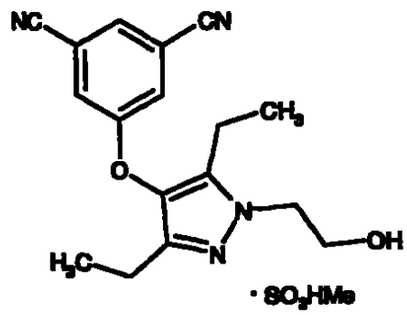


To a stirred suspension of the pyrazole from Example 119 (300mg, 1.00mmol) in ethanol (2ml) was added *p*-toluenesulfonic acid (202mg, 1.10mmol) and the mixture was heated on an oil bath until the solids dissolved. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was crystallised (diethyl ether), filtered and recrystallised (isopropyl alcohol) to give the title compound (200mg) as a white solid, m.p. 120°C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.00 (m, 6H), 2.24 (m, 5H), 2.49 (m, 2H), 4.00 (m, 2H), 7.11 (d, 2H), 7.45 (d, 2H), 7.73 (s, 2H), 8.09 (s, 1H).
Microanalysis: Found C, 59.64; H, 5.46; N, 11.60. $C_{24}H_{28}N_4O_6S$ requires C, 59.74; H, 5.43; N, 11.61%.

EXAMPLE 276

5-[(3,5-Diethyl-1-(2-hydroxyethyl)-1*H*-pyrazol-4-yl)oxy]isophthalonitrile mesylate salt

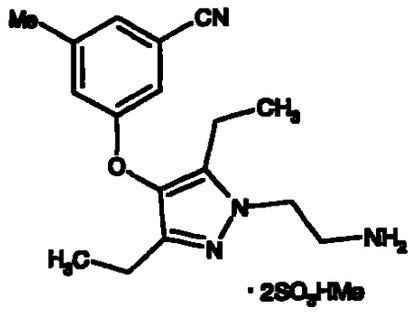


To a stirred suspension of the pyrazole from Example 119 (250mg, 0.83mmol) in isopropyl alcohol (3ml) was added methanesulfonic acid (52µl, 0.91mmol) and the mixture was heated on an oil bath until the solids dissolved. The reaction mixture was cooled to room temperature and concentrated under reduced pressure to a volume of 1ml. A white solid precipitated out which was washed with cold isopropyl alcohol to give the title compound (239mg) as a white solid, m.p. 144-146°C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.02 (m, 6H), 2.32 (q, 2H), 2.43 (s, 3H), 2.52 (m, 2H), 3.73 (m, 2H), 4.02 (m, 2H), 7.75 (s, 2H), 8.11 (s, 1H).
Microanalysis: Found C, 53.20; H, 5.52; N, 13.68. $C_{18}H_{22}N_4O_5S$ requires C, 53.19; H, 5.46; N, 13.78%.

EXAMPLE 277

3-[(1-(2-Aminoethyl)-3,5-diethyl-1*H*-pyrazol-4-yl)oxy]-5-methylbenzonitrile bis-mesylate salt

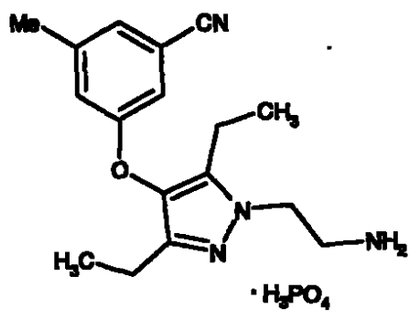


To a stirred solution of the amine from Example 125 (119mg, 0.40mmol) in ethanol (2ml) was added methanesulfonic acid (1.00ml of a 0.84M solution in ethanol, 0.84mmol). The reaction mixture was concentrated under reduced pressure to remove some of the ethanol. A mixture of diethyl ether and acetone were added and a white solid precipitated out which was filtered and washed (diethyl ether/acetone) to give the title compound (153mg) as a white solid, m.p. 146-148°C.

^{1}H NMR (400 MHz, CD_3OD): δ = 1.09 (m, 6H), 2.33 (s, 3H), 2.39 (q, 2H), 2.55 (q, 2H), 2.68 (s, 6H), 3.42 (t, 2H), 4.29 (t, 2H), 6.93 (s, 1H), 7.06 (s, 1H), 7.19 (s, 1H).
LRMS (thermospray): m/z [free base+H$^+$] 299
Microanalysis: Found C, 45.83; H, 6.12; N, 11.27. $C_{19}H_{30}N_4O_7S_2.0.50H_2O$ requires C, 45.68; H, 6.25; N, 11.21%.

EXAMPLE 278

3-[[1-(2-Aminoethyl)-3,5-diethyl-1*H*-pyrazol-4-yl]oxy]-5-methylbenzonitrile phosphate salt

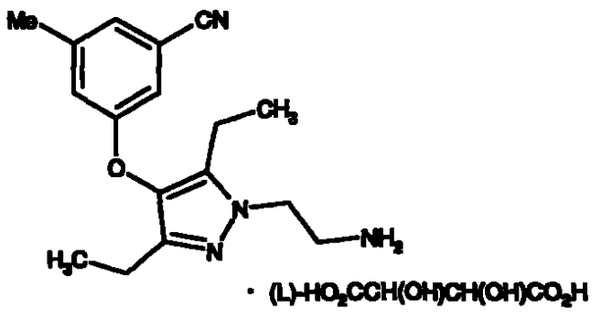


To a stirred solution of the amine from Example 125 (251mg, 0.84mmol) in ethanol (5ml) was added phosphoric acid (63µl, 0.93mmol). The resulting precipitate was filtered, washed (ethanol then diethyl ether) and dried to give the title compound (265mg) as a white solid, m.p. 210-211°C.

^{1}H NMR (400 MHz, CD_3OD): δ = 1.08 (m, 6H), 2.32 (s, 3H), 2.39 (q, 2H), 2.56 (q, 2H), 3.39 (m, 2H), 4.29 (m, 2H), 6.93 (s, 1H), 7.05 (s, 1H), 7.18 (s, 1H).
LRMS (thermospray): m/z [free base+H$^+$] 299
Microanalysis: Found C, 51.26; H, 6.36; N, 14.08. $C_{17}H_{25}N_4O_5P$ requires C, 51.51; H, 6.36; N, 14.14%.

EXAMPLE 279

3-[[1-(2-Aminoethyl)-3,5-diethyl-1*H*-pyrazol-4-yl]oxy]-5-methylbenzonitrile (L) tartrate salt

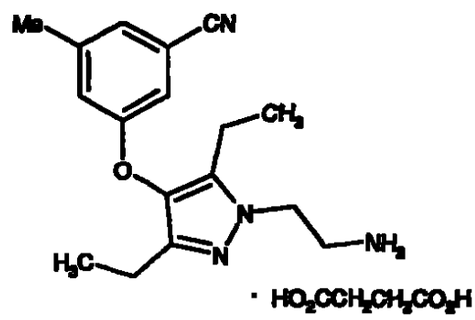


To a stirred solution of the amine from Example 125 (500mg, 1.68mmol) in acetone (15ml) was added (L)-tartaric acid (252mg, 1.68mmol) and the mixture was heated on an oil bath until complete dissolution had occurred. The mixture was cooled to room temperature and a white precipitate formed which was filtered and washed (acetone) to give the title compound (515mg) as a white powder, m.p. 159-161°C.

^{1}H NMR (400 MHz, CD_3OD): δ = 1.05-1.10 (m, 6H), 2.32 (s, 3H), 2.34-2.41 (m, 2H), 2.53-2.57 (m, 2H), 3.40 (m, 2H), 4.27 (m, 2H), 4.35 (s, 2H), 6.93 (s, 1H), 7.05 (s, 1H), 7.17 (s, 1H).
LRMS (electrospray): m/z [free base+H^+] 299
Microanalysis: Found C, 54.80; H, 6.38; N, 12.11. $C_{21}H_{28}N_4O_7.0.65H_2O$ requires C, 54.81; H, 6.42; N, 12.10%.

EXAMPLE 280

3-[[1-(2-Aminoethyl)-3,5-diethyl-1*H*-pyrazol-4-yl]oxy]-5-methylbenzonitrile succinate salt

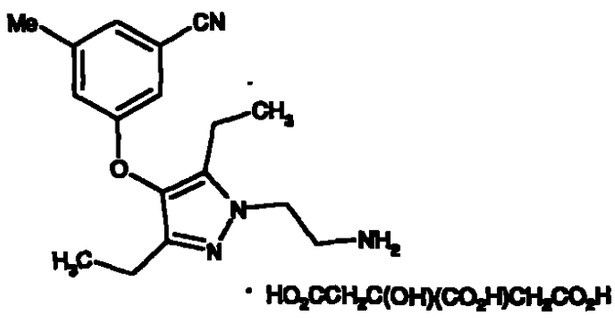


To a stirred solution of the amine from Example 125 (235mg, 0.79mmol) in acetone (7ml) was added succinic acid (93mg, 0.79mmol). After two minutes the mixture was concentrated to ~ 3ml using a stream of nitrogen gas which resulted in the formation of white crystals. The precipitate was filtered and washed (acetone) to give the title compound (172mg) as white crystals, m.p. 155°C.

^{1}H NMR (400 MHz, CD_3OD): δ = 1.03-1.07 (m, 6H), 2.34 (s, 3H), 2.40 (q, 2H), 2.50 (s, 4H), 2.59 (q, 2H); 3.34 (t, 2H), 4.23 (t, 2H), 6.95 (s, 1H), 7.06 (s, 1H), 7.22 (s, 1H).
LRMS (electrospray): m/z [free base+H^+] 299
Microanalysis: Found C, 60.47; H, 6.77; N, 13.39. $C_{21}H_{26}N_4O_8$ requires C, 60.56; H, 6.78; N, 13.45%.

EXAMPLE 281

3-[[1-(2-Aminoethyl)-3,5-diethyl-1*H*-pyrazol-4-yl]oxy]-5-methylbenzonitrile (L) citrate salt

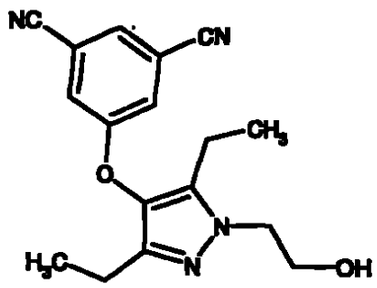


To a stirred solution of the amine from Example 125 (140mg, 0.47mmol) in acetone (3ml) was added citric acid (90mg, 0.47mmol). The mixture was stirred until complete dissolution had occurred. The mixture was concentrated to ~ 1ml using a stream of nitrogen gas and cooled in a freezer for 1.5 hours. A precipitate collected which was filtered to give the title compound (149mg) as a white powder, m.p. 180-182°C.

^{1}H NMR (400 MHz, CD_3OD): δ = 1.04-1.07 (m, 6H), 2.35 (s, 3H), 2.40 (q, 2H), 2.58 (q, 2H), 2.73 (d, 2H), 2.80 (d, 2H), 3.42 (t, 2H), 4.30 (t, 2H), 6.95 (s, 1H), 7.08 (s, 1H), 7.21 (s, 1H).
LRMS (electrospray): m/z [free base+H^+] 299
Microanalysis: Found C, 56.19; H, 6.20; N, 11.31. $C_{23}H_{30}N_4O_3$ requires C, 56.32; H, 6.16; N, 11.42%.

EXAMPLE 282

5-[(3,5-Diethyl-1-(2-hydroxyethyl)-1*H*-pyrazol-4-yl)oxy]isophthalonitrile

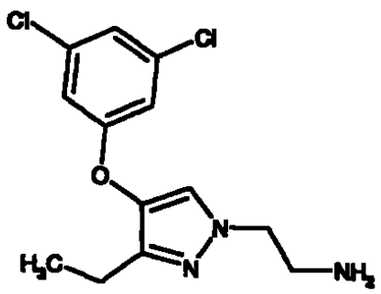


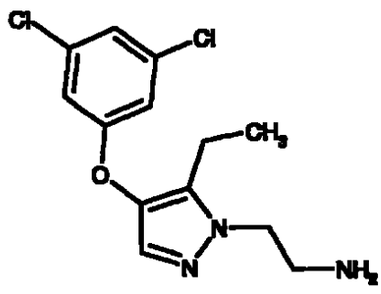
2-Hydroxyethylhydrazine (8.43ml, 124mmol) was added dropwise to a solution of the diketone of Preparation 45 (30.5g, 113mmol) in acetic acid (300ml) at room temperature under nitrogen. The reaction was stirred at room temperature for 90 minutes and the solvent removed under reduced pressure to give an orange solid. This was combined with an orange solid from another reaction carried out in an identical manner to this. The combined crude product was purified by flash column chromatography on silica gel eluting with ethyl acetate:pentane (75:25 by volume) to provide the title compound as a white solid. Analysis of the proton nmr showed minor impurities were present so the product was purified by flash column chromatography on silica gel eluting with ethyl acetate:pentane (50:50 by volume) to provide the title compound (50g) as a white solid, m.p. 125°C.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.13 (6H, m), 2.40 (2H, q), 2.53 (2H, q), 3.53 (1H, m), 4.11 (4H, m), 7.40 (2H, s), 7.58 (1H, s).
LRMS (electrospray): m/z [MH^+] 311.
Microanalysis: Found: C, 65.62; H, 5.85; N, 18.04. $C_{17}H_{18}N_4O_2$ requires C, 65.64; H, 5.84; N, 18.05%.

EXAMPLE 283

2-[4-(3,5-Dichlorophenoxy)-3-ethyl-1*H*-pyrazol-1-yl]ethylamine and 2-[4-(3,5-Dichlorophenoxy)-5-ethyl-1*H*-pyrazol-1-yl]ethylamine





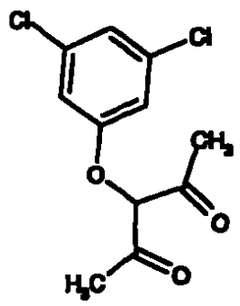
The pyrazole from Example 42 (1.03g, 4.00mmol) and 2-chloroethylamine hydrochloride (510mg, 4.40mmol) were heated as a melt at 150°C for 24 hours. The reaction was cooled and a solution of the residue in dichloromethane (100ml) was washed with an aqueous solution of 1M potassium carbonate (50ml), brine (50ml), dried over magnesium sulphate, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with dichloromethane:methanol:ammonia (93:7:1, by volume) to afford the title compounds (768mg) in a 85:15 ratio of regioisomers as a colourless oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.16 (major, t, 3H), 1.16 (minor, t, 3H), 2.47 (major, q, 2H), 2.60 (minor, q, 2H), 3.13 (major, m, 2H), 3.13 (minor, m, 2H), 4.10 (major, m, 2H), 4.10 (minor, m, 2H), 4.24 (major, t, 2H), 4.24 (minor, t, 2H), 6.85 (major, s, 2H), 6.85 (minor, s, 2H), 7.02 (major, s, 1H), 7.02 (minor, s, 1H), 7.27 (major, s, 1H), 7.31 (minor, s, 1H).
LRMS (thermospray): m/z [MH^+] 300.

The following Preparations describe the preparation of certain intermediates used in the preceding Examples.

PREPARATION 1

3-(3,5-Dichlorophenoxy)-2,4-pentanedione



3-Chloro-2,4-pentanedione (183µL, 1.53mmol)) was added to a stirred suspension of 3,5-dichlorophenol (250mg, 1.53mmol) and potassium carbonate (239mg, 1.69mmol) in acetone (7.7ml) at room temperature under nitrogen. The mixture was stirred for 30 minutes and then heated under reflux for 3½ hours. After cooling, sodium iodide (230mg, 1.53mmol) was added and refluxing continued for a further 3½ hours. After cooling again the mixture was diluted with water (5ml) and concentrated under reduced pressure in a fumehood (Caution: possible residual lachrymator) to remove acetone. The resulting red aqueous solution was diluted with 2M hydrochloric acid (5ml) and extracted with dichloromethane (3x10ml). The combined organic layers were washed with saturated aqueous sodium sulphite solution (10ml) and brine (10ml), dried over magnesium sulphate, filtered and evaporated under reduced pressure to leave a red oil (344mg). The crude product was purified by flash chromatography on silica gel eluting with pentane:ethyl acetate (20:1, by volume) to give the title compound (118mg) as a cream solid m.p. 91-92°C.

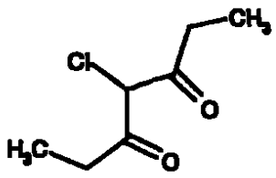
^{1}H-NMR (400MHz, $CDCl_3$): δ = 2.04 (s, 6H), 6.84 (s, 2H), 7.06 (s, 1H), 14.38 (br.s, 1H)

LRMS (thermospray): m/z [MNH_4^+] 278.

Microanalysis: Found: C, 50.43; H, 3.84. $C_{11}H_{10}Cl_2O_3$ requires C, 50.60; H, 3.86%.

PREPARATION 2

4-Chloro-3,5-heptanedione



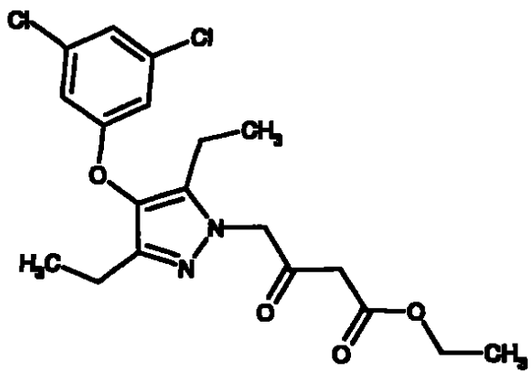
Chlorotrimethylsilane (29.7ml, 0.234mol) was added dropwise to a stirred pale yellow solution of tetrabutylammonium bromide (1.26g, 3.9mmol) in dry acetonitrile (116ml) at room temperature under nitrogen. The resulting solution was cooled in ice and 3,5-heptanedione (10.6ml, 78.0mmol) and then dry dimethylsulphoxide (16.6ml, 0.234mol) were added dropwise over 5 minutes producing a yellow solution which was allowed to warm slowly to room temperature, with stirring, over 4 hours. The mixture was diluted with water (1litre), stirred for 10min and then extracted with ether (1x500ml, 2x250ml). The combined ether layers were dried over magnesium sulphate, filtered and concentrated under reduced pressure to leave a yellow oil. The crude product was purified by distillation under reduced pressure to afford the title compound (5.5g) as a pale yellow oil, b.p. 102-105°C/54mmHg containing *ca.* 10% 4,4-dichloro-3,5-heptanedione as estimated by microanalysis.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.12 (t, 6H), 2.59 (q, 4H), 4.77 (s, 0.2H, diketone), 15.50 (s, 0.8H, enol).

LRMS (thermospray): *m/z* [MNH_4^+] 180 for title compound and 214 for dichlorinated impurity.

PREPARATION 3

Ethyl 4-[4-(3,5-dichlorophenoxy)-3,5-diethyl-1*H*-pyrazol-1-yl]-3-oxobutanoate



Sodium hydride (60% dispersion in oil, 250mg, 6.17mmol) was added to a stirred solution of 4-(3,5-dichlorophenoxy)-3,5-diethyl-1*H*-pyrazole (800mg, 2.81mmol, Example 3) in dry N,N-dimethylformamide (5ml) at 0°C under nitrogen. The mixture was stirred for 5 minutes during which time hydrogen was evolved and then ethyl 4-chloroacetoacetate (0.42ml, 3.09mmol) was added. After 30 minutes the reaction mixture was quenched by the addition of water (0.5ml) and concentrated under reduced pressure. A solution of the residue in ethyl acetate (50ml) was washed with saturated aqueous ammonium chloride solution (20ml) and water (20ml), dried over magnesium sulphate and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with ethyl acetate:pentane (30:70, by volume) to provide the title compound (1.1g) as a white solid, m.p. 82-84°C.

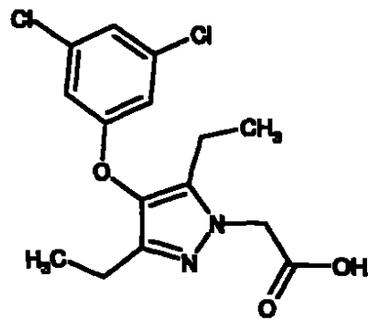
^{1}H-NMR (300MHz, $CDCl_3$): δ = 1.40 (6H, m), 1.26 (3H, t), 2.44 (4H, q), 3.47 (2H, s), 4.22 (2H, q), 4.96 (2H, s), 6.82 (2H, s), 7.02 (1H, s).

LRMS (thermospray): m/z [MH^+] 413.

Microanalysis: Found: C, 55.13; H, 5.34; N, 6.98. $C_{18}H_{18}Cl_2N_2O$ requires C, 55.22; H, 5.37; N, 6.78%.

PREPARATION 4

[4-(3,5-Dichlorophenoxy)-3,5-diethyl-1*H*-pyrazol-1-yl]acetic acid

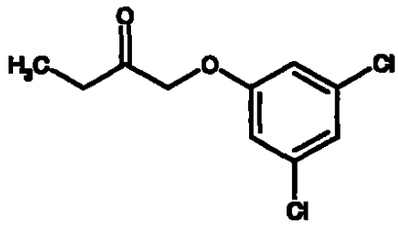


Aqueous sodium hydroxide solution (1N, 6.2ml, 6.2mmol) was added dropwise to a stirred solution of the ester (2g, 5.6mmol) of Example 9 in tetrahydrofuran (20ml) at 0°C. After 1 hour the solvent was removed under reduced pressure and aqueous hydrochloric acid (20ml) was added with vigorous stirring. The resulting white precipitate was collected by filtration, washed with ether (3x30ml) and dried in a vacuum pistol at 60°C/10mmHg to afford the title compound as a white solid (1.5g), m.p. 157-158°C.

^{1}H-NMR (300MHz, $CDCl_3$): δ = 1.13 (6H, m), 2.52 (2H, q), 2.60(2H, q), 5.03 (2H, s), 6.95 (2H, s), 7.14 (1H, s).
LRMS (electrospray): m/z [M-H$^+$] 341.

PREPARATION 5

1-(3,5-Dichlorophenoxy)-2-butanone



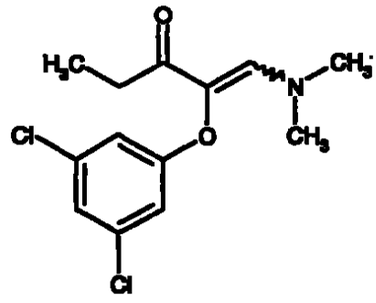
Cesium carbonate (108g, 0.33mol) was added in one portion to a stirred solution of 3,5-dichlorophenol (49g, 0.30mol) in acetone (900ml) at room temperature under nitrogen. To this suspension a solution of 1-bromo-2-butanone (30.6ml, 0.30mol) in

acetone (300ml) was added dropwise and the resultant suspension was heated under reflux for 2 hours. The suspension was cooled to room temperature, water (200ml) was added and the acetone was removed under reduced pressure. The mixture was extracted with dichloromethane (2x300ml) and the combined organic phases were dried over magnesium sulphate, filtered and concentrated under reduced pressure to leave a clear oil. The crude product was purified by flash column chromatography on silica gel eluting with dichloromethane:cyclohexane (50:50, by volume) to provide the title compound (65g) as a yellow oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.13 (t, 3H), 2.60 (q, 2H), 4.58 (s, 2H), 6.78 (s, 2H), 7.01 (s, 1H).
LRMS (thermospray): m/z [MNH_4^+] 250.

PREPARATION 6

2-(3,5-Dichlorophenoxy)-1-(dimethylamino)-1-penten-3-one



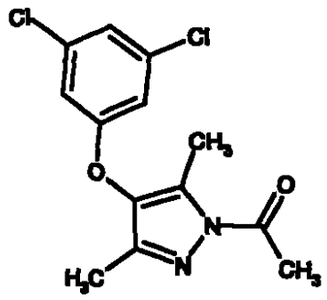
A solution of the ketone of Preparation 5 (65g, 0.28mol) in *N,N*-dimethylformamide dimethylacetal (75ml, 0.56mol) was heated at 100°C using a Dean-Stark apparatus for 10 hours. The reaction was cooled and concentrated under reduced pressure to leave a brown oil. The crude product was purified by flash column chromatography on silica gel eluting with pentane:ethyl acetate (90:10, by volume) and then pentane:ethyl acetate (60:40, by volume) to provide the title compound (55g) as a yellow oil that solidified upon standing. The resultant yellow solid was washed with pentane (100ml) and dried to provide the title compound (28g) as a yellow solid, m.p. 96-97°C.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 0.98 (t, 3H), 2.30 (br s, 2H), 2.94 (s, 6H), 6.77 (s, 2H), 6.95 (s, 1H), 7.24 (s, 1H).

LRMS (thermospray): m/z [MNH_4^+] 288.

PREPARATION 7

1-Acetyl-4-(3,5-dichlorophenoxy)-3,5-dimethyl-1*H*-pyrazole

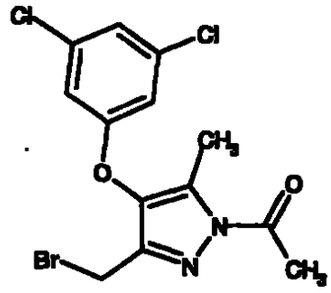


Sodium hydride (60% dispersion in oil, 684mg, 17.1mmol) was added to a stirred solution of acetyl chloride (1.21ml, 17.1mmol) and the pyrazole of Example 53 (4.00g, 15.6mmol) in *N,N*-dimethylformamide (20ml) at 0°C under nitrogen. The reaction was stirred at 0°C for 1 hour and then quenched by the addition of water (100ml). The aqueous extracted was with ether (2x50ml). The combined organic phases were washed with water (30ml) and brine (30ml), dried over magnesium sulphate, filtered and concentrated under reduced pressure to leave a yellow solid. The crude product was purified by flash column chromatography on silica gel eluting with pentane:ether (90:10, by volume) to provide the title compound (3.0g) as a white solid, m.p. <60°C.

^{1}H-NMR (300MHz, $CDCl_3$): δ = 2.11 (s, 3H), 2.43 (s, 3H), 2.70 (s, 3H), 6.78 (s, 2H), 7.03 (s, 1H).
LRMS (thermospray): m/z [MH^+] 299.

PREPARATION 8

1-Acetyl-3-(bromomethyl)-4-(3,5-dichlorophenoxy)-5-methyl-1*H*-pyrazole



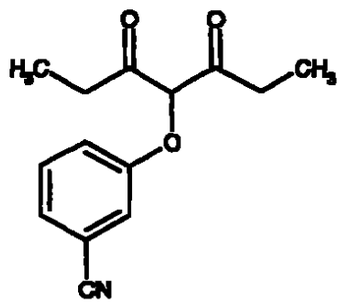
N-Bromosuccinimide (2.70g, 15.0mmol) was added to a stirred solution of the pyrazole of Preparation 7 (3.00g, 10.0mmol) in 1,1,1-trichloroethane (40ml) at room temperature under nitrogen. The reaction was heated at 80°C for 1 hour and then azobisisobutyronitrile (2mg) was added and the reaction mixture was heated for a further 3 hours. The reaction was cooled to room temperature and a solid removed by filtration. The filtrate was concentrated under reduced pressure and the resulting yellow oil was dissolved in ethyl acetate (100ml). The ethyl acetate was washed with 1M aqueous sodium carbonate solution (30ml), water (30ml) and brine (30ml), dried over magnesium sulphate, filtered and concentrated under reduced pressure to leave a yellow solid. The crude product was purified by flash column chromatography on silica gel eluting with pentane:ethyl acetate (90:10, by volume) to provide a yellow solid that was washed with ice cold ether (20ml) to provide the title compound (2.3g) as a white solid, m.p. 111-113°C.

^{1}H-NMR (300MHz, $CDCl_3$): δ = 2.10 (s, 3H), 2.73 (s, 3H), 4.73 (s, 2H), 6.86 (s, 2H), 7.11 (s, 1H).

LRMS (thermospray): m/z [MH^+] 379.

PREPARATION 9

4-(3-Cyanophenoxy)-3,5-heptanedione



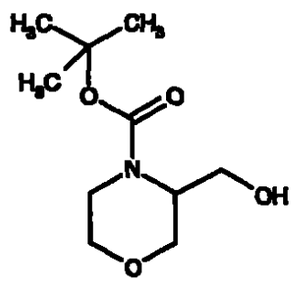
A mixture of the β-diketone of Preparation 2 (1.79g, 11.0mmol), 3-cyanophenol (1.31g, 11.0mmol), cesium carbonate (3.58g, 11.0mmol) and acetone (44ml) was heated under reflux for 2 hours. After cooling, the mixture was concentrated under reduced pressure and the residue was partitioned between dichloromethane (50ml) and water (25ml). The organic layer was separated, washed with brine (25ml), dried over magnesium sulphate, filtered and concentrated under reduced pressure to leave a yellow oil. The crude product was purified by flash column chromatography on silica gel eluting with ethyl acetate:pentane (10:90, by volume) to provide the title compound (1.10g) as a yellow oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.04 (t, 6H), 2.49 (q, 4H), 7.16 (m, 2H), 7.30 (d, 1H), 7.39 (t, 2H), 14.51 (s, 1H).

LRMS (thermospray): m/z [MNH_4^+] 263.

PREPARATION 10

tert-Butyl 3-(hydroxymethyl)-4-morpholinecarboxylate

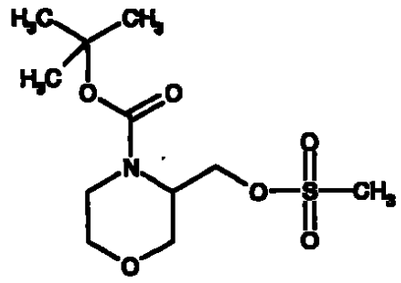


Borane (38.1ml of a 1.0M solution in tetrahydrofuran, 38.1mmol) was added dropwise to a stirred suspension of 3-morpholinecarboxylic acid (1.00g, 7.63mmol) in tetrahydrofuran (50ml) at room temperature under nitrogen. The reaction was heated under reflux and the reaction became homogeneous and heating was continued for 12 hours. The reaction was cooled to room temperature and concentrated under reduced pressure to leave a brown oil. The residue was dissolved in 1M aqueous sodium hydroxide solution and stirred at room temperature for 5 days. After this time di-*tert*-butyl dicarbonate (1.66g, 7.63mmol) was added and the reaction was stirred for 12 hours. The reaction was diluted with ether (100ml). The organic layer was separated, washed with brine (10ml), dried over magnesium sulphate, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel eluting with pentane:ethyl acetate (50:50, by volume) and then ethyl acetate to provide the title compound (1.30g) as a colourless oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.48 (s, 9H), 2.05 (s, 1H), 3.19 (br t, 1H), 3.47 (td, 1H), 3.60 (dd, 1H), 3.87 (m, 6H).
LRMS (thermospray): m/z [MH^+] 218.

PREPARATION 11

tert-Butyl 3-[[(methylsulfonyl)oxy]methyl]-4-morpholinecarboxylate



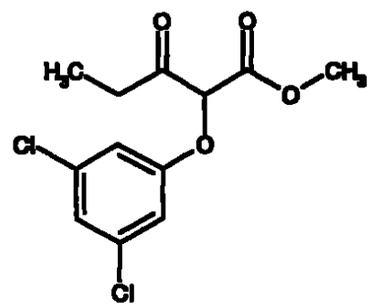
Triethylamine (1.15ml, 8.29mmol) was added dropwise to a stirred solution of the alcohol of Preparation 10 (1.20g, 5.52mmol) and methanesulfonic anhydride (1.44g, 5.52mmol) in dichloromethane (50ml) at room temperature under nitrogen. The reaction was stirred for 1 hour and then poured onto water (50ml). The organic layer was separated, dried over magnesium sulphate, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography

on silica gel eluting with pentane:ethyl acetate (50:50, by volume) to provide the title compound (1.20g) as a colourless oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.49 (s, 9H), 3.06 (s, 3H), 3.50 (td, 1H), 3.60 (dd, 1H), 3.80 (m, 4H), 4.26 (br s, 1H), 4.39 (m, 2H).
LRMS (thermospray): m/z [MNH_4^+] 313.

PREPARATION 12

Methyl-2-(3,5-dichlorophenoxy)-3-oxopentanoate

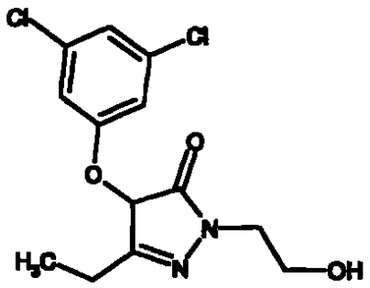


A mixture of methyl-2-chloro-3-pentanoate (25.0g, 152mmol), 3,5-dichlorophenol (24.6g, 152mmol), cesium carbonate (54.4g, 167mmol) and acetone (500ml) was heated under reflux for 2 hours. After cooling the mixture was concentrated under reduced pressure and the residue was partitioned between dichloromethane (100ml) and water (50ml). The organic layer was separated, washed with brine (25ml), dried over magnesium sulphate, filtered and concentrated under reduced pressure to leave an orange oil. The crude product was purified by flash column chromatography on silica gel eluting with pentane:toluene (90:10, by volume) to provide the title compound (40.0g) as a pink oil.

^{1}H-NMR (300MHz, $CDCl_3$): δ = 1.16 (t, 3H), 2.60 (m, 2H), 3.77 (s, 3H), 5.13 (s, 1H), 6.84 (s, 2H), 7.10 (s, 1H).
LRMS (thermospray): m/z [MNH_4^+] 306.

PREPARATION 13

4-(3,5-Dichlorophenoxy)-5-ethyl-2-(2-hydroxyethyl)-2,4-dihydro-3*H*-pyrazol-3-one

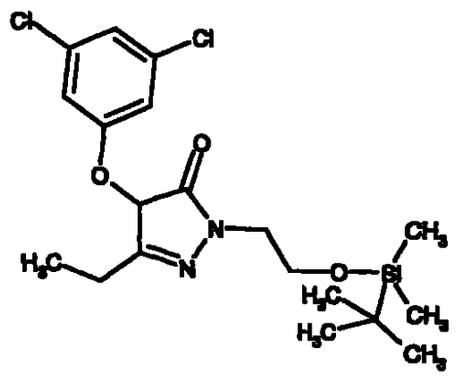


A solution of 2-hydroxyethylhydrazine (4.30g, 56.7mmol) in glacial acetic acid (2.0ml) was added to a stirred solution of the ketoester of Preparation 12 (15.0g, 51.5mol) in glacial acetic acid (100ml) and the resulting solution was stirred at room temperature for 48 hours. The mixture was concentrated under reduced pressure and the crude product was purified by flash column chromatography on silica gel eluting with dichloromethane:methanol (95:5, by volume) to provide the title compound (10.1g) as a colourless oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.02 (t, 3H), 2.29 (m, 2H), 3.63 (m, 2H), 3.80 (m, 2H), 6.92 (s, 2H), 7.21 (s, 1H).
LRMS (thermospray): m/z [MH^+] 317.
Microanalysis: Found: C, 48.86; H, 4.44; N, 9.01. $C_{13}H_{14}N_2O_3Cl_2$ requires C, 49.23; H, 4.45; N, 8.83%.

PREPARATION 14

2-(2-{[*tert*-Butyl(dimethyl)silyl]oxy}ethyl)-4-(3,5-dichlorophenoxy)-5-ethyl-2,4-dihydro-3*H*-pyrazol-3-one

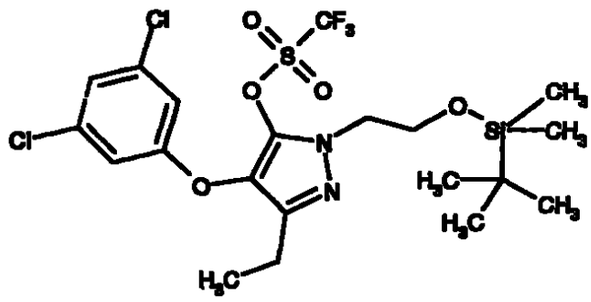


tert-Butyldimethylsilyl chloride (8.14g, 54.0mmol) was added in one portion to a stirred solution of the pyrazole of Preparation 13 (14.3g, 45.0mmol) and imidazole (3.98g, 58.5mmol) in *N,N*-dimethylformamide (90ml) and the resulting solution was stirred at room temperature for 48 hours. The mixture was partitioned between ethyl acetate (100ml) and water (300ml). The organic layer was separated, dried over magnesium sulphate, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel eluting with dichloromethane:methanol (95:5, by volume) to provide the title compound (9.56g) as a colourless oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 0.15 (s, 6H), 0.94 (s, 9H), 1.16 (t, 3H), 2.45 (m, 2H), 3.94 (m, 4H), 6.85 (s, 2H), 6.97 (s, 1H).
LRMS (thermospray): m/z [MH^+] 431.
Microanalysis: Found: C, 52.87; H, 6.52; N, 6.46. $C_{19}H_{28}N_2O_3Cl_2Si$ requires C, 52.90; H, 6.54; N, 6.49%.

PREPARATION 15

1-(2-[*tert*-Butyl(dimethyl)silyloxy]ethyl)-4-(3,5-dichlorophenoxy)-3-ethyl-1*H*-pyrazol-5-yl trifluoromethanesulfonate

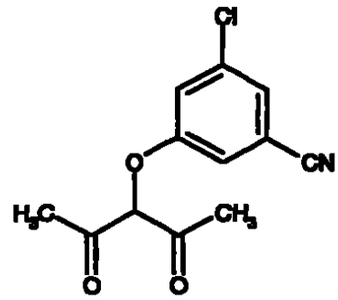


Phenyltriflamide (3.70g, 10.5mmol) was added in one portion to a stirred solution of the pyrazole of Preparation 14 (4.10g, 9.50mmol) and triethylamine (1.60ml, 11.4mmol) in dichloromethane (20ml) at room temperature under nitrogen. The reaction was stirred for 2 hours and then poured onto water (50ml). The organic layer was separated, dried over magnesium sulphate, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel eluting with dichloromethane to provide the title compound (5.10g) as a purple oil.

^{1}H-NMR (300MHz, $CDCl_3$): δ = 0.01 (s, 6H), 0.86 (s, 9H), 1.17 (t, 3H), 2.45 (q, 2H), 4.01 (m, 2H), 4.14 (m, 2H), 6.84 (s, 2H), 7.08 (s, 1H).
LRMS (thermospray): m/z [MH^+] 563.

PREPARATION 16

3-(1-Acetyl-2-oxopropoxy)-5-chlorobenzonitrile

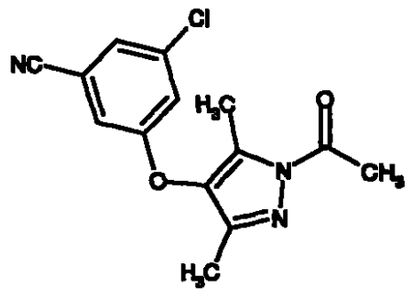


A mixture of 3-chloro-2,4-pentanedione (6.73g, 50.0mmol), the phenol of Preparation 36 (7.67g, 50.0mmol), cesium carbonate (18.0g, 55.4mmol) and acetone (40ml) was heated under reflux for 2 hours. The reaction was cooled to room temperature, *N,N*-dimethylformamide (6ml) and acetone (30ml) were added and the reaction was heated at 70°C for a further 12 hours. After cooling, the solid was removed by filtration and dissolved in 1M aqueous hydrochloric acid (150ml). The resulting solution was extracted with dichloromethane (3x100ml) and the combined organic phases were washed with brine (30ml), dried over magnesium sulphate, filtered and concentrated under reduced pressure to provide the title compound (5.50g) as a brown solid, m.p. 105-108°C.

^{1}H-NMR (300MHz, $CDCl_3$): δ = 2.04 (s, 6H), 7.13 (s, 1H), 7.19 (s, 1H), 7.35 (s, 1H), 14.40 (s, 1H).

PREPARATION 17

3-[(1-Acetyl-3,5-dimethyl-1*H*-pyrazol-4-yl)oxy]-5-chlorobenzonitrile

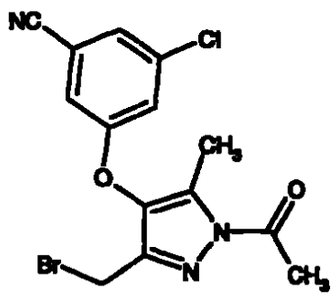


Sodium hydride (60% dispersion in oil, 840mg, 21.0mmol) was added to a stirred solution of acetyl chloride (1.50ml, 21.0mmol) and the pyrazole of Example 76 (4.80g, 19.4mmol) in *N,N*-dimethylformamide (20ml) at 0°C under nitrogen. The reaction was stirred at 0°C for 15 minutes and then quenched by the addition of water (200ml). The reaction mixture was extracted with ethyl acetate (3x120ml). The combined organic phases were washed with water (50ml) and brine (50ml), dried over magnesium sulphate, filtered and concentrated under reduced pressure to leave a yellow solid. The crude product was purified by flash column chromatography on silica gel eluting with dichloromethane to provide the title compound (5.00g) as a white solid, m.p. <60°C.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 2.06 (s, 3H), 2.38 (s, 3H), 2.65 (s, 3H), 6.99 (m, 1H), 7.08 (m, 1H), 7.29 (m, 1H).
LRMS (thermospray): m/z [MH^+] 290.

PREPARATION 18

3-[[1-Acetyl-3-(bromomethyl)-5-methyl-1*H*-pyrazol-4-yl]oxy]-5-chlorobenzonitrile

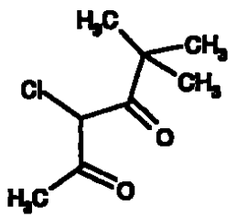


N-Bromosuccinimide (4.60g, 25.6mmol) was added to a stirred solution of the pyrazole of Preparation 17 (5.00g, 17.3mmol) in 1,1,1-trichloroethane (70ml) and azobisisobutyronitrile (20mg) at room temperature under nitrogen. The reaction was heated at 80°C for 3 hours and then cooled to room temperature. A second portion of *N*-bromosuccinimide (2.00g, 11.2mmol) was added and the reaction mixture was heated at 80°C for a further 4 hours. The reaction was cooled to room temperature and concentrated under reduced pressure and the resulting yellow oil was purified by flash column chromatography on silica gel eluting with pentane:dichloromethane (25:75, by volume) to provide the title compound (2.30g) as a white solid, m.p. 122-123°C.

^{1}H-NMR (300MHz, $CDCl_3$): δ = 2.10 (s, 3H), 2.74 (s, 3H), 4.73 (s, 2H), 7.12 (s, 1H), 7.22 (s, 1H), 7.39 (s, 1H).

PREPARATION 19

3-Chloro-5,5-dimethyl-2,4-hexanedione

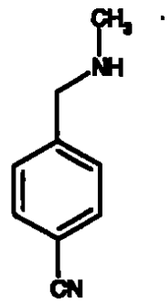


Chlorotrimethylsilane (26.8ml, 0.21mol) was added dropwise to a stirred pale yellow solution of tetrabutylammonium bromide (1.13g, 3.50mmol) in dry acetonitrile (100ml) at room temperature under nitrogen. The resulting solution was cooled in ice and 5,5-dimethylhexane-2,4-dione (10.0g, 70.4mmol) and then dry dimethylsulphoxide (14.7ml, 0.21mol) were added dropwise over 5 minutes producing a yellow solution which was allowed to warm slowly to room temperature with stirring over 3 hours. The mixture was diluted with water (1000ml) and stirred for 10min and then extracted with ether (1x500ml, 2x250ml). The combined eth r layers were dried over magnesium sulphate, filtered and concentrated under reduced pressure to leave a yellow oil. The crude product was purified by distillation under reduced pressure to provide the title compound (10.0g) as a pale yellow oil, b.p. 220-225°C/60mmHg.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.25 (s, 9H), 2.39 (s, 3H), 5.10 (s, 1H).
LRMS (thermospray): m/z [MNH_4^+] 194.

PREPARATION 20

4-[(Methylamino)methyl]benzonitrile

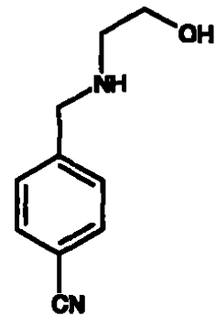


4-Cyanobenzaldehyde (12.0g, 92.0mmol), methylamine (69ml of a 2.0M solution in tetrahydrofuran, 137mmol) and magnesium sulphate (45g) were stirred in dichloromethane (300ml) at room temperature for 5 days. The mixture was filtered and the filtrate was concentrated under reduced pressure to leave a yellow oil. The oil was dissolved in methanol (200ml) and sodium borohydride (4.10g, 109mmol) was added cautiously with vigorous stirring. Once the addition was complete the reaction was stirred for 1 hour and the mixture was concentrated under reduced pressure. The residue was dissolved in 1M aqueous sodium hydroxide solution (200ml) and the mixture was stirred at room temperature for 1 hour. The resulting solution was extracted with dichloromethane (2x200ml) and the combined organic phases were dried over magnesium sulphate, filtered and concentrated under reduced pressure to provide the title compound (13.4g) as a pale yellow oil.

^{1}H-NMR (300MHz, $CDCl_3$): δ = 1.46 (s, 1H), 2.46 (s, 3H), 3.82 (s, 2H), 7.47 (d, 2H), 7.64 (d, 2H).
LRMS (electrospray): m/z [MH^+] 147.

PREPARATION 21

4-[[(2-Hydroxyethyl)amino]methyl]benzonitrile



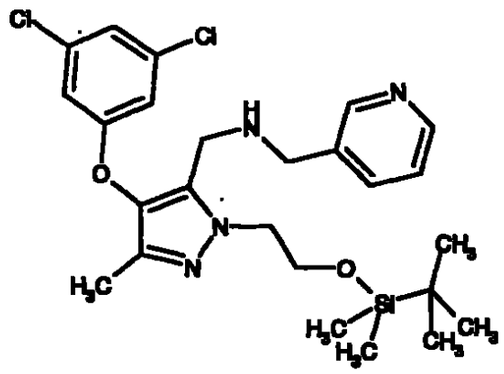
A mixture of 4-Cyanobenzaldehyde (14.1g, 107mmol), ethanolamine (6.56g, 107mmol) and toluene (100ml) was heated under reflux for 14 hours using a Dean-Stark apparatus to remove water. The reaction was cooled to room temperature and concentrated under reduced pressure to leave a yellow oil. The oil was dissolved in dichloromethane (200ml), cooled to 0°C and triethylamine (16.3ml, 117mmol) and chlorotrimethylsilane (14.9ml, 117mmol) were added dropwise. A white precipitate formed and after stirring for 1 hour the mixture was filtered. The filtrate was

concentrated under reduced pressure to leave an orange solid (25.0g). The orange solid was dissolved in methanol (200ml) and sodium borohydride (4.50g, 122mmol) was added cautiously with vigorous stirring. Once the addition was complete the reaction was stirred for 1 hour and the mixture was then concentrated under reduced pressure. The residue was dissolved in 1M aqueous sodium hydroxide solution (200ml) and the mixture was stirred at room temperature for 1 hour. The resulting solution was extracted with dichloromethane (3x200ml) and the combined organic phases were dried over magnesium sulphate, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel eluting with dichloromethane:methanol:ammonia (95:4:1, by volume) to provide the title compound (12.0g) as a pale yellow oil which solidified on standing to leave a yellow solid, m.p. <60°C.

^{1}H-NMR (300MHz, $CDCl_3$): δ = 1.84 (s, 2H), 2.84 (t, 2H), 3.68 (t, 2H), 3.89 (s, 2H), 7.45 (d, 2H), 7.65 (d, 2H).
LRMS (thermospray): m/z [MH^+] 177.

PREPARATION 22

N-[1-(2-{[*tert*-Butyl(dimethyl)silyl]oxy}ethyl)-4-(3,5-dichlorophenoxy)-3-methyl-1*H*-pyrazol-5-yl]methyl}-*N*-(3-pyridinylmethyl)amine



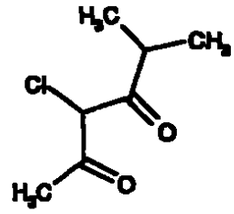
3-(Methylamino)pyridine (327mg, 3.04mmol) was added in one portion to a stirred solution of the bromide of Preparation 28 (300mg, 0.610mmol) in isopropanol (5ml) at room temperature. The mixture was heated at 50°C for 1 hour, cooled to room temperature and concentrated under reduced pressure to leave an orange oil. The crude product was purified by flash column chromatography on silica gel eluting with

dichloromethane:methanol:ammonia (95:4:1, by volume) to provide the title compound (50mg) as a colourless oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 0.15 (s, 6H), 0.77 (s, 9H), 2.02 (s, 3H), 3.64 (s, 2H), 3.70 (s, 2H), 3.95 (t, 2H), 4.17 (t, 2H), 6.75 (s, 2H), 6.97 (s, 1H), 7.15 (dd, 1H), 7.53 (d, 1H), 8.47 (m, 2H).
LRMS (thermospray): m/z [MH^+] 521.

PREPARATION 23

3-Chloro-5-methyl-2,4-hexanedione

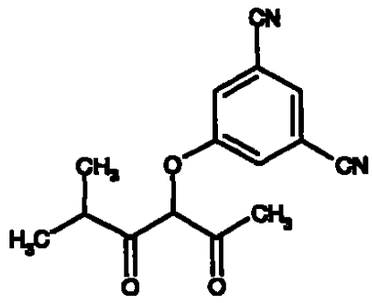


Chlorotrimethylsilane (13.4ml, 105mmol) was added dropwise to a stirred pale yellow solution of tetrabutylammonium iodide (566mg, 1.53mmol) in dry acetonitrile (100ml) at room temperature under nitrogen. The resulting solution was cooled in ice and 5-methylhexane-2,4-dione (4.50g, 35.1mmol) and then dry dimethylsulphoxide (7.47ml, 105mmol) were added dropwise over 5 minutes producing a yellow solution which was allowed to warm slowly to room temperature with stirring over 1 hour. Tetrabutylammonium bromide (566mg, 1.75mmol) was then added in one portion and the reaction was stirred at room temperature for 2 hours. The mixture was diluted with water (200ml), stirred for 10min and then extracted with ether (3x100ml). The combined ether layers were dried over magnesium sulphate, filtered and concentrated under reduced pressure to leave a yellow oil. The crude product was purified by flash column chromatography on silica gel eluting with pentane:ethyl acetate (98:2, by volume) to provide the title compound (2.00g) as a colourless oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.15 (d, 6H), 2.29 (s, 3H), 3.25 (sept, 1H), 15.60 (s, 1H).
LRMS (thermospray): m/z [MNH_4^+] 180.

PREPARATION 24

5-(1-Acetyl-3-methyl-2-oxobutoxy)isophthalonitrile

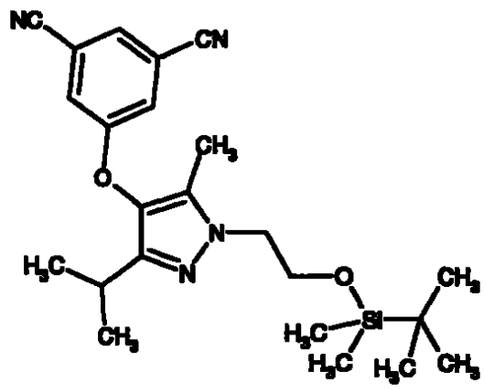


A mixture of the dione of Preparation 23 (1.12g, 6.94mmol), the phenol of Preparation 39 (1.00g, 6.94mmol), cesium carbonate (2.25g, 6.94mmol) and acetone (30ml) was heated under reflux for 4 hours. The reaction was cooled to room temperature and concentrated under reduced pressure to leave a brown solid. The solid was dissolved in 1M aqueous hydrochloric acid (50ml) and the solution was extracted with dichloromethane (3x30ml). The combined organic phases were washed with brine (30ml), dried over magnesium sulphate, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel eluting with pentane:ethyl acetate (90:10, by volume) to provide the title compound (580mg) as a yellow solid.

^{1}H-NMR (300MHz, $CDCl_3$): δ = 1.08 (d, 6H), 2.02 (s, 3H), 2.24 (sept, 1H), 7.47 (s, 2H), 7.63 (s, 1H), 14.71 (s, 1H).
LRMS (electrospray): m/z [M-H$^+$] 269.

PREPARATION 25

5-[[1-(2-[[*tert*-Butyl(dimethyl)silyl]oxy]ethyl)-3-isopropyl-5-methyl-1*H*-pyrazol-4-yl]oxy]isophthalonitrile

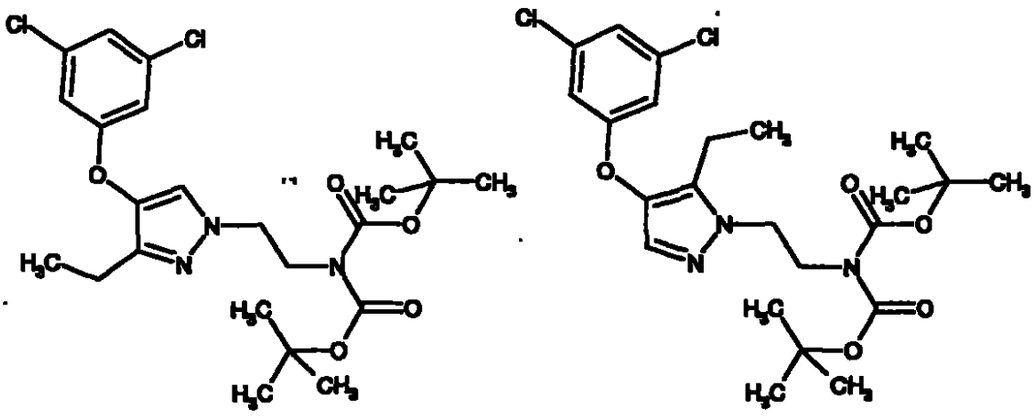


Sodium hydride (60% dispersion in oil, 45mg, 1.12mmol) was added to a stirred solution of 2-bromoethoxy-t-butyldimethylsilane (270mg, 1.12mmol) and the pyrazole of Example 95 (250mg, 0.930mmol) in *N,N*-dimethylformamide (5ml) at 0°C under nitrogen. The reaction was warmed to room temperature and stirred for 12 hours. The reaction mixture was quenched by the addition of water (50ml) and the aqueous phase was extracted with ethyl acetate (3x30ml). The combined organic phases were dried over magnesium sulphate, filtered and concentrated under reduced pressure to leave a brown oil. The crude product was purified by flash column chromatography on silica gel eluting pentane:ethyl acetate (80:20, by volume) to provide the title compound (60mg) as a colourless oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 0.02 (s, 6H), 0.85 (s, 9H), 1.19 (d, 6H), 2.09 (s, 3H), 2.79 (sept, 1H), 3.99 (m, 2H), 4.10 (m, 2H), 7.39 (s, 2H), 7.57 (s, 1H).
LRMS (electrospray): m/z [MH^+] 425.

PREPARATION 26

di(*tert*-Butyl) 2-[4-(3,5-dichlorophenoxy)-3-ethyl-1*H*-pyrazol-1-yl]ethylimidodicarbonate and di(*tert*-butyl) 2-[4-(3,5-dichlorophenoxy)-5-ethyl-1*H*-pyrazol-1-yl]ethylimidodicarbonate



Di-t-butyldicarbonate (14.0g, 64.2mmol) and 4,4-dimethylaminopyridine (630mg, 5.14mmol) were added portionwise to a stirred solution of the amines of Example 283 (7.72g, 25.7mmol) in acetonitrile (128ml) at room temperature under nitrogen. The reaction was stirred for 14 hours and concentrated under reduced pressure. A solution of the residue in dichloromethane (300ml) was washed with water (100ml), dried over magnesium sulphate, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with dichloromethane:methanol (99:1, by volume) to afford the title compounds (12.3g) in a 85:15 ratio of regioisomers as a colourless oil.

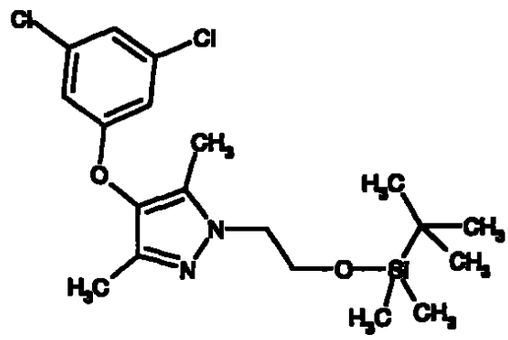
^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.15 (major, t, 3H), 1.15 (minor, t, 3H), 1.52 (major, s, 18H), 1.52 (minor, s, 18H), 2.47 (major, q, 2H), 2.56 (minor, q, 2H), 4.00 (maj r, t, 2H), 4.00 (minor, t, 2H), 4.24 (major, t, 2H), 4.24 (minor, t, 2H), 6.85 (major, s, 2H), 6.85 (minor, s, 2H), 7.00 (major, s, 1H), 7.00 (minor, s, 1H), 7.21 (major, s, 1H), 7.25 (minor, s, 1H).

LRMS (thermospray): m/z [MH^+] 500.

Microanalysis: Found: C, 54.94; H, 6.26; N, 8.27. $C_{23}H_{31}Cl_2N_3O_5$ requires C, 55.20; H, 6.24; N, 8.40%.

PREPARATION 27

1-(2-[[*tert*-Butyl(dimethyl)silyl]oxy]ethyl)-4-(3,5-dichlorophenoxy)-3,5-dimethyl-1*H*-pyrazole

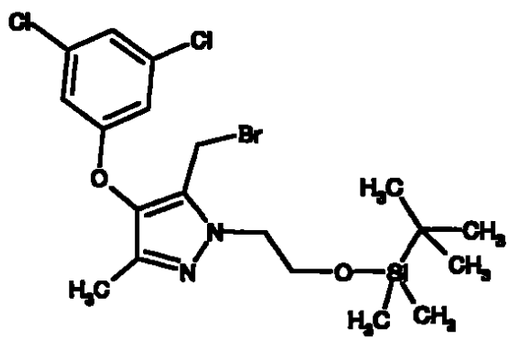


Chloro-t-butyldimethylsilane (1.93g, 12.8mmol) was added in one portion to a stirred solution of the pyrazole of Example 1 (3.50g, 11.6mmol) and imidazole (1.03g, 15.1mmol) in *N,N*-dimethylformamide (23ml) at room temperature under nitrogen. The reaction was stirred for 2 days and water (200ml) was added. The aqueous phase was extracted with diethyl ether (3x200ml) and the combined organic phases were washed with water (2x50ml) and brine (2x50ml), dried over magnesium sulphate, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with pentane:ethyl acetate (80:20, by volume) to provide the title compound (4.82g) as a colourless oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 0.09 (s, 6H), 0.78 (s, 9H), 2.01 (s, 3H), 2.05 (s, 3H), 3.88 (q, 2H), 4.02 (q, 2H), 6.76 (s, 2H), 6.88 (s, 1H).
LRMS (thermospray): m/z [MH^+] 415.

PREPARATION 28

5-(Bromomethyl)-1-(2-[[*tert*-butyl(dimethyl)silyl]oxy]ethyl)-4-(3,5-dichlorophenoxy)-3-methyl-1*H*-pyrazole

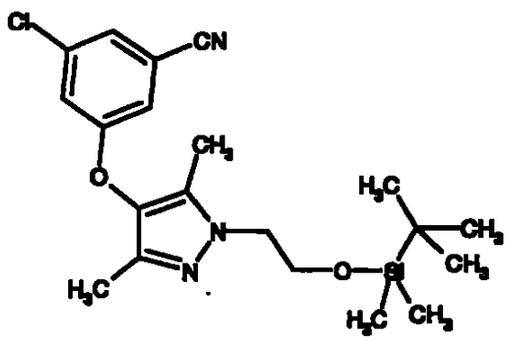


N-Bromosuccinimide (640mg, 3.60mmol) was added to a stirred solution of the pyrazole of Preparation 27 (1.00g, 2.40mmol) in carbon tetrachloride (15ml) and azobisisobutyronitrile (20mg) at room temperature under nitrogen. The reaction was heated under reflux for 5 hours then cooled to room temperature and filtered. The filtrate was concentrated under reduced pressure and the crude product was purified by flash column chromatography on silica gel eluting with dichloromethane:methanol:ammonia (97:2.5:0.5, by volume) to provide the title compound (300mg) as a colourless oil.

^{1}H-NMR (300MHz, $CDCl_3$): δ = 0.04 (s, 6H), 0.82 (s, 9H), 2.02 (s, 3H), 3.96 (m, 2H), 4.22 (m, 2H), 4.41 (s, 2H), 6.81 (s, 2H), 7.01 (s, 1H).
LRMS (thermospray): m/z [MH^+] 495.

PREPARATION 29

3-[1-(2-[[*tert*-Butyl(dimethyl)silyl]oxy]ethyl)-3,5-dimethyl-1*H*-pyrazol-4-yl]oxy}-5-chlorobenzonitrile

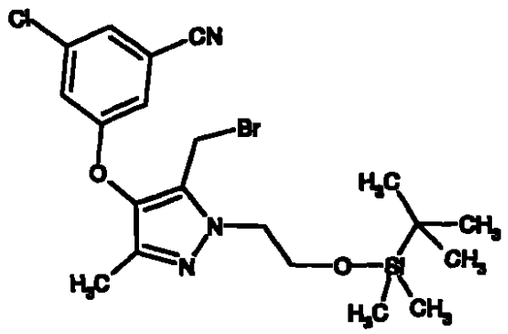


Chloro-t-butyldimethylsilane (2.78g, 18.5mmol) was added in one portion to a stirred solution of the pyrazole of Example 114 (4.89g, 16.8mmol) and imidazole (1.48g, 21.8mmol) in *N,N*-dimethylformamide (30ml) at room temperature under nitrogen. The reaction was stirred for 3 days and water (200ml) was added. The aqueous phase was extracted with diethyl ether (3x200ml) and the combined organic phases were washed with water (2x50ml) and brine (2x50ml), dried over magnesium sulphate, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with dichloromethane to provide the title compound (5.60g) as a yellow oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ = -0.02 (s, 6H), 0.82 (s, 9H), 2.02 (s, 3H), 2.12 (s, 3H), 3.97 (q, 2H), 4.06 (m, 2H), 7.02 (s, 1H), 7.11 (s, 1H), 7.24 (s, 1H).
LRMS (thermospray): m/z [MH^+] 408.
Microanalysis: Found: C, 58.95; H, 6.96; N, 10.22. $C_{20}H_{29}N_3O_2ClSi$ requires C, 59.13; H, 6.95; N, 10.35%.

PREPARATION 30

3-{[5-(Bromomethyl)-1-(2-[[*tert*-butyl(dimethyl)silyl]oxy]ethyl)-3-methyl-1*H*-pyrazol-4-yl]oxy}-5-chlorobenzonitrile

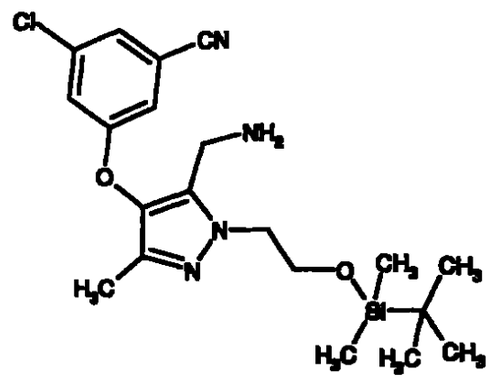


N-Bromosuccinimide (2.44g, 13.7mmol) was added to a stirred solution of the pyrazole of Preparation 29 (5,56g, 13.7mmol) in carbon tetrachloride (50ml) and azobisisobutyronitrile (20mg) at room temperature under nitrogen. The reaction was heated under reflux for 1 hour, cooled to room temperature and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel eluting with pentane:dichloromethane acetate (75:25, by volume) to provide the title compound (3.00g) as a colourless oil.

^{1}H-NMR (300MHz, $CDCl_3$): δ = -0.02 (s, 6H), 0.83 (s, 9H), 2.04 (s, 3H), 3.97 (q, 2H), 4.25 (m, 2H), 4.43 (s, 2H), 7.09 (s, 1H), 7.18 (s, 1H), 7.33 (s, 1H).
LRMS (thermospray): m/z [MH^+] 486.

PREPARATION 31

3-[[5-(Aminomethyl)-1-(2-[[*tert*-butyl(dimethyl)silyl]oxy]ethyl)-3-methyl-1*H*-pyrazol-4-yl]oxy]-5-chlorobenzonitrile

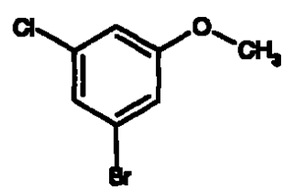


The bromide of Preparation 30 (1.58g, 3.26mmol) was added to a saturated solution of ammonia in isopropanol (50ml) at 0°C. The reaction was stirred for 6 hours and allowed to slowly warm to room temperature. The mixture was concentrated under reduced pressure and the resulting yellow oil was dissolved in dichloromethane (50ml). The solution was washed with 1M aqueous sodium carbonate solution (2x20ml) and brine (20ml), dried over magnesium sulphate, filtered and concentrated under reduced pressure to provide the title compound (1.00g) as a yellow oil.

^{1}H-NMR (300MHz, $CDCl_3$): δ = -0.23 (s, 6H), 0.62 (s, 9H), 1.22 (s, 2H), 1.82 (s, 3H), 2.56 (s, 2H), 3.78 (m, 2H), 4.02 (m, 2H), 6.85 (s, 1H), 6.96 (s, 1H), 7.06 (s, 1H).
LRMS (thermospray): m/z [MH^+] 421.

PREPARATION 32

1-Bromo-3-chloro-5-methoxybenzene

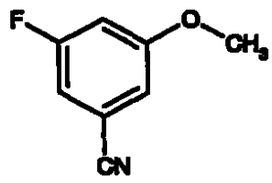


Sodium methoxide (2.20ml of a 4.5M solution in methanol, 10.0mmol) was added dropwise to a stirred solution of 1-fluoro-3-chloro-5-bromobenzene (1.00g, 4.77mmol) in methanol (28ml) at room temperature under nitrogen. The reaction was heated under reflux for 3 days and cooled to room temperature. The mixture was concentrated under reduced pressure and the resulting yellow oil was dissolved in dichloromethane (30ml). The resulting solution was washed with water (2x20ml) dried over magnesium sulphate, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel eluting with cyclohexane to provide the title compound (302mg) as a colourless oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 3.77 (s, 3H), 6.82 (s, 1H), 6.94 (s, 1H), 7.09 (s, 1H).
Microanalysis: Found: C, 37.94; H, 2.75. C_7H_5BrClO requires C, 37.96; H, 2.73%.

PREPARATION 33

3-Fluoro-5-methoxybenzonitrile

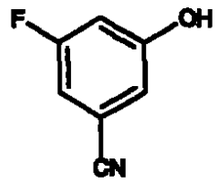


Sodium methoxide (1.50ml of a 4.5M solution in methanol, 7.10mmol) was added dropwise to a stirred solution of 3,5-difluorobenzonitrile (1.00g, 7.10mmol) in *N,N*-dimethylformamide (36ml) at 0°C under nitrogen. The reaction was allowed to warm to room temperature and stirred for 14 hours. The reaction was diluted with ether (40ml), washed with water (3x100ml) and brine (100ml), dried over magnesium sulphate, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with cyclohexane:ethyl acetate (95:5, by volume) to provide the title compound (418mg) as a yellow oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 3.84 (s, 3H), 6.82 (dd, 1H), 6.95 (dd, 1H), 6.96 (s, 1H).
LRMS (thermospray): m/z [MNH_4^+] 169.
Microanalysis: Found: C, 63.46; H, 3.95; N, 9.14. C_8H_6NOF requires C, 63.58; H, 4.00; N, 9.27%.

PREPARATION 34

3-Fluoro-5-hydroxybenzonitrile

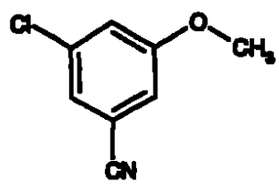


Boron trichloride (1.65ml of a 1.0M solution in dichloromethane, 1.65mmol) was added dropwise to a stirred solution of the nitrile of Preparation 33 (100mg, 0.660mmol) and tetrabutylammonium iodide (268mg, 0.728mmol) in dichloromethane (3ml) at -78°C. The reaction was allowed to warm 0°C, stirred for 2 hours and then allowed to warm to room temperature and stirred for 14 hours. The reaction was cooled to 0°C, cautiously quenched with ice and then concentrated under reduced pressure. The residue was dissolved in ether (40ml) and the resulting solution was washed with water (3x40ml) and brine (40ml), dried over magnesium sulphate, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with cyclohexane:ethyl acetate (90:10, by volume) to provide the title compound (50mg) as a white solid, m.p. 138-139°C.

^{1}H-NMR (300MHz, $CDCl_3$): δ = 5.81 (s, 1H), 6.80 (dd, 1H), 6.94 (dd, 1H), 6.95 (s, 1H).
Microanalysis: Found: C, 60.99; H, 3.01; N, 10.16. C_7H_4NOF requires C, 61.32; H, 2.94; N, 10.22%.

PREPARATION 35

3-Chloro-5-methoxybenzonitrile



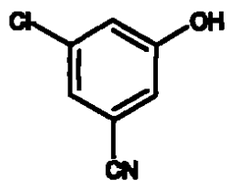
Palladiumtetrakis(triphenylphosphine) (174mg, 0.150mmol) was added in one portion to a stirred solution of the bromide of Preparation 32 (500mg, 2.26mmol) and

zinc cyanide (146mg, 1.24mmol) in *N,N*-dimethylformamide (3ml) at room temperature under nitrogen. The reaction was heated at 100°C for 14 hours and cooled to room temperature. The mixture was concentrated under reduced pressure and the crude product was purified by flash chromatography on silica gel eluting with cyclohexane:ethyl acetate (95:5, by volume) to provide the title compound (380mg) as a yellow oil.

^{1}H-NMR (300MHz, $CDCl_3$): δ = 3.82 (3H, s), 7.04 (s, 1H), 7.12 (s, 1H), 7.23 (s, 1H).
Microanalysis: Found: C, 57.50; H, 3.63; N, 8.16. C_8H_6NOCl requires C, 57.33; H, 3.61; N, 8.36%.

PREPARATION 36

3-Chloro-5-hydroxybenzonitrile

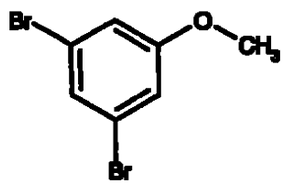


Boron trichloride (26.0ml of a 1.0M solution in dichloromethane, 26.0mmol) was added dropwise to a stirred solution of the nitrile of Preparation 35 (1.80g, 10.0mmol) and tetrabutylammonium iodide (4.36g, 11.0mmol) in dichloromethane (50ml) at -78°C. The reaction was allowed to warm to room temperature and stirred for 14 hours. The reaction was cooled to 0°C, cautiously quenched with ice and diluted with dichloromethane (100ml). The organic phase was washed with water (3x40ml) and brine (40ml), dried over magnesium sulphate, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with cyclohexane:ethyl acetate (80:20, by volume) to provide the title compound (900mg) as a white solid.

^{1}H-NMR (400MHz, d_6DMSO): δ = 7.12 (m, 2H), 7.38 (s, 1H), 10.65 (s, 1H).
Microanalysis: Found: C, 54.76; H, 2.81; N, 8.94. C_7H_4NOCl requires C, 54.75; H, 2.63; N, 9.12%.

PREPARATION 37

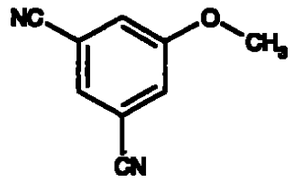
1,3-Dibromo-5-methoxybenzene



Sodium methoxide (8.80ml of a 4.5M solution in methanol, 41.0mmol) was added dropwise to a stirred solution of 3,5-dibromofluorobenzene (5.00g, 19.0mmol) in *N,N*-dimethylformamide (95ml) at 0°C under nitrogen. The reaction was allowed to warm to room temperature, stirred for 1 hour and then concentrated under reduced pressure. The residue was dissolved in ether and the resulting solution was washed with water (3x300ml) and brine (300ml), dried over magnesium sulphate, filtered and concentrated under reduced pressure to provide the title compound (5.13g) as a white solid.

^{1}H-NMR (300MHz, $CDCl_3$): δ = 3.79 (s, 3H), 7.00 (s, 2H), 7.26 (s, 1H).
LRMS (thermospray): m/z [MH^+] 266.
Microanalysis: Found: C, 31.56; H, 2.29. $C_7H_6OBr_2$ requires C, 31.62; H, 2.27%.

PREPARATION 38
3,5-Dicyanomethoxybenzene



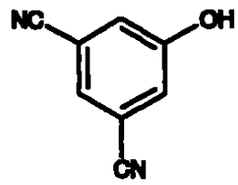
Tris(dibenzylideneacetone)dipalladium (6.53g, 7.15mmol) was added in one portion to a stirred solution of the bromide of Preparation 37 (38.0g, 143mmol) and zinc cyanide (20.0g, 172mmol) in *N,N*-dimethylformamide (300ml) at room temperature under nitrogen. The reaction was heated at 100°C for 14 hours and cooled to room temperature. Water (1500ml) was added and the mixture was extracted with ethyl acetate (3x500ml). The combined organics were filtered and the filtrate was washed with water (500ml), dried over magnesium sulphate, filtered and concentrated under

reduced pressure. The resulting solid was triturated with toluene (1000ml) to provide the title compound (18.0g) as a tan solid.

^{1}H-NMR (300MHz, $CDCl_3$): δ = 3.83 (3H, s), 7.31 (2H, s), 7.48 (1H, s).

PREPARATION 39

3,5-Dicyanohydroxybenzene

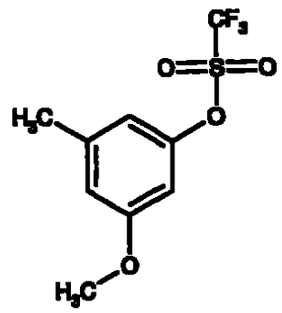


The nitrile of Preparation 38 (9.60g, 60.7mmol) was added portionwise to a stirred suspension of aluminium trichloride (32.4g, 243mmol) in dichloromethane (250ml) at 0°C under nitrogen. The suspension was heated to 45°C and stirred for 6 days. The reaction was cooled to room temperature and cautiously poured onto ice (450ml). Concentrated hydrochloric acid (450ml) was added dropwise and the resulting suspension was stirred for 10 minutes at room temperature. The resulting solid was collected by filtration, washed with water and dried over phosphorus pentoxide to provide the title compound (7.83g) as a tan solid containing approximately 11 % starting material by ^{1}H-NMR and microanalysis.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 7.36 (m, 2H), 7.56 (m, 1H).

PREPARATION 40

3-Methoxy-5-methylphenyl trifluoromethanesulfonate

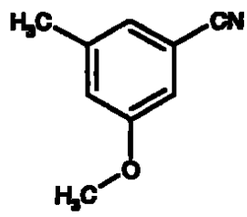


Trifluoromethanesulphonic anhydride (2.02ml, 12.0mmol) was added dropwise to a stirred solution of 3-methoxy-5-methylphenol (1.50g, 10.9mmol) in pyridine (20ml) at -20°C under nitrogen. The reaction was warmed to 0°C, stirred for 90 minutes and re-cooled to -20°C. More trifluoromethanesulphonic anhydride (1.01ml, 6.00mmol) was added dropwise. The reaction was allowed to warm to room temperature, stirred for 14 hours and cautiously poured into water (100ml). The aqueous phase was extracted with ether (150ml) and the organic phases were washed with water (3x75ml), 0.2M hydrochloric acid (3x75ml), 1.0M aqueous sodium carbonate solution (2x75ml), water (75ml) and brine (75ml), dried over magnesium sulphate, filtered and concentrated under reduced pressure to provide the title compound (2.86g) as a pale brown oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 2.35 (s, 3H), 3.80 (s, 3H), 6.60 (s, 1H), 6.68 (s, 1H), 6.73 (s, 1H).

PREPARATION 41

3-Methoxy-5-methylbenzonitrile



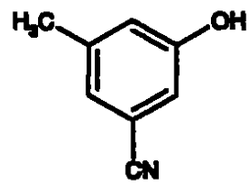
The triflate of Preparation 40 (1.94g, 7.10mmol), dibromobis(triphenylphosphine)nickel (369mg, 0.490mmol), 1,1'bis(diphenylphosphino)ferrocene (331mg, 0.590mmol) and potassium cyanide (1.38g, 21.3mmol) were added consecutively to a stirred suspension of Rieke® zinc (supplied by the Aldrich chemical company as a suspension; 5g Zinc in 100ml tetrahydrofuran) (74mg, 1.14mmol) in acetonitrile (4ml) at room temperature. The reaction was heated to 75°C for 8 hours and then cooled to room temperature. The mixture was partitioned between ether (200ml) and water (150ml) and the organic phase was separated, washed with water (2x100ml) and brine (75ml), dried over magnesium sulphate, filtered and concentrated under reduced pressure to give a pale brown oil. The crude product was purified by flash chromatography on silica gel

eluting with pentane:ethyl acetate (85:15, by volume) to provide the title compound (815mg) as a white solid.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 2.34 (s, 3H), 3.80 (s, 3H), 6.93 (s, 1H), 6.94 (s, 1H), 7.04 (s, 1H).

PREPARATION 42

3-Hydroxy-5-methylbenzonitrile

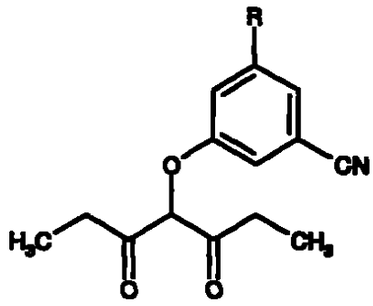


Boron trichloride (17.6ml of a 1.0M solution in dichloromethane, 17.6mmol) was added dropwise to a stirred solution of the nitrile of Preparation 41 (868mg, 5.88mmol) and tetrabutylammonium iodide (2.61g, 7.05mmol) in dichloromethane (50ml) at -78°C. The reaction was allowed to warm to room temperature and stirred for 20 minutes. The reaction was cooled to 0°C, cautiously quenched with ice and diluted with dichloromethane (100ml). The organic phase was separated, dried over magnesium sulphate, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with pentane:ethyl acetate (50:50, by volume) to provide the title compound (677mg) as a white solid.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 2.32 (s, 3H), 5.05 (s, 1H), 6.88 (s, 1H), 6.90 (s, 1H), 7.04 (s, 1H).

PREPARATIONS 43 TO 46

The compounds of the following tabulated Preparations of the general formula:

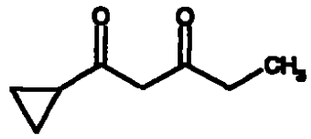


were prepared by a similar method to that of Preparation 9 using the appropriate phenol starting material and the chloride of Preparation 2.

Preparation No (Phenol No)	R	LRMS	Analytical Data
43 (Phenol Preparation 34)	F	m/z [MNH_4^+] 281 (thermospray)	^{1}H-NMR (300MHz, $CDCl_3$) δ = 1 05 (t, 6H), 2 27 (q, 4H), 6 89 (m, 1H), 7 03 (s, 1H), 7 04 (m, 1H)
44 (Phenol Preparation 42)	Me	m/z [$M-H^+$] 258 (electrospray)	^{1}H-NMR (400MHz, $CDCl_3$) δ = 1 09 (t, 6H), 2 32 (q, 4H), 2 37 (s, 3H), 6 96 (s, 1H), 6 97 (s, 1H), 7 15 (s, 1H), 14 50 (s, 1H)
45 (Phenol Preparation 39)	CN	m/z [$M-H^+$] 269 (electrospray)	^{1}H-NMR (300MHz, $CDCl_3$) δ = 1 09 (m, 6H), 2 30 (m, 4H), 7 42 (s, 2H), 7 61 (s, 1H), 14 56 (s, 1H)
46 (Phenol Preparation 36)	Cl	m/z [MH^+] 280 (thermospray)	^{1}H-NMR (400MHz, $CDCl_3$) δ = 1 08 (m, 6H), 2 31 (q, 4H), 7 12 (s, 1H), 7 19 (s, 1H), 7 31 (s, 1H)

PREPARATION 47

1-Cyclopropyl-1,3-pentanedione

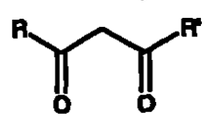


A stirred suspension of magnesium turnings (1.83g, 75.0mmol) in methanol (85ml) was heated under reflux for 90 minutes. The suspension was cooled to room temperature and a solution of 3-ketopentanoic acid (17.4g, 150.0mmol) in methanol (15ml) was added. The white suspension dissolved to give a pale yellow solution. The reaction was stirred at room temperature for 1 hour and then concentrated under reduced pressure to give a pale yellow solid which was dissolved in *N,N*-dimethylformamide (50ml). In a separate flask carbonyldiimidazole (13.4g, 83.0mmol) was added portionwise to a stirred solution of cyclopropanecarboxylic acid (6.46g, 75.0mmol) in *N,N*-dimethylformamide (150ml) at room temperature under nitrogen. The reaction was stirred for 90 minutes and then the magnesium salt previously prepared was added dropwise. The reaction was stirred for 3 days and then poured into 1.0M hydrochloric acid (150ml). The aqueous phase was extracted with ether (3x200ml) and the combined organic phases were dried over magnesium sulphate, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with pentane:ethyl acetate (90:10, by volume) to provide the title compound (9.33g) as a yellow oil.

^{1}H-NMR (400MHz, $CDCl_3$): keto and enol forms present with enol as major component; enol signals δ = 1.00 (m, 7H), 1.60 (m, 1H), 2.25 (m, 2H), 5.59 (s, 1H), 15.62 (s, 1H); keto signals δ = 1.00 (m, 7H), 2.01 (m, 1H), 2.52 (m, 2H), 3.68 (s, 2H).
LRMS (electrospray): m/z [M-H$^+$] 139.
Microanalysis: Found: C, 68.35; H, 8.72. $C_8H_{12}O_2$ requires C, 68.55; H, 8.63%.

PREPARATION 48

The compound of the following tabulated Preparation of the general formula:

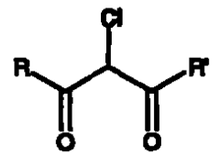


was prepared by a similar method to that of Preparation 47 using the appropriate ketoacid and carboxylic acid starting materials.

Preparation No	R	R'	LRMS	Analytical Data
48	iPr	Et	m/z [M-H$^+$] 141 (electrospray)	^{1}H-NMR (400MHz, $CDCl_3$) keto and enol forms present with enol major δ = 1 12 (m, 18H, keto and enol), 2.32 (m, 4H, keto and enol), 2 49 (m, 2H, keto and enol), 3 61 (s, 2H, keto), 5.49 (s, 1H, enol), 15.52 (s, 1H, enol) Microanalysis. Found C, 67 22, H, 9 95 $C_8H_{14}O_2$ requires C, 67.57, H, 9 92%

PREPARATIONS 49 TO 51

The compounds of the following tabulated Preparations of the general formula:

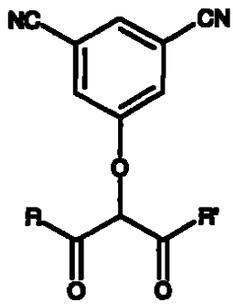


were prepared by a similar method to that of Preparation 2 using the appropriate diketone starting material.

Preparation No (Diketone No)	R	R'	LRMS	Analytical Data
49 (Preparation 47)	cycloPr	Et	m/z [M-H$^+$] 173 (electrospray)	^{1}H-NMR (400MHz, $CDCl_3$) 1 10 (m, 7H), 2 41 (m, 1H), 2 61 (m, 2H), 15 90 (s, 1H)
50 (Commercially available diketone used)	Me	Et	m/z [MNH_4^+] 166 (thermospray)	^{1}H-NMR (300MHz, $CDCl_3$)' 1 19 (m, 3H), 2 27 (s, 3H), 2 67 (q, 2H), 15 40 (s, 1H)
51 (Preparation 48)	IPr	Et	m/z [M-H$^+$] 175 (electrospray)	^{1}H-NMR (400MHz, $CDCl_3$) 1 18 (m, 9H), 2 64 (q, 2H), 3 20 (m, 1H), 15 80 (s, 1H)

PREPARATIONS 52 TO 54

The compounds of the following tabulated Preparations of the general formula:

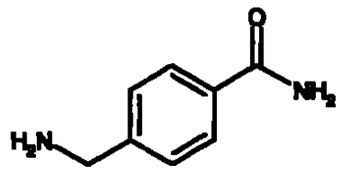


were prepared by a similar method to that of Preparation 9 using the appropriate diketone starting material and the phenol of Preparation 39.

Preparation No (Diketone No)	R	R'	LRMS	Analytical Data
52 (Preparation 49)	cycloPr	Et	m/z [M-H$^+$] 282 (electrospray)	^{1}H-NMR (400MHz, $CDCl_3$) 0 93 (m, 2H), 1 12 (t, 3H), 1 21 (m, 2H), 1 78 (m, 1H), 2 29 (q, 2H), 7 49 (s, 2H), 7 61 (s, 1H), 14 87 (s, 1H)
53 (Preparation 19)	tBu	Me	m/z [MNH_4^+] 301 (thermospray)	^{1}H-NMR (400MHz, $CDCl_3$) 1 08 (s, 9H), 1 84 (s, 3H), 7 30 (s, 1H), 7 57 (s, 2H), 15 42 (s, 1H)
54 (Preparation 51)	IPr	Et	m/z [M-H$^+$] 283 (electrospray)	^{1}H-NMR (400MHz, $CDCl_3$) 1 03 (m, 9H), 2 23 (q, 2H), 2 58 (m, 1H), 7 41 (s, 2H), 7 59 (s, 1H), 14 63 (s, 1H)

PREPARATION 55

4-(Aminomethyl)benzamide

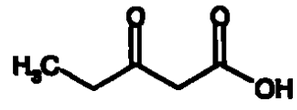


Powdered potassium hydroxide (340mg, 6mmol) was added in one portion to a stirred solution of 4-(aminomethyl)benzonitrile (200mg, 1.5mmol) in 2-methyl-2-propanol (20ml) at reflux under nitrogen. The reaction was heated at reflux for 30 minutes and cooled to room temperature. The mixture was concentrated under reduced pressure and the crude product was purified by flash chromatography on silica gel eluting with dichloromethane:methanol:ammonia (95:5:0.5, by volume) to provide the title compound (150mg) as a white solid.

^{1}H-NMR (300MHz, CD_3OD): δ = 3.85 (s, 2H), 7.43 (d, 2H), 7.82 (d, 2H).
LRMS (thermospray): m/z [MH^+] 151.

PREPARATION 56

3-Oxopentanoic acid

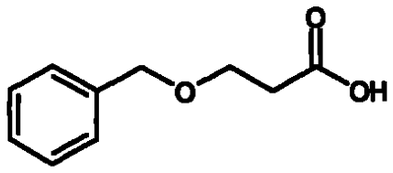


Sodium hydroxide (54g, 1.35mol) was added portionwise to a solution of 3-oxo-pentanoic acid methyl ester (80g, 0.62mol) in tetrahydrofuran (300ml) and water (300ml) at 0°C. The reaction was allowed to warm to room temperature and was stirred for 18 hours. The reaction mixture was washed with diethylether (500ml) and the aqueous phase was acidified to pH1 at 0°C with concentrated hydrochloric acid (140ml). The aqueous phase was extracted with dichloromethane (2x300ml) and the combined organic extracts dried over magnesium sulphate and concentrated under reduced pressure to provide the title compound (44g) as a white solid.

^{1}H NMR (400MHz, $CDCl_3$): δ = 1.12 (t, 3H), 2.59 (q, 2H), 3.49 (s, 2H).

PREPARATI N 57

3-(Benzyloxy)propanoic acid

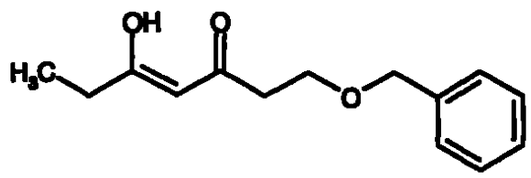


Sodium metal (249mg, 10.8mmol) was added to benzyl alcohol (30g, 278mmol) at room temperature under nitrogen and the reaction was stirred for 30 minutes. Methyl acrylate (25.9ml, 259mmol) was then added dropwise and the reaction was stirred at room temperature for 18h. After quenching with saturated aqueous ammonium chloride solution (200ml) the mixture was extracted with ethyl acetate (2x300ml) and the combined organic extracts were washed with brine (100ml), dried over magnesium sulphate and concentrated under reduced pressure. The residual oil was dissolved in ethanol (300ml) and 1M aqueous sodium hydroxide solution (300ml) was added dropwise. After 3 hours the ethanol was removed under reduced pressure and the aqueous residue was washed with dichloromethane (200ml). The aqueous phase was then acidified with 2N aqueous hydrochloric acid (150ml), extracted with dichloromethane (2x250ml) and the combined organic extracts were dried over magnesium sulphate and concentrated under reduced pressure. The residual oil was dissolved in 10% aqueous potassium carbonate solution (300ml), washed with diethylether (300ml) and the aqueous phase was acidified to pH1 using concentrated hydrochloric acid. The mixture was then extracted with dichloromethane (2x300ml) and the combined organic extracts were dried over magnesium sulphate and concentrated under reduced pressure to provide the title compound (44.4g) as a colourless oil.

^{1}H NMR (300MHz, $CDCl_3$): δ = 2.67 (t, 2H), 3.89 (t, 2H), 4.58 (s, 2H), 7.18 (m, 5H).

PREPARATION 58

(4Z)-1-(Benzyloxy)-5-hydroxy-4-hepten-3-one

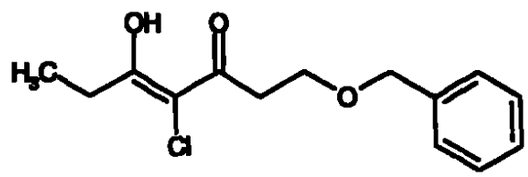


A suspension of magnesium turnings (1.74g, 71.6mmol) in methanol (85ml) was heated to reflux under nitrogen for 1.5 hours, cooled to room temperature and the β-keto acid from Preparation 58 (16.6g, 143mmol) was added. The reaction was stirred for 1.5 hours and the solvent was removed under reduced pressure to give the magnesium salt of the acid as a white solid. Meanwhile, the acid from Preparation 57 (12.9g, 71.6mmol) was dissolved in dimethylformamide (150ml) and carbonyldiimidazole (12.8g, 78.8mmol) was added portionwise under nitrogen at room temperature. This was stirred for 1 hour and the magnesium salt from above was added as a solution in dimethylformamide (50ml). Evolution of gas was noted, and the reaction was allowed to stir at room temperature for 18 hours. The mixture was concentrated under reduced pressure and the residual orange oil was dissolved in dichloromethane (300ml), washed with 0.5M aqueous hydrochloric acid (250ml) containing methanol (10ml) and the aqueous phase was separated and extracted with dichloromethane (2x300ml). The combined organic extracts were washed with brine (300ml) containing methanol (20ml), dried over magnesium sulphate and concentrated under reduced pressure. The residual orange oil was purified by flash chromatography on silica gel eluting with cyclohexane:ethyl acetate (80:20, by volume) to provide the title compound (12.0g) as an orange oil.

^{1}H NMR (400MHz, $CDCl_3$): δ = 1.17 (t, 3H), 2.33 (q, 2H), 2.58 (t, 2H), 3.76 (t, 2H), 4.53 (s, 2H), 5.57 (s, 1H), 7.13 (m, 5H).
LRMS (electrospray) : m/z [MNa^+] 257.
Microanalysis: Found C, 71.77; H, 7.74. $C_{14}H_{18}O_3$ requires C, 71.76; H, 7.69%.

PREPARATION 59

(4*E*)-1-(Benzyloxy)-4-chloro-5-hydroxy-4-hepten-3-one



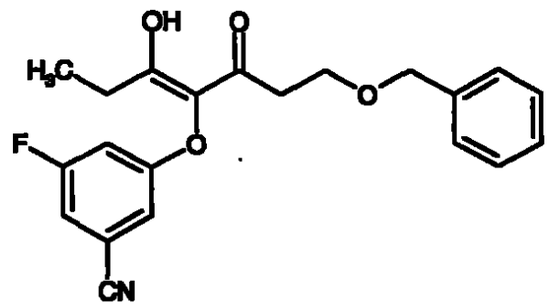
Trimethylsilyl chloride (10ml, 51.3mmol) was added to a solution of the enol from Preparation 58 (4.0g, 17.1mmol) in acetonitrile (25ml) under nitrogen at 0°C. Dimethylsulfoxide (3.6ml, 51.3mmol) followed by tert-butylammonium bromide (275mg, 0.85mmol) were then added and the reaction was stirred at 0°C for 2 hours. The mixture was diluted with water (100ml), extracted with diethylether

(100ml) and the organic phase was washed with brine (50ml), dried over magnesium sulphate and concentrated under reduced pressure. The residual pink oil was purified by flash chromatography on silica gel eluting with cyclohexane:ethyl acetate (80:20, by volume) to provide the title compound (3.76g) as a pink oil.

^{1}H NMR (400MHz, $CDCl_3$): δ = 1.17 (t, 3H), 2.62 (q, 2H), 2.96 (t, 2H), 3.79 (t, 2H), 4.57 (s, 2H), 7.12 (m, 5H), 15.49 (s, 1H).
LRMS (electrospray) : m/z [MNa^+] 291.

PREPARATION 60

3-(((1*E*)-1-[3-(benzyloxy)propanoyl]-2-hydroxy-1-butenyl)oxy)-5-fluorobenzonitrile

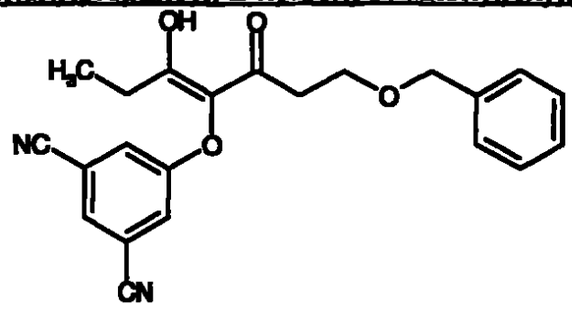


Sodium hydride (60% dispersion in oil, (1.92g, 48.0mmol) was added to a stirred solution of the phenol from Preparation 34 (8.80g, 48.0mmol) in tetrahydrofuran (450ml) under nitrogen at room temperature. After stirring for 1 hour, the enol from Preparation 59 (12.9g, 48.0mmol) was added and the reaction was stirred for 64 hours. The mixture was diluted with water (200ml) and 2N aqueous hydrochloric acid (40ml), extracted with ethyl acetate (2x150ml) and the combined organic extracts were washed with brine (100ml), dried over magnesium sulphate and concentrated under reduced pressure. The residual orange oil was purified by flash chromatography on silica gel eluting with cyclohexane:pentane (10:90, by volume) to provide the title compound (5.80g) as an orange oil.

^{1}H NMR (400MHz, $CDCl_3$): δ = 1.08 (t, 3H), 2.31 (q, 2H), 2.59 (t, 2H), 3.75 (t, 2H), 4.45 (s, 2H), 6.92 (m, 1H), 7.02 (m, 2H), 7.29 (m, 5H), 14.50 (s, 1H).
LRMS (electrospray) : m/z [MNa^+] 392.

PREPARATION 61

5-(((1*E*)-1-[3-(Benzyloxy)propanoyl]-2-hydroxy-1-butenyl)oxy)isophthalonitrile

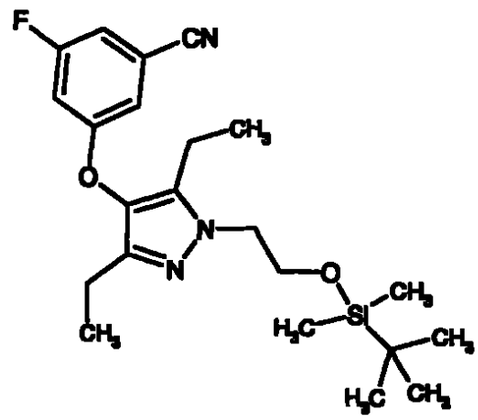


Sodium hydride (60% dispersion in oil, 412mg, 12.3mmol) was added to a stirred solution of the phenol from Preparation 39 (1.48g, 10.3mmol) in tetrahydrofuran (70ml) under nitrogen at room temperature. After stirring for 30 minutes, the enol from Preparation 59 (2.76g, 10.3mmol) was added and the reaction was stirred for 18 hours. Water (100ml) and 2N aqueous hydrochloric acid (10ml) were cautiously added and the mixture extracted with ethyl acetate (2x150ml). The organics were combined, washed with brine (100ml), dried over magnesium sulphate and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with (pentane:ethyl acetate 90:10, by volume) to provide the title compound (1.00g) as a yellow oil.

LRMS (thermospray) : m/z [MH^+] 375.

PREPARATION 62

3-[[1-(2-[[*tert*-Butyl(dimethyl)silyl]oxy}ethyl)-3,5-diethyl-1*H*-pyrazol-4-yl]oxy]-5-fluorobenzonitrile

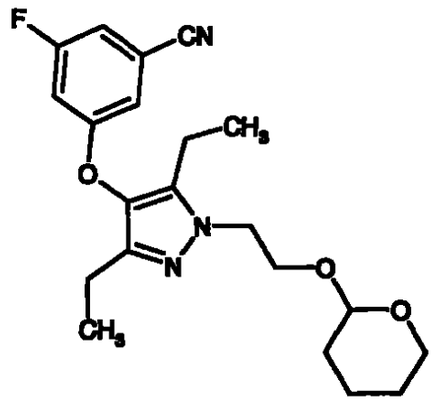


Imidazole (477mg, 7.02mmol) and tert-butyl-dimethyl-silyl chloride (977mg, 6.48mmol) were sequentially added to a solution of the alcohol from Example 117 (1.65g, 5.40mmol) in dimethylformamide (11ml) at room temperature under nitrogen. The reaction was stirred for 18 hours and the mixture was diluted with water (100ml) and extracted with diethylether (4x50ml). The combined organic extracts were dried over magnesium sulphate, concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel eluting with dichloromethane:methanol (99:1, by volume) to provide the title compound (2.12g) as a colourless oil.

^{1}H NMR (400MHz, $CDCl_3$): δ = 0.03 (s, 6H), 0.84 (s, 9H), 1.10 (m, 6H), 2.42 (q, 2H), 2.56 (q, 2H), 4.00 (t, 2H), 4.09 (t, 2H), 6.86 (d, 1H), 6.99 (m, 2H).
LRMS (thermospray) : m/z [MH^+] 419.
Microanalysis: Found C, 62.73; H, 7.83; N, 9.75. $C_{22}H_{32}FN_3O_2Si.0.06CH_2Cl_2$ requires C, 62.68; H, 7.66; N, 9.94%.

PREPARATION 63

3-({3,5-Diethyl-1-[2-(tetrahydro-2*H*-pyran-2-yloxy)ethyl]-1*H*-pyrazol-4-yl}oxy)-5-fluorobenzonitrile



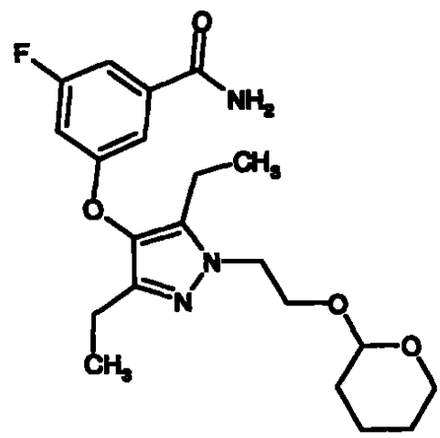
p-Toluene-sulphonic acid (32mg, 0.17mmol) was added to a solution of the alcohol from Example 117 (5.04g, 16.6mmol) and dihydropyran (7.57ml, 83mmol) in dichloromethane (65ml) at room temperature under nitrogen. The reaction was stirred for 2 hours, but starting material still remained so a further aliquot of p-toluene-sulphonic acid (284mg, 1.49mmol) was added and the reaction was stirred for 1 hour. The mixture was diluted with diethylether (90ml) and washed with a mixed aqueous solution (water (50ml), brine (25ml) and saturated aqueous sodium bicarbonate solution (25ml)). The aqueous phase was extracted with diethylether (2x60ml) and the combined organic extracts were

dried over magnesium sulphate, concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel eluting with dichloromethane:methanol (98:2, by volume) to provide the title compound (6.31g) as an oil.

^{1}H NMR (400MHz, $CDCl_3$): δ = 1.08 (m, 6H), 1.52 (m, 6H), 2.39 (q, 2H), 2.54 (q, 2H), 3.45 (m, 1H), 3.64 (m, 1H), 3.75 (m, 1H), 4.06 (m, 1H), 4.17 (t, 2H), 4.51 (s, 1H), 6.82 (d, 1H), 7.22 (m, 2H).
LRMS (thermospray) : m/z [MH^+] 388.

PREPARATION 64

3-({3,5-Diethyl-1-[2-(tetrahydro-2*H*-pyran-2-yloxy)ethyl]-1*H*-pyrazol-4-yl}oxy)-5-fluorobenzamide



Cesium carbonate (269mg, 0.82mmol) was added to a solution of 3-methyl-3-pyrazolin-5-one (74mg, 0.75mmol) in dimethylsulfoxide (1ml) under nitrogen at room temperature and the reaction was stirred for 15 minutes. The aryl fluoride from Preparation 63 (291mg, 0.75mmol) dissolved in dimethylsulfoxide (1ml) was then added and the reaction was heated to 100°C for 18 hours. After cooling to room temperature the reaction was diluted with water (7ml) and extracted with diethylether (12ml). The organic phase was washed with brine (3.5ml), dried over magnesium sulphate, concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel eluting with a solvent gradient of dichloromethane:methanol (99:1 changing to 95:5, by volume) to provide the unexpected title compound (108mg) as an oil.

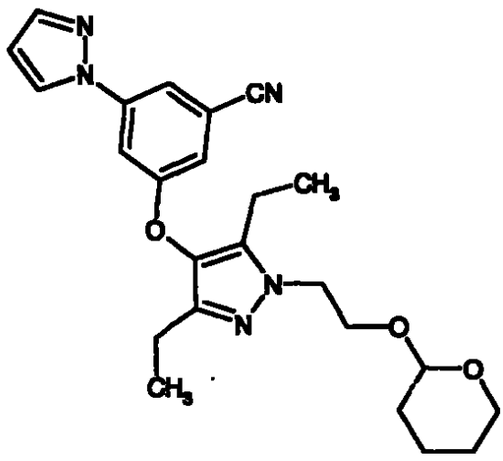
^{1}H NMR (400MHz, $CDCl_3$): δ = 1.12 (m, 6H), 1.56 (m, 6H), 2.44 (q, 2H), 2.59 (q, 2H), 3.48 (m, 1H), 3.69 (m, 1H), 3.79 (m, 1H), 4.08 (m, 1H), 4.20 (t, 2H), 4.54 (s, 1H), 6.72 (d, 1H), 7.15 (m, 2H).

LRMS (thermospray) : m/z [MH^+] 406.

Microanalysis: Found C, 60.57; H, 6.97; N, 9.97. $C_{21}H_{28}FN_5O_4.0.08CH_2Cl_2.0.32H_2O$ requires C, 60.57; H, 6.94; N, 10.05%.

PREPARATION 65

3-({3,5-Diethyl-1-[2-(tetrahydro-2*H*-pyran-2-yloxy)ethyl]-1*H*-pyrazol-4-yl}oxy)-5-(1*H*-pyrazol-1-yl)benzonitrile



Cesium Carbonate (269mg, 0.82mmol) was added to a solution of pyrazole (51mg, 0.75mmol) in dry dimethylsulfoxide (1ml) under nitrogen at room temperature and the reaction was stirred for 15 minutes. The aryl fluoride from Preparation 63 (291mg, 0.75mmol) dissolved in dry dimethylsulfoxide (1ml) was then added and the reaction was heated to 100°C for 18 hours. After cooling to room temperature the reaction was diluted with water (7ml) and extracted with diethylether (10ml). The organic phase was washed with brine (3ml), dried over magnesium sulphate, concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel eluting with a solvent gradient of dichloromethane:methanol (100:0 changing to 90:10, by volume) to provide the title compound (55mg).

^{1}H NMR (400MHz, $CDCl_3$): δ = 1.13 (m, 6H), 1.58 (m, 6H), 2.44 (q, 2H), 2.60 (q, 2H), 3.49 (m, 1H), 3.69 (m, 1H), 3.80 (m, 1H), 4.10 (m, 1H), 4.21 (t, 2H), 4.55 (s, 1H), 6.50 (s, 1H), 6.98 (s, 1H), 7.57 (s, 1H), 7.63 (s, 1H), 7.72 (s, 1H), 7.89 (s, 1H).

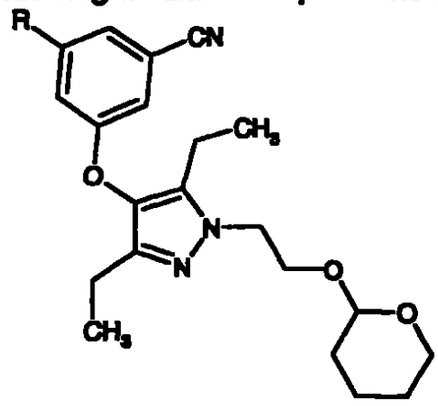
LRMS (thermospray) : m/z [MH^+] 436, [MNa^+] 458.

HRMS: [MH^+] Found 436.2352. $C_{24}H_{30}N_5O_3$ requires 436.2343

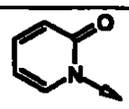
[MNa^+] Found 458.2168. $C_{24}H_{29}N_5O_3Na$ requires 458.2162.

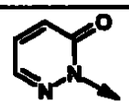
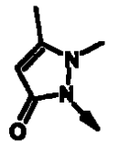
PREPARATIONS 66-68

The preparation of the following tabulated Preparations of the general formula



were performed by a similar method to that of Preparation 65 using the appropriate heterocycle as the starting material.

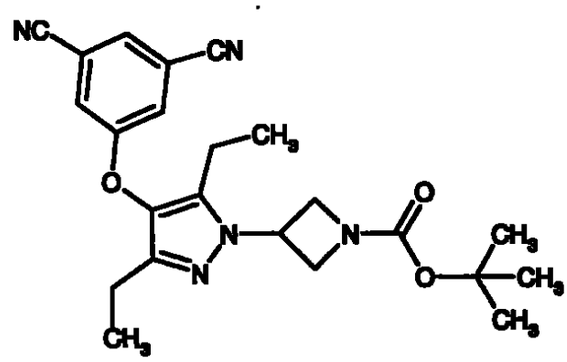
Preparation No. (Starting material preparation no.)	R	Analytical Data
66 (63)		^{1}H NMR (400MHz, $CDCl_3$): δ = 1.13 (m, 6H), 1.63 (m, 6H), 2.44 (q, 2H), 2.60 (q, 2H), 3.46 (m, 1H), 3.67 (m, 1H), 3.79 (m, 1H), 4.08 (m, 1H), 4.20 (t, 2H), 4.53 (s, 1H), 6.26 (t, 1H), 6.64 (d, 1H), 7.17 (s, 1H), 7.21 (s, 1H), 7.34 (s, 1H), 7.41 (t, 1H). LRMS (thermospray) : m/z [MH^+] 463, [MNa^+] 485. HRMS: [MH^+] Found 463.2353. $C_{28}H_{31}N_4O_4$ requires 463.2340 [MNa^+] Found 485.2166. $C_{28}H_{30}N_4O_4Na$ requires 485.2159.

67 (63)		^{1}H NMR (400MHz, $CDCl_3$): δ = 1.10 (m, 6H), 1.56 (m, 6H), 2.41 (q, 2H), 2.56 (q, 2H), 3.44 (m, 1H), 3.64 (m, 1H), 3.75 (m, 1H), 4.05 (m, 1H), 4.17 (t, 2H), 4.50 (s, 1H), 7.00 (d, 1H), 7.08 (s, 1H), 7.20 (m, 1H), 7.51 (s, 1H), 7.64 (s, 1H), 7.86 (s, 1H). LRMS (thermospray) : m/z [MH^+] 464, [MNa^+] 486. HRMS: [MH^+] Found 464.2297. $C_{25}H_{30}N_5O_4$ requires 464.2293 [MNa^+] Found 486.2113. $C_{25}H_{29}N_5O_4Na$ requires 486.2112.
68[1] (63)		^{1}H NMR (400MHz, $CDCl_3$): δ = 1.08 (m, 6H), 1.48 (m, 6H), 2.23 (s, 3H), 2.38 (q, 2H), 2.53 (q, 2H), 3.43 (m, 1H), 3.63 (m, 1H), 3.66 (s, 3H), 3.73 (m, 1H), 4.04 (m, 1H), 4.15 (t, 2H), 4.50 (s, 1H), 5.59 (s, 1H), 6.76 (s, 1H), 6.88 (s, 1H), 6.95 (s, 1H). LRMS (thermospray) : m/z [MH^+] 460, [MNa^+] 502.

[1] The eluent used for flash column chromatography purification of this compound was dichloromethane:methanol (99:1 changing to 95:5, by volume).

PREPARATION 69

tert-Butyl 3-[4-(3,5-dicyanophenoxy)-3,5-diethyl-1*H*-pyrazol-1-yl]-1-azetidinecarboxylate



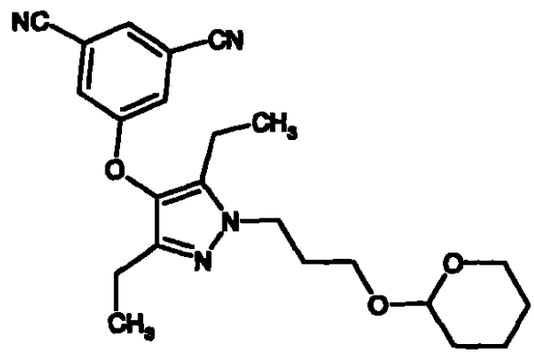
Sodium hydride (60% dispersion in oil, 33mg, 0.82mmol) was added to a solution of the pyrazole from Example 122 (200mg, 0.75mmol) in dimethylformamide (3ml) at 0°C under nitrogen and the reaction was stirred for 10 minutes. 3-Iodo-

azetidine-1-carboxylic acid tert-butyl ester (234mg, 0.82mmol) was added and the reaction was stirred at room temperature for 18 hours. The reaction was quenched with water (0.2ml) and concentrated under reduced pressure. The residue was partitioned between dichloromethane (5ml) and water (5ml) and the organic phase was isolated using a 5µM Whatman PTFE fritted cartridge, then concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with a solvent gradient of ethyl acetate:pentane (20:80 then 25:75 then 34:66 then 50:50 then 75:25 then 100:0, by volume) changing to ethyl acetate:methanol (10:1, by volume) then dichloromethane:methanol:0.88 ammonia (90:10:1 then 80:20:1, by volume) to provide the title compound (189mg) as a pale yellow oil.

^{1}H NMR (400MHz, $CDCl_3$): δ = 1.03-1.17 (m, 6H), 1.49 (s, 9H), 2.39-2.52 (m, 4H), 4.32 (m, 2H), 4.50 (m, 2H), 4.94 (m, 1H), 7.38 (s, 2H), 7.56 (s, 1H).
LRMS (thermospray) : m/z [MH^+] 422, [MNa^+] 444.
Microanalysis: Found C, 65.08; H, 6.49; N, 16.48. $C_{23}H_{27}N_5O_3.0.18H_2O$ requires C, 65.04; H, 6.49; N, 16.49%.

PREPARATION 70

5-({3,5-Diethyl-1-[3-(tetrahydro-2*H*-pyran-2-yloxy)propyl]-1*H*-pyrazol-4-yl}oxy)isophthalonitrile



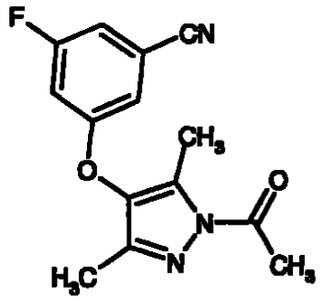
Sodium hydride (60% dispersion in oil, 33mg, 0.82mmol) was added to a solution of the pyrazole from Example 122 (200mg, 0.75mmol) in dimethylformamide (3ml) at 0°C under nitrogen and the reaction was stirred for 10 minutes. 2-(3-bromo-propoxy)-tetrahydro-pyran (184mg, 0.82mmol) was added and the reaction was stirred at room temperature for 18 hours. The reaction was quenched with water (0.2ml) and concentrated under reduced pressure. The residue was partitioned between dichloromethane (5ml) and water (5ml) and the

organic phase was isolated using a 5µM Whatman PTFE fritted cartridge, then concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with a solvent gradient of ethyl acetate:pentane (20:80 then 25:75 then 34:66 then 50:50 then 75:25 then 100:0, by volume) changing to ethyl acetate:methanol (10:1, by volume) then dichloromethane:methanol:0.88 ammonia (90:10:1 then 80:20:1, by volume) to provide the title compound (238mg) as a pale yellow oil.

^{1}H NMR (400MHz, $CDCl_3$): δ = 1.09 (m, 6H), 1.47-1.63 (m, 2H), 1.66-1.88 (m, 2H), 2.15 (dd, 2H), 2.38 (q, 2H), 2.53 (q, 2H), 3.37-3.55 (m, 2H), 3.75-3.90 (m, 2H), 4.11 (m, 2H), 4.56 (m, 1H), 7.37 (s, 2H), 7.55 (s, 1H).
LRMS (electro) : m/z [MH^+] 409, [MNa^+] 421.
Microanalysis: Found C, 66.59; H, 6.91; N, 13.40. $C_{23}H_{28}N_4O_3.0.36H_2O$ requires C, 66.57; H, 6.98; N, 13.50%.

PREPARATION 71

3-[(1-Acetyl-3,5-dimethyl-1*H*-pyrazol-4-yl)oxy]-5-fluorobenzonitrile



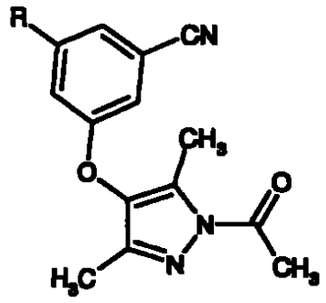
The phenol from Preparation 34 (10.0g, 72.7mmol), 3-chloro-2,4-pentanedione (7.10g, 72.7mmol) and cesium carbonate (23.6g, 72.9mmol) were heated to reflux in acetone (100ml) under nitrogen for 2 hours. The reaction was cooled to room temperature, 1N aqueous hydrochloric acid (50ml) was added slowly and the mixture was extracted with ethyl acetate (3x100ml). The combined organic extracts dried over magnesium sulphate and concentrated under reduced pressure. The residual yellow oil was dissolved in methanol (100ml), hydrazine (5.3ml, 109mmol) was added and the reaction was stirred at room temperature under nitrogen for 2 hours. The solvent was removed under reduced pressure and the residue was dissolved in dimethylformamide (50ml) at 0°C. Acetyl chloride (5.1ml, 72.0mmol) was added slowly followed by sodium hydride (60% dispersion in oil, 2.8g, 72.0mmol) portionwise. The reaction was stirred for 15 minutes and sat. ammonium chloride solution (50ml) was added, and the reaction was allowed to warm to room temperature. The mixture was extracted

with ethyl acetate (3x100ml) and the combined organic extracts were dried over magnesium sulphate and concentrated under reduced pressure giving an oil. After standing for 18 hours, a solid had formed within the oil which was isolated by filtration, washing with diethylether (50ml) to provide the title compound (3.50g) as a white solid, m.p. 109-111°C.

^{1}H NMR (400MHz, $CDCl_3$): δ = 2.06 (s, 3H), 2.37 (s, 3H), 2.65 (s, 3H), 6.81 (d, 1H), 6.91 (s, 1H), 7.04 (d, 1H).
LRMS (thermospray) : m/z [MH^+] 273.
Microanalysis: Found C, 61.62; H, 4.44; N, 15.09. $C_{14}H_{12}N_3O_2F$ requires C, 61.53; H, 4.43; N, 15.38%.

PREPARATIONS 72-74

The tabulated compounds of the general formula



were performed by a similar method to that of Preparation 71 using the appropriate phenol as the starting material.

Preparation no. (Starting material preparation no.)	R'	Analytical Data
72 (39)	CN	m.p. 204-206°C ^{1}H NMR (400MHz, $CDCl_3$): δ = 2.06 (s, 3H), 2.38 (s, 3H), 2.66 (s, 3H), 7.33 (s, 2H), 7.58 (s, 1H). LRMS (thermospray) : m/z [MH^+] 281. Microanalysis: Found C, 63.30; H, 4.25; N, 19.59. $C_{15}H_{12}N_4O_2.0.30H_2O$ requires C, 63.06; H, 4.45; N, 19.61%.
73[1] (42)	Me	m.p. 152-154°C ^{1}H NMR (400MHz, $CDCl_3$): δ = 2.05 (s, 3H), 2.33 (s, 3H), 2.38 (s, 3H), 2.66 (s, 3H), 6.88 (s, 1H), 6.91 (s, 1H), 7.12 (s, 1H).

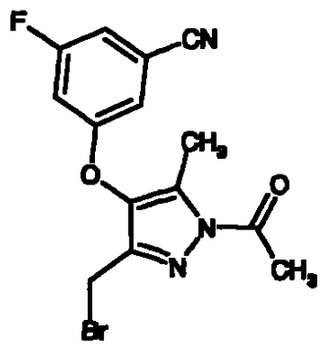
		LRMS (thermospray) : m/z [MH$^+$] 270. Microanalysis: Found C, 66.67; H, 5.71; N, 15.25. $C_{15}H_{15}N_3O_2$ requires C, 66.9; H, 5.61; N, 15.60%.
74[2] (Commercial)	H	m.p. 131-133°C ^{1}H NMR (400MHz, $CDCl_3$): δ = 2.13 (s, 3H), 2.40 (s, 3H), 2.70 (s, 3H), 7.15 (m, 2H), 7.35 (m, 1H), 7.40 (m, 1H). LRMS (thermospray) : m/z [MH$^+$] 278. Microanalysis: Found C, 65.87; H, 5.11; N, 16.33. $C_{14}H_{13}N_3O_2$ requires C, 65.87; H, 5.13; N, 14.46%.

[1] The product was purified by flash column chromatography on silica gel eluting with ethyl acetate:pentane (10:90, by volume).

[2] The product was purified by flash column chromatography on silica gel eluting with ethyl acetate:pentane (10:90 changing to 20:80, by volume).

PREPARATION 75

3-[[1-Acetyl-3-(bromomethyl)-5-methyl-1*H*-pyrazol-4-yl]oxy]-5-fluorobenzonitrile



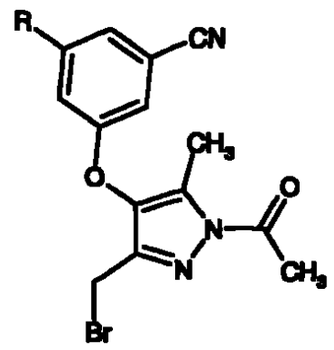
The pyrazole from Preparation 71 (1.00g, 3.66mmol) was dissolved in carbon tetrachloride (20ml) and the solution was degassed by bubbling nitrogen through it for 20 minutes at room temperature. *N*-Bromosuccinimide (973mg, 5.49mmol) followed by 2,2'-azobisisobutyronitrile (30mg) were added and the reaction was heated to 95°C for 1 hour. The reaction was cooled to room temperature, concentrated under reduced pressure and purified by flash chromatography on silica gel eluting with pentane:ethyl acetate (80:20, by volume) to provide the title compound (1.30g) as a pale yellow oil.

^{1}H NMR (400MHz, $CDCl_3$): δ = 2.05 (s, 3H), 2.69 (s, 3H), 4.68 (s, 2H), 6.89 (d, 1H), 6.99 (s, 1H), 7.08 (d, 1H).
LRMS (thermospray) : m/z [M-BrH$^+$] 272.

Microanalysis: Found C, 45.08; H, 3.14; N, 11.44. $C_{14}H_{11}BrN_3O_2F.1.05H_2O$ requires C, 45.31; H, 3.56; N, 11.32%.

PREPARATIONS 76-78

The preparation of the following tabulated Preparations of the general formula



were performed by a similar method to that of Preparation 75 using the appropriate pyrazole as the starting material.

Preparation no. (Starting material preparation no.)	R	Analytical Data
76 (72)	CN	m.p. 132-134 °C ^{1}H NMR (400MHz, $CDCl_3$): δ = 2.06 (s, 3H), 2.66 (s, 3H), 4.67 (s, 2H), 7.40 (s, 2H), 7.63 (s, 1H). Microanalysis: Found C, 47.65; H, 3.03; N, 14.79. $C_{15}H_{11}BrN_4O_2.0.93H_2O$ requires C, 47.92; H, 3.45; N, 14.90%.
77[1,2] (73)	Me	m.p. 107-109°C ^{1}H NMR (400MHz, $CDCl_3$): δ = 2.05 (s, 3H), 2.35 (s, 3H), 2.70 (s, 3H), 4.70 (s, 2H), 6.95 (s, 1H), 6.99 (s, 1H), 7.18 (s, 1H). Microanalysis: Found C, 50.34; H, 3.89; N, 11.58. $C_{16}H_{14}BrN_3O_2.0.40H_2O$ requires C, 50.69; H, 4.20; N, 11.82%.
78[1,3] (74)	H	m.p. 120-124°C ^{1}H NMR (400MHz, $CDCl_3$): δ = 2.05 (s, 3H), 2.70 (s, 3H), 4.75 (s, 2H), 7.20 (m, 2H), 7.45 (m, 1H).

		Microanalysis: Found C, 49.01; H, 3.47; N, 12.14. $C_{14}H_{12}BrN_3O_2.0.50H_2O$ requires C, 49.00; H, 3.82; N, 12.24%.

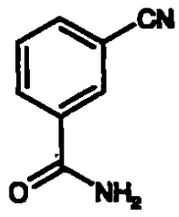
[1] A further aliquot of 2,2'-azobisisobutyronitrile (30mg) was added to this reaction, and refluxing was continued for a further 2 hours.

[2]The product was purified by flash column chromatography on silica gel eluting with a solvent gradient of ethyl acetate:pentane (0:100 then 2:98 then 5:95 then 10:90 then 15:85 then 30:70, by volume).

[3] The product was purified by flash column chromatography on silica gel eluting with ethyl acetate:pentane (10:90 changing to 20:80, by volume).

PREPARATION 79

3-Cyanobenzamide

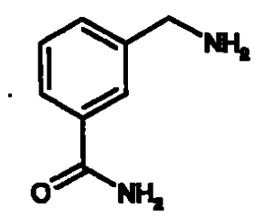


0.88 Ammonia solution (30ml) was slowly added to a solution of 3-cyanobenzoyl chloride (10g, 60.3mmol) in dichloromethane (100ml) at 0°C under nitrogen and the reaction was stirred for 20 minutes. The mixture was filtered and the solid was washed with water (50ml) then diethylether (50ml), azeotroped with toluene and dried *in vacuo* to provide the title compound (9g) as a white solid.

^{1}H NMR (400MHz, CD_3OD): δ = 7.62 (m, 1H), 7.86 (m, 1H), 8.12 (m, 1H), 8.18 (s, 1H).

PREPARATION 80

3-(Aminomethyl)benzamide



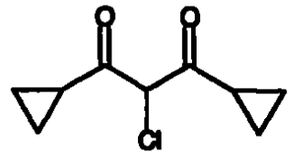
The nitrile from Preparation 79 (6.4g, 43.8mmol) was suspended in acetic acid (60ml) and10% palladium on carbon (100mg) was added. The reaction was

pressurised to 60psi at room temperature with hydrogen, and stirred for 18 hours. Starting material remained, so a further aliquot of 10% palladium on carbon (500mg) was added and the procedure was repeated. The reaction mixture was filtered through arbocel washing with acetic acid and the filtrate was concentrated under reduced pressure. The residue was azeotroped with toluene and purified by flash chromatography on silica gel eluting with dichloromethane:methanol:0.88 ammonia (100:0:0 changing to 90:10:1 then 85:15:1.5, by volume) to provide the title compound (5.3g) as a colourless oil.

^{1}H NMR (400MHz, CD_3OD): δ = 3.83 (s, 2H), 7.39 (dd, 1H), 7.49 (d, 1H), 7.73 (d, 1H), 7.81 (s, 1H).

PREPARATION 81

2-Chloro-1,3-dicyclopropyl-1,3-propanedione

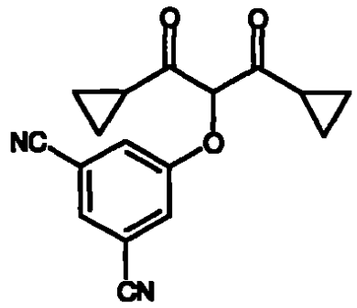


Trimethylsilyl chloride (16.6ml, 130mmol) was added to a solution of tert-butylammonium bromide (0.70g, 2.17mmol) in acetonitrile (50ml) under nitrogen at 0°C. 1,3-Dicyclopropyl-propane-1,3-dione (ref: WO98155438) (6.62g, 43.5mmol) in acetonitrile (15ml) was then added followed by dimethylsulfoxide (9.25ml, 130mmol) dropwise, and the reaction was allowed to warm to room temperature over 4 hours. The mixture was diluted with water (75ml), extracted with diethylether (3x35ml) and the combined organic extracts dried over magnesium sulphate and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with pentane:diethylether (95:5, by volume) to provide the title compound (3.76g) as an oil, which was an 80:20 mixture of enol:keto forms.

^{1}H NMR (400MHz, $CDCl_3$): δ = 1.02 (m, 4H), 1.17 (m, 4H), 2.24 (m, 0.2H), 2.39 (m, 0.8H), 5.05 (s, 0.2H), 16.34 (s, 0.8H).
Microanalysis: Found C, 57.59; H, 5.89. $C_9H_{11}ClO_2.0.02CH_2Cl_2$ requires C, 57.92; H, 5.94.

PREPARATION 82

5-[2-Cyclopropyl-1-(cyclopropylcarbonyl)-2-oxoethoxy]isophthalonitrile

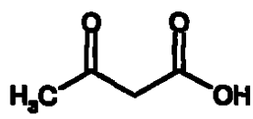


Cesium carbonate (1.97g, 6.06mmol) was added to a stirred solution of the phenol from Preparation 39 (0.865g, 6.00mmol) in acetone (24ml) under nitrogen at reflux. After stirring for 5 minutes, the diketone from Preparation 81 (1.12g, 6.00mmol) in acetone (6ml) was added and the reaction was stirred for 4 hours. After cooling the mixture was diluted with water (25ml) and the acetone was removed under reduced pressure. The aqueous phase was acidified with 2N aqueous hydrochloric acid, extracted with dichloromethane (50ml) and the organic phase was dried over magnesium sulphate and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with a solvent gradient of pentane:ethyl acetate (95:5 changing to 90:10 then 80:20, by volume) to provide the title compound (1.03g) as a white solid, which existed as the enol tautomer, m.p. 135-137°C.

^{1}H NMR (400MHz, $CDCl_3$): δ = 0.93 (m, 4H), 1.19 (m, 4H), 1.74 (m, 2H), 7.53 (s, 2H), 15.25 (s, 1H).
LRMS (electrospray) : m/z [M-H$^+$] 293.
Microanalysis: Found C, 69.18; H, 4.82; N, 9.35. $C_{17}H_{14}N_2O_3$ requires C, 69.38; H, 4.79; N, 9.52%.

PREPARATION 83

3-Oxobutanoic acid



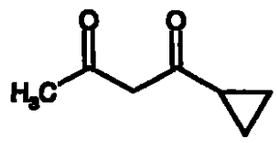
Sodium hydroxide (37.9g, 0.947mol) was dissolved in water (770ml) and added to a solution of 3-oxo-butanoic acid methyl ester (100g, 0.861mol) at room temperature over 20 minutes. The reaction was stirred for 18 hours, quenched

with ammonium sulfate (700g) and acidified slowly with a solution of concentrated Hydrochloric acid (21.5ml) in water (250ml) with ice cooling. The reaction mixture was extracted with diethylether (6x200ml) and the combined organic extracts were dried over magnesium sulphate and concentrated under reduced pressure to provide the title compound (58.2g) as a pale yellow oil which was a mixture of keto:enol tautomers.

^{1}H NMR (400MHz, $CDCl_3$): δ = 2.00 (s, 3H-enol), 2.30 (s, 3H-keto), 3.51 (s, 2H-keto), 5.02 (s, 1H-enol).

PREPARATION 84

1-Cyclopropyl-1,3-butanedione



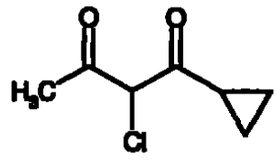
Magnesium turnings (3.04g, 125mmol) suspended in methanol (145ml) were heated to reflux under nitrogen for 1 hour, cooled to room temperature and the β-keto acid from Preparation 83 (25.5g, 250mmol) dissolved in methanol (25ml) was added dropwise with ice-cooling. The reaction was stirred for 1 hour at room temperature and the solvent was removed under reduced pressure to give the magnesium salt of the acid. Meanwhile, cyclopropane-carboxylic acid (9.91ml, 125mmol) was dissolved in dimethylformamide (200ml) and carbonyldiimidazole (22.4g, 138mmol) was added portionwise under nitrogen at 0°C. This was stirred for 1.5 hour and the magnesium salt from above was added as a solution in dimethylformamide (100ml) at 0°C. The reaction was allowed to stir at room temperature for 92 hours and the mixture was poured into 2M aqueous hydrochloric acid (85ml) then diluted with water (170ml). The mixture was extracted with diethylether (6x200ml) and the combined organic extracts were washed with brine (3x200ml), dried over magnesium sulphate and concentrated under reduced pressure. The residual orange oil was purified by flash chromatography on silica gel eluting with pentane:diethylether (100:0 changing to 90:10 then 80:20, by volume) to provide the title compound (7.39g) as a yellow oil.

^{1}H NMR (400MHz, $CDCl_3$): δ = 0.83-0.95 (m, 2H), 1.06-1.10 (m, 2H), 1.54-1.63 (m, 1H), 2.00 (s, 3H).

LRMS (electrospray) : m/z [MNa^+] 149.

PREPARATION 85

2-Chloro-1-cyclopropyl-1,3-butanedione

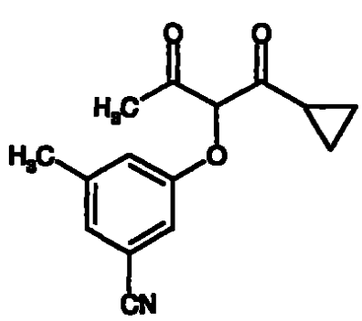


Trimethylsilyl chloride (18.9ml, 174mmol) was added to a solution of tert-butylammonium bromide (932mg, 2.89mmol) in dry acetonitrile (50ml) under nitrogen at room temperature and the mixture was cooled to 0°C. The diketone from Preparation 84 (7.3g, 57.9mmol) in acetonitrile (36ml) was then added followed by dropwise addition of dry dimethylsulfoxide (12.3ml, 174mmol). The reaction was stirred at 0°C for 1.5 hours and the mixture was diluted with water (500ml), extracted with diethylether (2x200ml and 100ml) and the combined organic extracts were dried over magnesium sulphate and concentrated under reduced pressure. The residual oil was purified by flash chromatography on silica gel eluting with pentane:diethylether (100:0 changing to 95:5 then 90:10, by volume) to provide the title compound (5.76g) as a colourless oil.

^{1}H NMR (400MHz, $CDCl_3$): δ = 0.99-1.08 (m, 2H), 1.15-1.20 (m, 2H), 2.27 (s, 3H), 2.38-2.46 (m, 1H).
LRMS (electrospray): m/z [$M-H^+$] 159.

PREPARATION 86

3-[1-(Cyclopropylcarbonyl)-2-oxopropoxyl-5-methylbenzonitrile



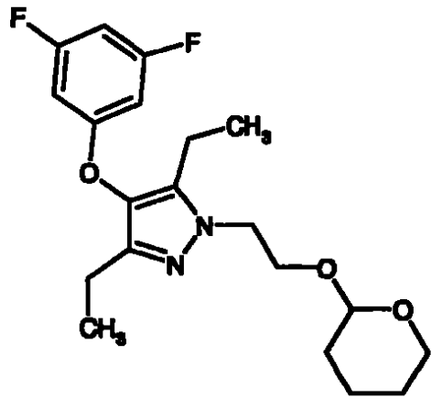
Cesium carbonate (2.45g, 8.30mmol) and the phenol from Preparation 42 (1g, 7.50mmol) were added to a stirred solution of the diketone from Preparation 85

(1.3g, 8.30mmol) in acetone (44ml) under nitrogen at 60°C and the reaction was stirred for 5 hours. After cooling the mixture was quenched with water and the acetone was removed under reduced pressure. The aqueous phase was acidified with 1N aqueous hydrochloric acid, extracted with ethyl acetate and the organic phase was dried over magnesium sulphate and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with pentane:ethyl acetate (85:15, by volume) to provide the title compound (1.03g) as a pale red solid.

^{1}H NMR (400MHz, $CDCl_3$): δ = 0.85 (m, 2H), 1.12 (m, 2H), 1.86 (m, 1H), 1.94 (s, 3H), 2.35 (s, 3H), 6.99 (m, 2H), 7.10 (s, 1H).
LRMS (electrospray) : m/z [M-H$^+$] 256.

PREPARATION 87

4-(3,5-Difluorophenoxy)-3,5-diethyl-1-[2-(tetrahydro-2*H*-pyran-2-yloxy)ethyl]-1*H*-pyrazole

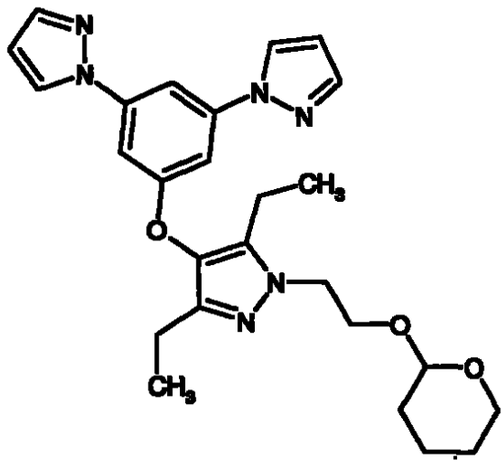


p-Toluene-sulphonic acid (360mg, 1.89mmol) was added to a solution of the alcohol from Example 38 (5.6g, 18.9mmol) and dihydropyran (8.62ml, 94.5mmol) in dichloromethane (75ml) at room temperature under nitrogen. The reaction was stirred for 2 hours, diluted with diethylether (100ml) and washed with a mixed aqueous solution (water (60ml), brine (30ml) and saturated aqueous sodium bicarbonate solution (30ml)). The aqueous phase was extracted with diethylether (2x60ml) and the combined organic extracts were dried over magnesium sulphate, concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel eluting with dichloromethane:methanol (98:2, by volume) to provide the title compound (6.31g) as an oil.

^{1}H NMR (400MHz, $CDCl_3$): δ = 1.09 (m, 6H), 1.57 (m, 6H), 2.40 (q, 2H), 2.55 (q, 2H), 3.44 (m, 1H), 3.62 (m, 1H), 3.73 (m, 1H), 4.05 (m, 1H), 4.16 (t, 2H), 4.50 (s, 1H), 6.39 (m, 3H).
LRMS (thermospray) : m/z [MH^+] 381.
Microanalysis: Found C, 62.16; H, 6.92; N, 7.16. $C_{20}H_{26}N_2O_3.0.09CH_2Cl_2$ requires C, 62.18; H, 6.80; N,7.22%.

PREPARATION 88

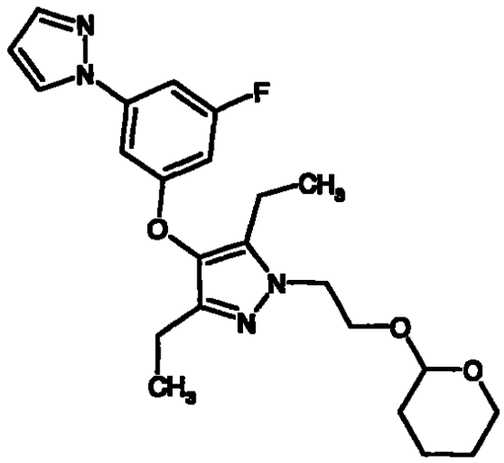
4-[3,5-Di(1*H*-pyrazol-1-yl)phenoxy]-3,5-diethyl-1-[2-(tetrahydro-2*H*-pyran-2-yloxy)ethyl]-1*H*-pyrazole



and

PREPARATION 89

3,5-Diethyl-4-[3-fluoro-5-(1*H*-pyrazol-1-yl)phenoxy]-1-[2-(tetrahydro-2*H*-pyran-2-yloxy)ethyl]-1*H*-pyrazole



Cesium Carbonate (538mg, 1.65mmol) was added to a solution of pyrazole (102mg, 1.50mmol) in dry dimethylsulfoxide (2ml) under nitrogen at room temperature and the reaction was stirred for 15 minutes. The aryl difluoride from Preparation 87 (570mg, 1.50mmol) dissolved in dry dimethylsulfoxide (2ml) was then added and the reaction was heated to 100°C for 18 hours. After cooling to room temperature the reaction was diluted with water (20ml) and extracted with diethylether (2x20ml). The organic phase was washed with brine (10ml), dried over magnesium sulphate, concentrated under reduced pressure. Some starting material remained, so the residue was dissolved in dimethylsulfoxide (12ml), pyrazole (510mg, 7.50mmol) followed by cesium carbonate (2.5g, 7.66mmol) were added and the reaction was heated to 100°C for 18 hours. After cooling to room temperature the reaction was diluted with water (6ml), extracted with diethylether (20ml) and the organic phase was washed with brine (10ml), dried over magnesium sulphate, concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel eluting with a solvent gradient of dichloromethane:methanol (100:0 changing to 96:4, by volume). This gave two fractions, the first of which was a single product (least polar) and the other a mixture of two products. The second fraction was re-purified eluting with dichloromethane:acetonitrile (93:7 changing to 90:10, by volume) to provide the most polar product.

Least Polar Product – Preparation 88 (254mg)

^{1}H NMR (400MHz, $CDCl_3$): δ = 1.11 (m, 6H), 1.50 (m, 6H), 2.46 (q, 2H), 2.58 (q, 2H), 3.43 (m, 1H), 3.64 (m, 1H), 3.75 (m, 1H), 4.04 (m, 1H), 4.18 (t, 2H), 4.50 (s, 1H), 6.42 (s, 2H), 7.15 (s, 2H), 7.67 (s, 3H), 7.90 (s, 2H).

LRMS (electrospray) : m/z [MH^+] 477, [MNa^+] 499.

HRMS: [MH^+] Found 477.2612. $C_{28}H_{33}N_6O_2$ requires 477.2609.

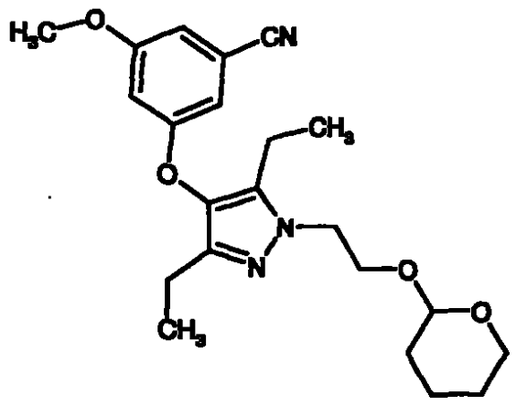
Most Polar Product – Preparation 89 (37.7mg)

^{1}H NMR (400MHz, $CDCl_3$): δ = 1.11 (m, 6H), 1.46 (m, 6H), 2.43 (q, 2H), 2.57 (q, 2H), 3.43 (m, 1H), 3.64 (m, 1H), 3.75 (m, 1H), 4.05 (m, 1H), 4.17 (t, 2H), 4.51 (s, 1H), 6.42 (m, 2H), 7.07 (m, 2H), 7.66 (s, 1H), 7.82 (s, 1H).

LRMS (thermospray) : m/z [MH^+] 429.

PREPARATI N 90

3-({3,5-Diethyl-1-[2-(tetrahydro-2*H*-pyran-2-yloxy)ethyl]-1*H*-pyrazol-4-yl}oxy)-5-methoxybenzonitrile



Sodium methoxide (25% w/v in methanol, 230µl, 1.00mmol) was added dropwise to a solution of the aryl fluoride from Preparation 63 (387mg, 1.00mmol) and in dimethylformamide (5ml) at room temperature under nitrogen. The reaction was stirred for 5 hours, diluted with water (10ml) and extracted with diethylether (50ml). The organic phase was dried over magnesium sulphate, concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel eluting with dichloromethane:methanol (97:3, by volume) to provide the title compound (400mg) as an oil.

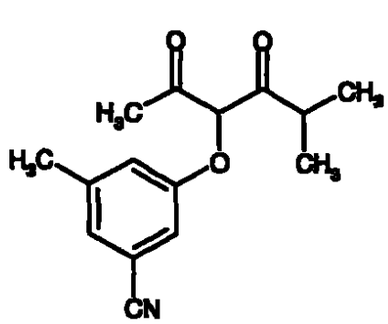
^{1}H NMR (400MHz, $CDCl_3$): δ = 1.09 (m, 6H), 1.49 (m, 6H), 2.41 (q, 2H), 2.55 (q, 2H), 3.46 (m, 1H), 3.66 (m, 1H), 3.77 (m + s, 4H), 4.07 (m, 1H), 4.19 (t, 2H), 4.52 (m, 1H), 6.66 (s, 1H), 6.69 (s, 1H), 6.77 (s, 1H).

LRMS (thermospray) : m/z [MH^+] 400.

Microanalysis: Found C, 65.59; H, 7.32; N, 10.42. $C_{22}H_{29}N_3O_4.0.04CH_2Cl_2$ requires C, 65.71; H, 7.28; N, 10.43%.

PREPARATION 91

3-(1-Acetyl-3-methyl-2-oxobutoxy)-5-methylbenzonitrile



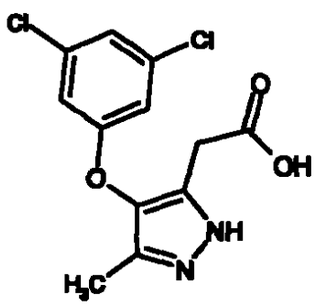
Cesium carbonate (1.50g, 4.61mmol) and the phenol from Preparation 42 (609mg, 4.61mmol) were added to a stirred solution of the diketone from Preparation 23 (750mg, 4.61mmol) in acetone (23ml) under nitrogen at 50°C and the reaction was stirred for 3 hours. After cooling the mixture was quenched with water (10ml) and the acetone was removed under reduced pressure. The aqueous phase was extracted with dichloromethane (4x25ml) and the combined organic extracts were dried over magnesium sulphate and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with pentane:ethyl acetate (90:10, by volume) to provide the title compound (544mg).

^{1}H NMR (400MHz, $CDCl_3$): δ = 1.10 (m, 6H), 2.09 (s, 3H), 2.42 (s, 3H), 2.69 (m, 1H), 7.00 (s, 2H), 7.19 (s, 1H).

LRMS (thermospray) : m/z[MNH_4^+] 277.

PREPARATION 92

[4-(3,5-Dichlorophenoxy)-3-methyl-1*H*-pyrazol-5-yl]acetic acid



The pyrazole of Example 208 (400mg, 1.41mmol) was stirred at 100°C for 14 hours in concentrated hydrochloric acid (20ml). The mixture was cooled to room temperature and the solvent removed under reduced pressure to give a yellow solid. The solid was dissolved in dichloromethane (50ml) and 1N aqueous hydrochloric acid (50ml) and the organic layer was separated. The organics were washed with 1N aqueous hydrochloric acid (50ml), dried over magnesium sulphate, filtered and the solvent removed under reduced pressure to provide the title compound (400mg) as pale yellow solid, m.p. 156-158°C.

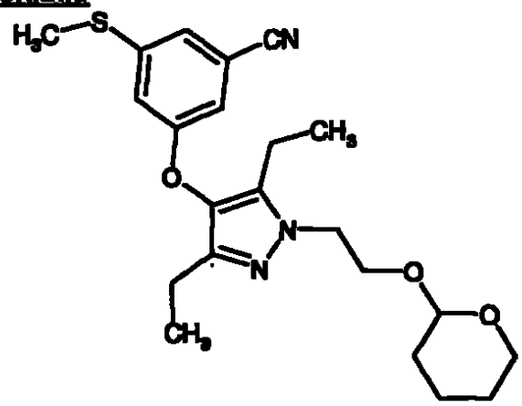
^{1}H NMR (400MHz, CD_3OD): δ = 2.02 (s, 3H), 4.89 (s, 2H), 6.82 (s, 2H), 7.02 (s, 1H).

LRMS (thermospray) : m/z [MH^+] 303.

Microanalysis: Found C, 47.50; H, 3.50; N, 9.46. $C_{12}H_{10}Cl_2N_2O_3$ requires C, 47.86; H, 3.35; N, 9.30%.

PREPARATION 93

3-({3,5-Diethyl-1-[2-(tetrahydro-2*H*-pyran-2-yloxy)ethyl]-1*H*-pyrazol-4-yl}oxy)-5-(methylsulfanyl)benzonitrile

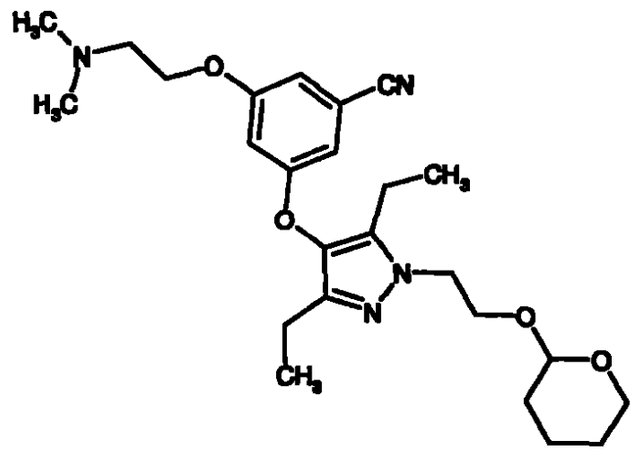


Sodium thiomethoxide (180mg, 2mmol) was added to a stirred solution of the aryl fluoride from Preparation 63 (774mg, 2.00mmol) in dimethylformamide (10ml) at room temperature under nitrogen. The reaction mixture was stirred for 5 hours before being heated at 100°C for 18 hours. A second portion of sodium thiomethoxide (90mg, 1mmol) was added and the reaction mixture was heated at 100°C for a further 5 hours. After cooling to room temperature the mixture was diluted with water (10ml) and extracted with diethylether (2x50ml). The organic phase was dried over magnesium sulphate, concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel eluting with dichloromethane:methanol (97:3, by volume) to provide the title compound (700mg) as an oil.

^{1}H NMR (400MHz, $CDCl_3$): δ = 1.14 (m, 6H), 1.52 (m, 6H), 2.44 (q, 2H), 2.49 (s, 3H), 2.59 (q, 3H), 3.50 (m, 1H), 3.70 (m, 1H), 3.80 (m, 1H), 4.10 (m, 1H), 4.23 (m, 2H), 4.55 (m, 1H), 6.82 (s, 1H), 7.01 (s, 1H), 7.09 (s, 1H).
LRMS (APCI+): m/z [MH^+] 416.

PREPARATI N 94

3-({3,5-Diethyl-1-[2-(tetrahydro-2*H*-pyran-2-yloxy)ethyl]-1*H*-pyrazol-4-yl}oxy)-5-[2-(dimethylamino)ethoxy]benzonitrile



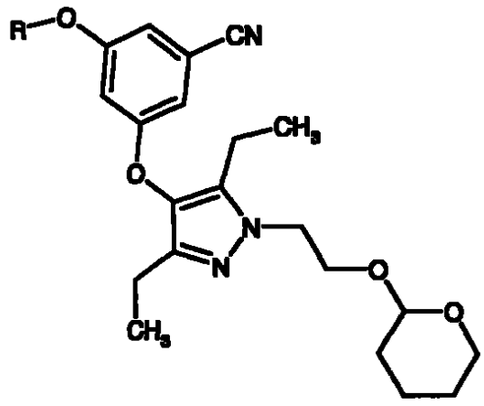
To a stirred solution of N,N-dimethylethanolamine (83µl, 0.83mmol) in dimethylformamide (2ml) was added sodium hydride (36mg of 60% by weight dispersion in oil, 0.90mmol). After 10 minutes a solution of the aryl fluoride from Preparation 63 (291mg, 0.75mmol) in dimethylformamide (2ml) was added and the reaction mixture was stirred at room temperature for 18 hours. The mixture was diluted with 10% aqueous potassium carbonate solution (12ml) and extracted with diethyl ether (2x7ml). The combined organic components were dried over magnesium sulphate and concentrated under reduced pressure. The crude product mixture was purified by flash chromatography on silica gel eluting with dichloromethane:methanol (a gradient from 99:1 to 90:10, by volume) to provide the title compound (180mg) as an oil.

^{1}H NMR (400MHz, $CDCl_3$): δ = 1.09 (m, 6H), 1.50 (m, 6H), 2.39 (q, 2H), 2.47 (s, 6H), 2.55 (q, 2H), 2.87 (m, 2H), 3.47 (m, 1H), 3.67 (m, 1H), 3.78 (m, 1H), 4.05 (m, 1H), 4.17 (m, 4H), 4.52 (m, 1H), 6.70 (s, 2H), 6.79 (s, 1H).
LRMS (electrospray): m/z [MH^+] 457.
HRMS: [MH^+] 457.2810. $C_{25}H_{37}N_4O_4$ requires 457.2810.

142
145

PREPARATI NS 95-97

The preparation of the following tabulated Preparations of the general formula



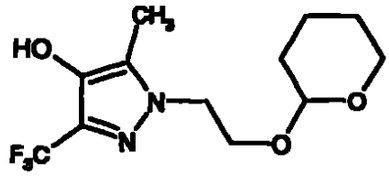
were performed by a similar method to that of Preparation 94 using the appropriate alcohol as the starting material.

Preparation no. (Starting material preparation no)	R	Analytical Data
95 (63)	CH_2CH_2 NHMe	^{1}H NMR (400MHz, $CDCl_3$): δ = 1.09 (m, 6H), 1.50 (m, 6H), 2.39 (q, 2H), 2.54 (m, 5H), 3.04 (t, 2H), 3.46 (m, 1H), 3.66 (m, 1H), 3.78 (m, 1H), 4.05 (m, 1H), 4.11 (t, 2H), 4.17 (t, 2H), 4.52 (s, 1H), 6.70 (s, 2H), 6.81 (s, 1H). LRMS (electrospray): m/z [MH^+] 443 HRMS: [MH^+] 443.2654. $C_{24}H_{35}N_4O_4$ requires 443.2653.

96 (63)	CH_2CONH_2	^1H NMR (400MHz, $CDCl_3$): δ = 1.11 (m, 6H), 1.48 (m, 6H), 2.43 (q, 2H), 2.58 (q, 2H), 3.46 (m, 1H), 3.67 (m, 1H), 3.80 (m, 1H), 4.08 (m, 1H), 4.25 (m, 2H), 4.45 (s, 2H), 4.52 (m, 1H), 5.54 (broad s, 1H), 6.37 (broad s, 1H), 6.72 (s, 1H), 6.85 (s, 2H). LRMS (electrospray): m/z 465 (MH^+) HRMS: [MH^+] 443.2282. $C_{23}H_{31}N_4O_5$ requires 443.2289.
97 (63)	$CH_2CH_2OCH_3$	^1H NMR (400MHz, $CDCl_3$): δ = 1.10 (m, 6H), 1.50 (m, 6H), 2.41 (q, 2H), 2.55 (q, 2H), 3.41 (s, 3H), 3.47 (m, 1H), 3.70 (m, 3H), 3.79 (m, 1H), 4.06 (m, 3H), 4.20 (m, 2H), 4.52 (s, 1H), 6.70 (s, 2H), 6.79 (s, 1H). LRMS (electrospray): m/z 466 (MH^+) HRMS: [MH^+] 443.2282. $C_{24}H_{34}N_3O_5$ requires 443.2289.

PREPARATION 98

5-Methyl-1-[2-(tetrahydro-2*H*-pyran-2-yloxy)ethyl]-3-(trifluoromethyl)-1*H*-pyrazol-4-ol



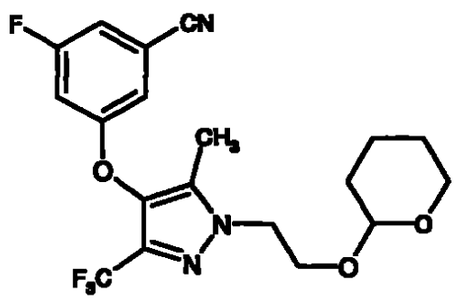
To a stirred solution of 1-(2-hydroxyethyl)-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-4-ol (600mg, 2.86mmol; Kenkyu Hokoku - Asahi Garasu Kogyo Gijutsu Shorelkai ,1988, 51, 139-49) in dichloromethane (10ml) and ethyl acetate (4ml) was added para-toluenesulphonic acid (27mg, 0.14mmol) followed by 3,4-dihydro-2H-pyran (340µl, 3.7mmol). The reaction mixture was stirred at room temperature for 3 hours before being concentrated under reduced pressure. The crude product mixture was purified by flash chromatography on silica gel eluting with

pentane:ethyl acetate (60:40, by volume) to provide the title compound (560mg) as white solid.

^{1}H NMR (400MHz, $CDCl_3$): δ = 1.60 (m, 6H), 2.23 (s, 3H), 3.44 (m, 1H), 3.60 (m, 1H), 3.72 (m, 1H), 4.04 (m, 1H), 4.18 (m, 2H), 4.50 (broad s, 1H).
LRMS (electrospray): m/z [M-H$^+$] 293.

PREPARATION 99

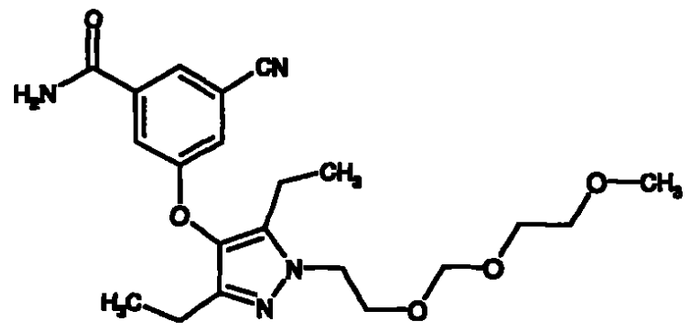
3-Fluoro-5-[5-methyl-1-[2-(tetrahydro-2*H*-pyran-2-yloxy)ethyl]-3-(trifluoromethyl)-1*H*-pyrazol-4-yloxy]benzonitrile



To a stirred solution of the pyrazole (214mg, 0.73mmol) from Preparation 98 in dimethylformamide (0.7ml) was added 3,5-difluorobenzonitrile (304mg, 2.2mmol) and potassium carbonate (304mg, 2.2mmol). The reaction mixture was heated at 90°C for 7 hours. After cooling to room temperature brine (20ml) was added and the mixture was extracted with ethyl acetate (20ml). The organic component was separated, washed with brine (20 ml), dried over magnesium sulphate and concentrated under reduced pressure. The crude product mixture was purified by flash chromatography on silica gel eluting with pentane:ethyl acetate (80:20, by volume) to provide the title compound (267mg) as a colourless oil.
^{1}H NMR (400MHz, $CDCl_3$): δ = 1.61 (m, 6H), 2.18 (s, 3H), 3.48 (m, 1H), 3.64 (m, 1H), 3.75 (m, 1H), 4.30 (t, 2H), 4.50 (broad s, 1H), 6.85 (d, 1H), 6.94 (s, 1H), 7.05 (d, 1H).
LRMS (electrospray): m/z [M-H$^+$] 412.

PREPARATION 100

3-Cyano-5-[(3,5-diethyl-1-{2-[(2-methoxyethoxy)methoxy]ethyl}-1*H*-pyrazol-4-yl)oxy]benzamide

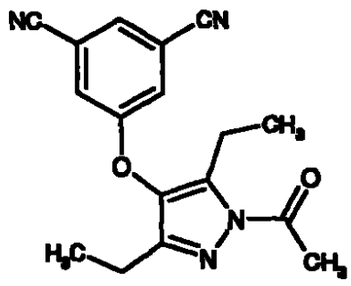


To a stirred solution of the pyrazole from Example 261 (193mg, 0.49mmol) in tetrahydrofuran (2ml) was added 2M aqueous sodium hydroxide solution (8.7µl, 0.49mmol) and the reaction mixture was heated at 65°C for 24 hours. After cooling to room temperature a second portion of 2M sodium hydroxide solution (8.7µl, 0.49mmol) was added and the mixture was heated at 65°C for 24 hours. 6M aqueous sodium hydroxide solution (100µl) was added and the mixture was heated at 65°C for 24 hours. The reaction mixture was concentrated under reduced pressure, diluted with water (75ml), neutralised to pH7 using 2M aqueous hydrochloric acid solution and extracted with dichloromethane (2x25ml). The combined organic components were dried over magnesium sulphate and concentrated under reduced pressure to give a crude product mixture which was purified by flash chromatography on silica gel eluting with dichloromethane:methanol (100:0, 98:2, 96.5:3.5 then 95:5, by volume) to provide the title compound (60mg) as a colourless oil.

^{1}H NMR (400MHz, $CDCl_3$): δ = 1.10 (m, 6H), 2.40 (q, 2H), 2.55 (q, 2H), 3.36 (s, 3H), 3.50 (q, 2H), 3.59 (q, 2H), 3.94 (q, 2H), 4.20 (q, 2H), 4.64 (s, 2H), 7.30 (s, 1H), 7.59 (s, 1H), 7.70 (s, 1H).

PREPARATI N 101

5-[(1-Acetyl-3,5-diethyl-1*H*-pyrazol-4-yl)oxy]isophthalonitrile

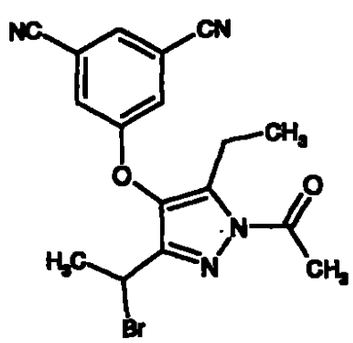


To a stirred solution of the pyrazole from Example 122 (3.0g, 11.3mmol) in dimethylformamide (45ml) at 0°C was added acetyl chloride (1.2ml, 17.0mmol), followed by sodium hydride portionwise (678mg of 60 % by weight dispersion in oil, 17.0mmol). The cooling bath was removed and the reaction mixture was stirred at room temperature for 40 minutes. The reaction was quenched by addition of saturated aqueous ammonium chloride solution (4ml) and concentrated under reduced pressure to give an orange residue. This material was partitioned between ethyl acetate (200ml) and water (200ml). The organic component was washed with water (100ml), brine (75ml) and then dried over magnesium sulphate before being concentrated under reduced pressure. The crude product mixture was purified by flash chromatography on silica gel eluting with dichloromethane:methanol (100:0, 99:1, then 98:2, by volume) to provide the title compound (2.67g) as a white solid.

^{1}H NMR (400MHz, $CDCl_3$): δ = 1.15 (t, 3H), 1.19 (t, 3H), 2.43 (q, 2H), 2.72 (s, 3H), 3.85 (q, 2H), 7.38 (s, 2H), 7.61 (s, 1H).
LRMS (electrospray): m/z 331 [M+Na^+].

PREPARATION 102

5-[[1-Acetyl-3-(1-bromoethyl)-5-ethyl-1*H*-pyrazol-4-yl]oxy]isophthalonitrile

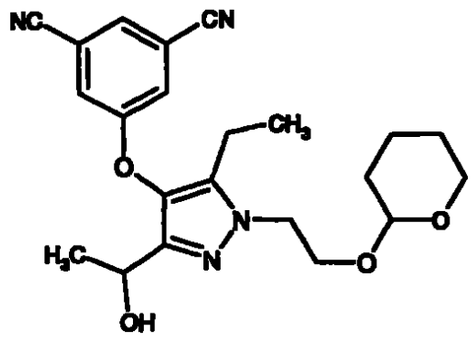


A solution of the pyrazole from Preparation 101 (881mg, 2.86mmol) in carbontetrachloride (12ml) was degassed by passing a stream of nitrogen through the solution for 20 minutes. N-bromosuccinimide (763mg, 4.28mmol) was added followed by AIBN (30mg) and the reaction mixture was heated at 85°C for 4 hours. After cooling to room temperature the mixture was concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel eluting with pentane:ethyl acetate (a gradient from 100:0 to 67:33, by volume) to provide the title compound (348mg) as a colourless oil.

^{1}H NMR (400MHz, $CDCl_3$): δ = 1.10 (t, 3h), 2.00 (d, 3H), 2.70 (s, 3H), 2.80 (m, 2H), 4.95 (q, 1H), 7.42 (s, 2H), 7.60 (s, 1H).
LRMS (electrospray): m/z 283 [MH^+].

PREPARATION 103

5-((5-Ethyl-3-(1-hydroxyethyl)-1-[2-(tetrahydro-2*H*-pyran-2-yloxy)ethyl]-1*H*-pyrazol-4-yl)oxy)isophthalonitrile



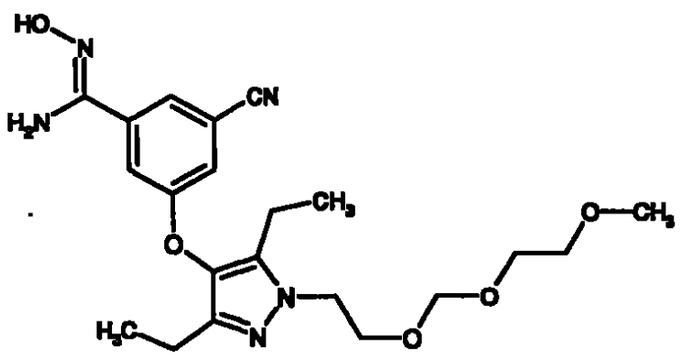
To a stirred solution of the pyrazole from Example 263 (197mg, 0.70mmol) in dimethylformamide (3ml) at 0°C was added 2-(2-bromoethoxy)tetrahydro-2*H*-pyran (105μl, 0.70mmol) followed by sodium hydride (31mg, 0.77mmol). After 15 minutes the cooling bath was removed and the mixture was stirred at room temperature for 60 hours. The reaction mixture was quenched by addition of saturated aqueous ammonium chloride solution (0.5ml) and then concentrated under reduced pressure. The crude product mixture was purified by flash chromatography on silica gel eluting with dichloromethane:methanol (a gradient from 100:0 to 95:5, by volume) to provide the title compound (84mg) as a white foam which reverts to an oil on standing.

145
148

^{1}H NMR (400MHz, $CDCl_3$): δ = 1.11 (t, 3H), 1.45 (d, 3H), 1.65 (m, 6H), 2.59 (q, 2H), 3.50 (m, 1H), 3.70 (m, 1H), 3.81 (m, 1H), 4.11 (m, 1H), 4.25 (t, 2H), 4.56 (m, 1H), 4.76 (m, 1H), 7.40 (s, 2H), 7.55 (s, 1H).
LRMS (electrospray): m/z 411 [MH^+].

PREPARATION 104

3-Cyano-5-[(3,5-diethyl-1-[2-[(2-methoxyethoxy)methoxy]ethyl]-1*H*-pyrazol-4-yl)oxy]-*N*'-hydroxybenzenecarboximidamide

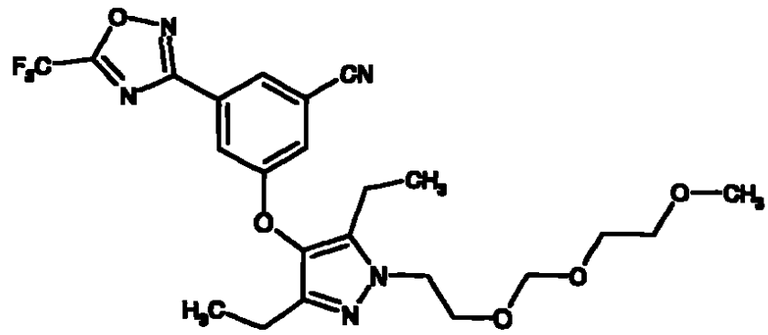


To a stirred solution of the pyrazole from Example 261 (1.5g, 3.76mmol) in ethanol (7.5ml) was added a solution of sodium carbonate (200mg, 1.88mmol) and hydroxylamine hydrochloride (262mg, 3.76mmol) in water (7.5ml). After stirring for 5 hours at room temperature the reaction mixture was concentrated under reduced pressure and the residue was partitioned between dichloromethane (50ml) and water (40ml). The aqueous phase was separated and extracted with dichloromethane (30ml). The organic components were combined, dried over magnesium sulphate and concentrated under reduced pressure. The crude product mixture was purified by flash chromatography on silica gel eluting with dichloromethane:methanol (a gradient from 100:0 to 96:4, by volume) to provide the title compound (1.13mg) as a colourless oil.

^{1}H NMR (400MHz, $CDCl_3$): δ = 1.11 (m, 6H), 2.42 (q, 2H), 2.58 (q, 2H), 3.41 (s, 3H), 3.59 (m, 4H), 3.95 (t, 2H), 4.17 (t, 2H), 4.61 (s, 2H), 4.77 (broad s, 2H), 7.38 (m, 1H), 7.49 (m, 2H).
LRMS (electrospray): m/z 432 [MH^+].
Microanalysis: Found C, 57.50; H, 6.71; N, 16.01. $C_{21}H_{29}N_4O_4$+0.4H_2O requires C, 57.50; H, 6.85; N, 15.96%.

PREPARATION 105

3-[(3,5-Diethyl-1-[2-[(2-methoxyethoxy)methoxy]ethyl]-1*H*-pyrazol-4-yl)oxy]-5-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]benzonitrile

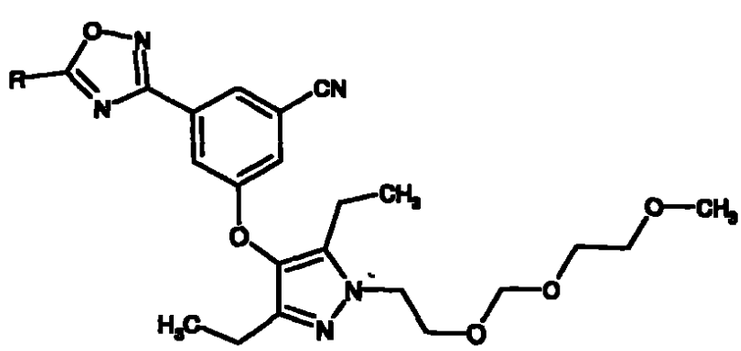


To a stirred solution of the amidoxime from Preparation 104 (300mg, 0.70mmol) in pyridine (3ml) was added trifluoroacetic anhydride (118µl, 0.83mmol). After stirring at room temperature for 2 hours the reaction mixture was heated at 110°C for 18 hours. After cooling to room temperature the mixture was concentrated under reduced pressure and the residue was partitioned between 2M aqueous HCl solution (6ml) and dichloromethane (6ml). The organic phase was separated and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with dichloromethane:methanol (a gradient from 100:0 to 90:10, by volume) to provide the title compound (259mg) as a colourless oil.

^{1}H NMR (400MHz, $CDCl_3$): δ =1.14 (m, 6H), 2.46 (q, 2H), 2.59 (q, 2H), 3.39 (s, 3H), 3.53 (q, 2H), 3.59 (q, 2H), 3.95 (q, 2H), 4.29 (q, 2H), 4.68 (s, 2H), 7.34 (s, 1H), 7.87 (s, 1H), 8.04 (s, 1H).
LRMS (APCI): m/z 532 (MH^+)

PREPARATIONS 106-108

The preparation of the following tabulated Preparations of the general formula

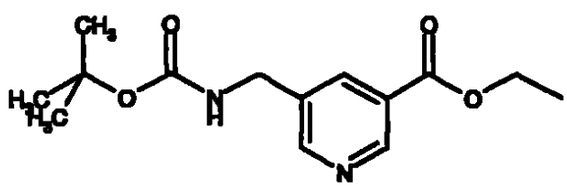


were performed by a similar method to that of Preparation 105 using the appropriate acid chloride as the acylating agent in place of trifluoroacetic anhydride.

Preparation no.	R	Analytical Data
106	Me	^{1}H NMR (400MHz, $CDCl_3$): δ = 1.14 (m, 6H), 2.46 (q, 2H), 2.59 (q, 2H), 2.67 (s, 3H), 3.39 (s, 3H), 3.55 (q, 2H), 3.59 (q, 2H), 3.95 (q, 2H), 4.22 (q, 2H), 4.68 (s, 2H), 7.27 (s, 1H), 7.82 (s, 1H), 8.00 (s, 1H). LRMS (electrospray): m/z 478 [M+Na$^+$] Microanalysis: Found C, 59.91; H, 6.27; N, 15.38. $C_{23}H_{29}N_5O_5$+0.3H_2O requires C, 59.94; H, 6.475; N, 15.19%.
107	Et	^{1}H NMR (400MHz, $CDCl_3$): δ = 1.14 (m, 6H), 1.44 (t, 3H), 2.42 (q, 2H), 2.48 (q, 2H), 2.98 (q, 2H), 3.39 (s, 3H), 3.53 (q, 2H), 3.59 (q, 2H), 3.95 (q, 2H), 4.20 (q, 2H), 4.48 (s, 2H), 7.30 (s, 1H), 7.84 (s, 1H), 8.01 (s, 1H). LRMS (electrospray): m/z 492 (M+Na$^+$)
108	^{i}Pr	^{1}H NMR (400MHz, $CDCl_3$): δ = 1.11 (m, 6H), 1.49 (d, 6H), 2.44 (q, 2H), 2.49 (q, 2H), 3.30 (sept, 1H), 3.39 (s, 3H), 3.54 (m, 2H), 3.59 (m, 2H), 3.95 (t, 2H), 4.23 (t, 2H), 4.91 (s, 2H), 7.22 (m, 1H), 7.83 (m, 1H), 8.02 (m, 1H). LRMS (electrospray): m/z 506 (M+Na$^+$) Microanalysis: Found C, 61.87; H, 6.76; N, 14.62. $C_{25}H_{33}N_5O_5$ requires C, 62.10; H, 6.88; N, 14.48%.

PREPARATION 109

Ethyl 5-[(*tert*-butoxycarbonyl)amino]methyl]nicotinate

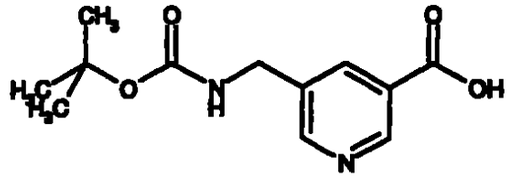


To a stirred solution of ethyl-5-cyanonicotinate (3.0g, 17.0mmol; Annalen Der Chemie, 1959, 621, 106-136) in ethanol (200ml) was added concentrated hydrochloric acid (3.4ml) followed by 5% palladium on carbon (300mg). The reaction mixture was stirred at room temperature under an hydrogen atmosphere (50psi) for 18 hours. The reaction mixture was filtered through Arbocel and concentrated under reduced pressure. The crude product mixture was purified by flash chromatography on silica gel eluting with dichloromethane:methanol:0.880 ammonia (a gradient from 95:5:0.5 to 85:5:1.5, by volume) to provide the intermediate amine (2.1g) as a yellow oily solid. This material (2.1g, 11.7mmol) was suspended in dichloromethane (22ml) to which was added triethylamine (1.8ml, 13.0mmol) followed by di-tert-butyl dicarbonate (2.84g, 13mmol). After 48 hours the reaction mixture was diluted with dichloromethane (50ml) and washed with water (50ml). The organic component was dried over magnesium sulphate and concentrated under reduced pressure before being purified by flash chromatography on silica gel eluting with dichloromethane:methanol:0.88 ammonia (a gradient from 100:0:0 to 95:5:0.5, by volume) to provide the title compound (2.0g) as a yellow oil.

^{1}H NMR (400MHz, $CDCl_3$): δ = 1.40 (m, 12H), 4.42 (m, 4H), 8.22 (s, 1H), 8.71 (s, 1H), 9.12 (s, 1H).
LRMS (APCI): m/z 279 ($M-H^+$)

PREPARATION 110

5-[[(*tert*-Butoxycarbonyl)amino]methyl]nicotinic acid

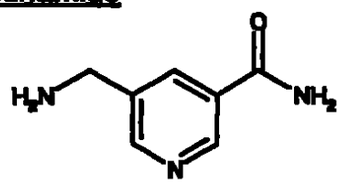


To a stirred solution of the ester from Preparation 109 (2.00g, 7.10mmol) in 1M aqueous sodium hydroxide solution (15ml, 15mmol) was added methanol (15ml). The reaction mixture was stirred at room temperature for 18 hours, after which time the methanol was removed under reduced pressure. The aqueous solution was washed with diethyl ether (2x25ml), cooled to 0°C and neutralised to pH7 by addition of 2M aqueous hydrochloric acid solution (7.5ml). The mixture was concentrated under reduced pressure to give a yellow oil (1.5g).

^{1}H NMR (400MHz, $(CD_3)_2SO$): δ = 1.37 (s, 9H), 4.16 (d, 2H), 7.51 (m, 1H), 8.07 (s, 1H), 8.50 (s, 1H), 8.88 (s, 1H).
LRMS (APCI): m/z 251 ($M-H^+$)

PREPARATION 111

5-(Aminomethyl)nicotinamide



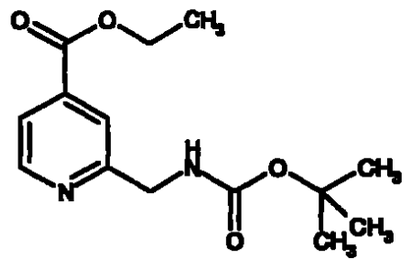
.2 x CF_3CO_2H

To a stirred solution of the acid from Preparation 110 (770mg, 3.10mmol) in dimethylformamide (15ml) was added carbonyldiimidazole (600mg, 3.70mmol). After 10 minutes 0.880 ammonia (1ml) was added. After a further 1 hour the reaction mixture was concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel eluting with dichloromethane:methanol:0.88 ammonia (a gradient from 95:5:0.5 to 80:20:1, by volume) to provide the boc-protected intermediate. To a stirred solution of this material in dichloromethane (20ml) was added trifluroacetic acid (6ml). After 18 hours a second portion of trifluoroacetic acid (6ml) was added and the reaction mixture was stirred at room temperature for 24 hours. The solution was concentrated under reduced pressure to give an oily residue which was purified by flash chromatography on silica gel eluting with dichloromethane:methanol:0.88 ammonia (100:0:0 then 90:10:1 then 80:20:1, by volume) to provide the title compound (650mg) as a yellow oil.

^{1}H NMR (400MHz, $(CD_3)_2SO$): δ = 4.11 (s, 2H), 7.5 (broad s), 7.59 (broad s), 8.14 (broad s), 8.31 (m, 1H), 8.72 (m, 1H), 8.90 (m, 1H).
LRMS (electrospray): m/z 152 (MH^+)
HRMS: [MH^+] 152.0819. $C_7H_{10}N_3O$ requires 152.0818

PREPARATI N 112

Ethyl 2-[[(*tert*-butoxycarbonyl)amino]methyl]isonicotinate



To a stirred solution of ethyl 2-cyanoisonicotinate (2.00g, 11.0mmol, J. Med. Chem., 1976, 19, 483) in ethanol (20ml) was added 2M aqueous hydrochloric acid solution (7.5ml) followed by 5% palladium on carbon (200mg). The reaction mixture was stirred at room temperature under a hydrogen atmosphere (60psi) for 48 hours. The mixture was filtered through arbocel and the filtrate was concentrated under reduced pressure. The residue was dried by azeotropic distillation using toluene under reduced pressure. To a stirred solution of the residue (3.00g) in dichloromethane (22ml) was added triethylamine (4.6ml, 33mmol) followed by di-tert-butyl dicarbonate (2.62g, 12.0mmol). After stirring for 1 hour at room temperature the reaction mixture was diluted with dichloromethane (100ml) and washed with water (50ml). The organic component was washed with brine (50ml), dried over magnesium sulphate and concentrated under reduced pressure to give a brown oily solid. The crude product mixture was purified by flash chromatography on silica gel eluting with dichloromethane:methanol:0.88 ammonia (98:2:0.2 then 97:3:0.3, by volume) to provide the title compound (2.20g) as a yellow oil.

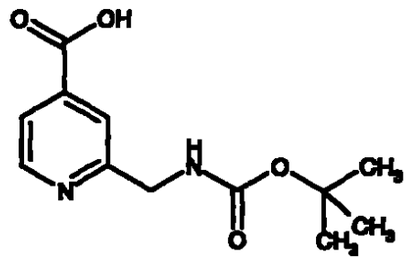
^{1}H NMR (400MHz, $CDCl_3$): δ = 1.38 (t, 3H), 1.45 (s, 9H), 4.38 (q, 2H), 4.50 (m, 2H), 5.50 (broad s, 1H), 7.73 (d, 1H), 7.81 (s, 1H), 8.65 (d, 1H).

LRMS (electrospray): m/z 281 (MH^+)

148
151

PREPARATION 113

2-[[(*tert*-Butoxycarbonyl)amino]methyl]isonicotinic acid

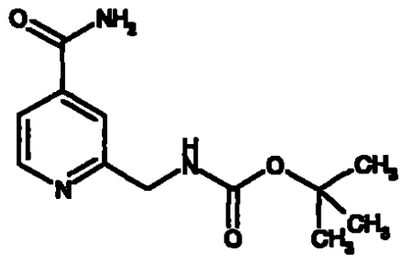


To a stirred solution of the ester from Preparation 112 (1.50g, 5.35mmol) in methanol (10ml) was added 1M aqueous sodium hydroxide solution (10ml). After 1 hour the reaction mixture was cooled to 0°C and neutralised by addition of 2M aqueous hydrochloric acid solution (5ml). The reaction mixture was concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel eluting with dichloromethane:methanol:0.880 ammonia (80:20:1, by volume) to provide the title compound (1.30g) as a yellow foam.

^{1}H NMR (400MHz, (CD_3OD): δ = 1.43 (s, 9H), 4.36, (s, 2H), 7.68 (m, 1H), 7.81 (s, 1H), 8.47 (m, 1H).
LRMS (electrospray): m/z 251 ($M-H^+$)
HRMS: [MH^+] 253.1179. $C_{12}H_{17}N_2O4$ requires 253.1183

PREPARATION 114

tert-Butyl [4-(aminocarbonyl)-2-pyridinyl]methylcarbamate



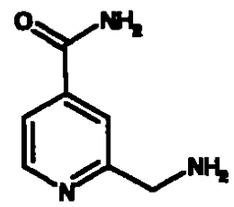
To a stirred solution of the acid from Preparation 113 (1.3g, 5.20mmol) in dimethylformamide (10ml) was added 1-hydroxybenzotriazole (950mg, 6.20mmol) followed by 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride salt (1.20g, 6.20mmol). After 1 hour 0.880 ammonia (5ml) was added and the reaction mixture was stirred at room temperature for 1.5 hours. The mixture was concentrated under reduced pressure and dried by azeotropic

distillition using toluene under reduced pressure to give a yellow semi-solid. The crude product mixture was purified by flash chromatography on silica gel eluting with dichloromethane:methanol:0.88 ammonia (95:5:0.5, by volume) to provide the title compound (1.1g) as a clear oil which crystallised on standing. This material was further purified by triturating with diethyl ether (10ml) which gave a sample of the desired product (1.0g) white powder/

^{1}H NMR (400MHz, D6-DMSO): δ = 1.39 (s, 9H), 4.25 (m, 2H), 7.44 (m, 1H), 7.61 (m, 1H), 7.66 (broad s, 2H), 8.21 (broad s, 1H), 8.59 (d, 1H).
LRMS (electrospray): m/z 250 ($M-H^+$)
Microanalysis: Found C, 57.26; H, 6.86; N, 16.65. $C_{12}H_{17}N_3O_3$ requires C, 57.36; H, 6.82; N, 16.72%.

PREPARATION 115

2-(Aminomethyl)isonicotinamide

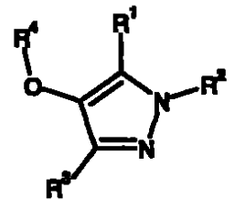


To a stirred solution of the pyridine from Preparation 114 (1.00g, 3.98mmol) in dichloromethane (50ml) was added trifluoroacetic acid (15ml). After stirring at room temperature for 18 hours the reaction mixture was concentrated under reduced pressure and purified by ion-exchange chromatography on Dowex 50-X8-200 eluting with water followed by 0.880 ammonia:methanol:water (5:5:90, by volume) to provide the title compound (265mg) as a white solid.

^{1}H NMR (400MHz, D6-DMSO) : δ = 2.1 (broad s, 1H), 3.4 (broad s, 1H), 3.85 (2H, s), 7.57 (m, 1H), 7.60 (broad s, 1H), 7.80 (m, 1H), 8.16 (broad s, 1H), 8.59 (m, 1H).
LRMS (APCI): m/z 152 (MH^+)

CLAIMS

1. A compound of the formula (I)



(I)

or a pharmaceutically acceptable salt, solvate or derivative thereof, wherein:

either R^1 is H, C_1-C_8 alkyl, C_3-C_7 cycloalkyl, phenyl, benzyl, halo, -CN, -OR^7, -CO_2R^{10}, -$CONR^5R^{10}$, R^8 or R^9, said C_1-C_8 alkyl, C_3-C_7 cycloalkyl, phenyl and benzyl being optionally substituted by halo, -CN, -OR^{10}, $S(O)_xR^{10}$, -CO_2R^{10}, -$CONR^5R^{10}$, -$OCONR^5R^{10}$, -$NR^5CO_2R^{10}$, -$NR^{10}R^{11}$, -NR^5COR^{10}, -$SO_2NR^5R^{10}$, -$NR^5CONR^5R^{10}$, -$NR^5SO_2R^{10}$ or R^{10}; and

R^2 is H, C_1-C_8 alkyl, C_3-C_8 alkenyl, C_3-C_8 alkynyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloalkenyl, phenyl, benzyl, R^8 or R^9, said C_1-C_8 alkyl, C_3-C_7 cycloalkyl, phenyl and benzyl being optionally substituted by halo, -OR^5, -OR^{12}, -CN, -CO_2R^7, -$OCONR^5R^5$, -$CONR^5R^5$, -$C(=NR^5)NR^5OR^5$, -$CONR^5NR^5R^5$, -NR^6R^6, -NR^5R^{12}, -NR^5COR^5, -NR^5COR^8, -NR^5COR^{12}, -$NR^5CO_2R^5$, -$NR^5CONR^5R^5$, -$SO_2NR^5R^5$, -$NR^5SO_2R^5$, -$NR^5SO_2NR^5R^5$, R^8 or R^9;

or, R^1 and R^2, when taken together, represent unbranched C_3-C_4 alkylene, optionally substituted by oxo, optionally wherein one methylene group of said C_3-C_4 alkylene is replaced by an oxygen atom or a nitrogen atom, said nitrogen atom being optionally substituted by R^{10};

R^3 is H, C_1-C_8 alkyl, C_3-C_7 cycloalkyl, phenyl, benzyl, halo, -CN, -OR^7, -CO_2R^5, -$CONR^5R^5$, R^8 or R^9, said C_1-C_8 alkyl, C_3-C_7 cycloalkyl, phenyl and benzyl being optionally substituted by halo, -CN, -OR^5, -CO_2R^5, -$CONR^5R^5$, -$OCONR^5R^5$, -$NR^5CO_2R^5$, -NR^6R^6, -NR^5COR^5, -$SO_2NR^5R^5$, -$NR^5CONR^5R^5$, -$NR^5SO_2R^5$, R^8 or R^9;

R^4 is phenyl, naphthyl or pyridyl, each being optionally substituted by R^8, halo, -CN, C_1-C_8 alkyl, C_1-C_8 haloalkyl, C_3-C_7 cycloalkyl, C_1-C_8 alkoxy, -$CONR^5R^5$,

OR^{13}, So_xR^6, O-(C_1-C_6 alkylene)-$CONR^5R^5$, O-(C_1-C_6 alkylene)-NR^5R^5, or O-(C_1-C_6 alkylene)-OR^6;

each R^5 is independently either H, C_1-C_6 alkyl or C_3-C_7 cycloalkyl or, when two R^5 groups are attached to the same nitrogen atom, those two groups taken together with the nitrogen atom to which they are attached represent azetidinyl, pyrrolidinyl, piperidinyl, homopiperidinyl, piperazinyl, homopiperazinyl or morpholinyl, said azetidinyl, pyrrolidinyl, piperidinyl, homopiperidinyl, piperazinyl, homopiperazinyl and morpholinyl being optionally substituted by C_1-C_6 alkyl or C_3-C_7 cycloalkyl;

each R^6 is independently either H, C_1-C_6 alkyl or C_3-C_7 cycloalkyl;

R^7 is C_1-C_6 alkyl or C_3-C_7 cycloalkyl;

R^8 is a five or six-membered, aromatic heterocyclic group containing (i) from 1 to 4 nitrogen heteroatom(s) or (ii) 1 or 2 nitrogen heteroatom(s) and 1 oxygen or 1 sulphur heteroatom or (iii) 1 or 2 oxygen or sulphur heteroatom(s), said heterocyclic group being optionally substituted by halo, oxo, -CN, $-COR^5$, $-CONR^5R^5$, $-SO_2NR^5R^5$, $-NR^5SO_2R^5$, $-OR^5$, $-NR^5R^5$, -(C_1-C_6 alkylene)-NR^5R^5, C_1-C_6 alkyl, fluoro(C_1-C_6)alkyl or C_3-C_7 cycloalkyl;

R^9 is a four to seven-membered, saturated or partially unsaturated heterocyclic group containing (i) 1 or 2 nitrogen heteroatom(s) or (ii) 1 nitrogen heteroatom and 1 oxygen or 1 sulphur heteroatom or (iii) 1 oxygen or sulphur heteroatom, said heterocyclic group being optionally substituted by oxo, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, $-SO_2R^5$, $-CONR^5R^5$, $-COOR^5$, -CO-(C_1-C_6 alkylene)-OR^5 or $-COR^5$ and optionally substituted on a carbon atom which is not adjacent to a heteroatom by halo, $-OR^5$, $-NR^5R^5$, $-NR^5COR^5$, $-NR^5COOR^5$, $-NR^5CONR^5R^5$, $-NR^5SO_2R^5$ or -CN;

R^{10} is H, R^8, R^9, R^{13}, C_1-C_6 alkyl, C_3-C_7 cycloalkyl or -(C_1-C_6 alkyl)-(C_3-C_7 cycloalkyl), said C_1-C_6 alkyl and C_3-C_7 cycloalkyl being optionally substituted by $-OR^5$, $-OR^{13}$, R^8, R^9, R^{13} or $-COR^{13}$;

R^{11} is H, C_1-C_6 alkyl or C_3-C_7 cycloalkyl, said C_1-C_6 alkyl and C_3-C_7 cycloalkyl being optionally substituted by $-OR^5$, $-NR^5R^5$, $-NR^5COR^5$, $-CONR^5R^5$, R^8 or R^9;

R^{12} is C_1-C_6 alkyl substituted by R^8, R^9, $-OR^5$, $-CONR^5R^5$, $-NR^5COR^5$ or $-NR^5R^5$;

R^{13} is phenyl optionally substituted by halo, -CN, $-COR^5$, $-CONR^5R^5$, $-SO_2NR^5R^5$, $-NR^5SO_2R^5$, $-OR^5$, $-NR^5R^5$, $-(C_1-C_6$ alkylene$)-NR^5R^5$, C_1-C_6 alkyl, halo(C_1-C_6)alkyl or C_3-C_7 cycloalkyl; and

x is 0, 1 or 2;

with the proviso that (a) when R^1 and R^3 are both phenyl, R^2 is not methyl; and (b) when R^1 is ethoxy and R^3 is ethoxycarbonyl, R^2 is not phenyl.

2. A compound according to claim 1 wherein R^1, when taken separately, is H, C_1-C_6 alkyl, C_3-C_7 cycloalkyl or $-OR^7$, said C_1-C_6 alkyl and C_3-C_7 cycloalkyl being optionally substituted by halo, -CN, $-OR^{10}$, $S(O)_xR^{10}$, $-CO_2R^{10}$, $-CONR^5R^{10}$, $-OCONR^5R^{10}$, $-NR^5CO_2R^{10}$, $-NR^{10}R^{11}$, $-NR^5COR^{10}$, $-SO_2NR^5R^{10}$, $-NR^5CONR^5R^{10}$, $-NR^5SO_2R^{10}$ or R^{10}.

3. A compound according to claim 1 or 2 wherein R^1, when taken separately, is H, C_1-C_6 alkyl, C_3-C_7 cycloalkyl or $-OR^7$, said C_1-C_6 alkyl being optionally substituted by halo, $-OR^{10}$, $-NR^{10}R^{11}$, $-NR^5COR^{10}$ or R^{10}.

4. A compound according to any preceding claim wherein R^2, when taken separately, is H, C_1-C_6 alkyl, C_3-C_6 alkenyl or R^9, said C_1-C_6 alkyl being optionally substituted by halo, $-OR^5$, $-OR^{12}$, -CN, $-CO_2R^7$, $-OCONR^5R^5$, $-CONR^5R^5$, $-C(=NR^5)NR^5OR^5$, $-CONR^5NR^5R^5$, $-NR^6R^6$, $-NR^5R^{12}$, $-NR^5COR^5$, $-NR^5COR^8$, $-NR^5COR^{12}$, $-NR^5CO_2R^5$, $-NR^5CONR^5R^5$, $-SO_2NR^5R^5$, $-NR^5SO_2R^5$, R^8 or R^9.

5. A compound according to any preceding claim wherein R^2, when taken separately, is H, C_1-C_6 alkyl, C_3-C_6 alkenyl or R^9, said C_1-C_6 alkyl being optionally substituted by $-OR^5$, $-OR^{12}$, -CN, $-CO_2R^7$, $-CONR^5R^5$, $-C(=NR^5)NR^5OR^5$, $-CONR^5NR^5R^5$, $-NR^6R^6$, $-NR^5R^{12}$, $-NR^5COR^8$, $-NR^5COR^{12}$, $-NR^5CO_2R^5$, R^8 or R^9.

6. A compound according to claim 1 wherein R^1 and R^2, when taken together, represent unbranched C_3-C_4 alkylene, optionally substituted by oxo, wherein one methylene group of said C_3-C_4 alkylene is replaced by an oxygen atom or a nitrogen atom, said nitrogen atom being optionally substituted by R^{10}.

7. A compound according to claims 1 or 6 wherein R^1 and R^2, when taken together, represent unbranched propylene wherein one methylene group is replaced by an oxygen atom or unbranched butylene wherein one methylene group is replaced by a nitrogen atom, said propylene and butylene being

optionally substituted by oxo and said nitrogen atom being optionally substituted by R^{10}.

8. A compound according to any preceding claim wherein R^3 is H or C_1-C_6 alkyl, said C_1-C_6 alkyl being optionally substituted by halo, -CN, $-OR^5$, $-CO_2R^5$, $-CONR^5R^5$, $-OCONR^5R^5$, $-NR^5CO_2R^5$, $-NR^6R^6$, $-NR^5COR^5$, $-SO_2NR^5R^5$, $-NR^5CONR^5R^5$, $-NR^5SO_2R^5$, R^8 or R^9.

9. A compound according to any preceding claim wherein R^3 is H or C_1-C_6 alkyl.

10. A compound according to any preceding claim wherein R^4 is phenyl optionally substituted by R^8, halo, -CN, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_7 cycloalkyl, C_1-C_6 alkoxy, $-CONR^5R^5$, OR^{13}, So_xR^6, O-(C_1-C_6 alkylene)-$CONR^5R^5$, O-(C_1-C_6 alkylene)-NR^5R^5, or O-(C_1-C_6 alkylene)-OR^6; or naphthyl.

11. A compound according to any preceding claim wherein R^4 is phenyl substituted by R^8, halo, -CN, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_7 cycloalkyl, C_1-C_6 alkoxy, $-CONR^5R^5$, OR^{13}, So_xR^6, O-(C_1-C_6 alkylene)-$CONR^5R^5$, O-(C_1-C_6 alkylene)-NR^5R^5, or O-(C_1-C_6 alkylene)-OR^6.

12. A compound according to any preceding claim wherein R^4 is phenyl substituted by R^8, halo, -CN, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_7 cycloalkyl or C_1-C_6 alkoxy.

13. A compound according to any preceding claim wherein R^4 is phenyl substituted by halo, -CN or C_1-C_6 alkyl.

14. A compound according to any preceding claim wherein R^8 is pyrrolyl, imidazolyl, pyrazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, furanyl, thienyl, pyridinyl, pyridazinyl, pyrimidinyl or pyrazinyl, each being optionally substituted by halo, -CN, $-COR^5$, $-CONR^5R^5$, $-SO_2NR^5R^5$, $-NR^5SO_2R^5$, $-OR^5$, $-NR^5R^5$, -(C_1-C_6 alkylene)-NR^5R^5, C_1-C_6 alkyl, fluoro(C_1-C_6)alkyl or C_3-C_7 cycloalkyl.

15. A compound according to any preceding claim wherein R^9 is imidazolyl, pyrazolyl, 1,2,4-triazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, pyridinyl, pyrazinyl or pyrimidinyl, each being optionally substituted by halo, -CN, $-COR^5$,

$-CONR^5R^5$, $-SO_2NR^5R^5$, $-NR^5SO_2R^5$, $-OR^5$, $-NR^5R^5$, $-(C_1-C_6$ alkylene$)-NR^5R^5$, C_1-C_6 alkyl, fluoro(C_1-C_6)alkyl or C_3-C_7 cycloalkyl.

16. A compound according to any preceding claim wherein R^8 is imidazolyl, pyrazolyl, 1,2,4-triazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, pyridinyl, pyrazinyl or pyrimidinyl, each being optionally substituted by $-OR^5$, $-NR^5R^5$ or C_1-C_6 alkyl.

17. A compound according to any preceding claim wherein R^9 is azetidinyl, tetrahydropyrrolyl, piperidinyl, azepinyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, oxepinyl, morpholinyl, piperazinyl or diazepinyl, each being optionally substituted by oxo, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, $-SO_2R^5$, $-CONR^5R^5$, $-COOR^5$, $-CO-(C_1-C_6$ alkylene$)-OR^5$ or $-COR^5$ and optionally substituted on a carbon atom which is not adjacent to a heteroatom by halo, $-OR^5$, $-NR^5R^5$, $-NR^5COR^5$, $-NR^5COOR^5$, $-NR^5CONR^5R^5$, $-NR^5SO_2R^5$ or -CN.

18. A compound according to any preceding claim wherein R^9 is azetidinyl, piperidinyl, tetrahydrofuranyl, piperazinyl or morpholinyl, each being optionally substituted by oxo, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, $-SO_2R^5$, $-CONR^5R^5$, $-COOR^5$, $-CO-(C_1-C_6$ alkylene$)-OR^5$ or $-COR^5$ and optionally substituted on a carbon atom which is not adjacent to a heteroatom by halo, $-OR^5$, $-NR^5R^5$, $-NR^5COR^5$, $-NR^5COOR^5$, $-NR^5CONR^5R^5$, $-NR^5SO_2R^5$ or -CN.

19. A compound according to any preceding claim wherein R^9 is azetidinyl, piperidinyl, tetrahydrofuranyl, piperazinyl or morpholinyl, each being optionally substituted by C_1-C_6 alkyl, $-SO_2R^5$, $-CONR^5R^5$, $-COOR^5$, $-CO-(C_1-C_6$ alkylene$)-OR^5$ or $-COR^5$ and optionally substituted on a carbon atom which is not adjacent to a heteroatom by $-OR^5$ or $-NR^5COR^5$.

20. A compound according to any preceding claim wherein R^{10} is H, R^8, R^9, R^{13}, C_1-C_6 alkyl or $-(C_1-C_6$ alkyl$)-(C_3-C_7$ cycloalkyl$)$, said C_1-C_6 alkyl being optionally substituted by $-OR^5$, $-OR^{13}$, R^8, R^9, R^{13} or $-COR^{13}$.

21. A compound according to any preceding claim wherein R^{10} is H, R^8, R^9, R^{13}, C_1-C_6 alkyl or $-(C_1-C_6$ alkyl$)-(C_3-C_7$ cycloalkyl$)$, said C_1-C_6 alkyl being optionally substituted by $-OR^5$ or R^{13}.

22. A compound according to any preceding claim wherein R^{11} is H or C_1-C_6 alkyl, said C_1-C_6 alkyl being optionally substituted by $-OR^5$, $-NR^5R^5$, $-NR^5COR^5$, $-CONR^5R^5$, R^8 or R^9.

23. A compound according to any preceding claim wherein R^{11} is H or C_1-C_6 alkyl, said C_1-C_6 alkyl being optionally substituted by -OR^5 or -NR^5COR^5.

24. A compound according to any preceding claim wherein R^{12} is C_1-C_4 alkyl substituted by R^8, R^9, -OR^5, -$CONR^5R^5$, -NR^5COR^5 or -NR^5R^5.

25. A compound according to any preceding claim wherein R^{12} is C_1-C_4 alkyl substituted by R^9, -OR^5, -NR^5COR^5 or -NR^5R^5.

26. A compound according to any preceding claim wherein R^{13} is phenyl substituted by halo, -CN, -COR^5, -$CONR^5R^5$, -$SO_2NR^5R^5$, -$NR^5SO_2R^5$, -OR^5, -NR^5R^5, -(C_1-C_6 alkylene)-NR^5R^5, C_1-C_6 alkyl, halo(C_1-C_6)alkyl or C_3-C_7 cycloalkyl.

27. A compound according to any preceding claim wherein R^{13} is phenyl substituted by halo, -CN, -$CONR^5R^5$, -$SO_2NR^5R^5$ or -OR^5.

28. 2-[4-(3,5-Dichlorophenoxy)-3,5-dimethyl-1*H*-pyrazol-1-yl]ethanol;
2-[4-(3,5-Dichlorophenoxy)-3,5-diethyl-1*H*-pyrazol-1-yl]ethanol;
4-(3,5-Dichlorophenoxy)-3,5-diethyl-1*H*-pyrazole;
[4-(3,5-Dichlorophenoxy)-3,5-diethyl-1*H*-pyrazol-1-yl]acetonitrile;
5-[[4-(3,5-Dichlorophenoxy)-3,5-diethyl-1*H*-pyrazol-1-yl]methyl]-1*H*-pyrazol-3-ol;
6-[[4-(3,5-Dichlorophenoxy)-3,5-diethyl-1*H*-pyrazol-1-yl]methyl]-2-methyl-4(3*H*)-pyrimidinone;
2-Amino-6-[[4-(3,5-dichlorophenoxy)-3,5-diethyl-1*H*-pyrazol-1-yl]methyl]-4(3*H*)-pyrimidinone;
2-[4-(3,5-Dichlorophenoxy)-3,5-diethyl-1*H*-pyrazol-1-yl]-*N*-hydroxyethanimidamide;
Methyl [4-(3,5-dichlorophenoxy)-3,5-diethyl-1*H*-pyrazol-1-yl]acetate;
2-[4-(3,5-Dichlorophenoxy)-3,5-diethyl-1*H*-pyrazol-1-yl]acetamide;
2-[4-(3,5-Dichlorophenoxy)-3,5-diethyl-1*H*-pyrazol-1-yl]acetohydrazide;
5-[[4-(3,5-Dichlorophenoxy)-3,5-diethyl-1*H*-pyrazol-1-yl]methyl]-1,3,4-oxadiazol-2(3*H*)-one;
2-[4-(3,5-Dichlorophenoxy)-3,5-diethyl-1*H*-pyrazol-1-yl]ethylamine;
3-[[4-(3,5-Dichlorophenoxy)-3,5-diethyl-1*H*-pyrazol-1-yl]methyl]-1,2,4-oxadiazol-5-ol;
5-[[4-(3,5-Dichlorophenoxy)-3,5-diethyl-1*H*-pyrazol-1-yl]methyl]-1,3,4-oxadiazol-2-amine;

N-[2-[4-(3,5-Dichlorophenoxy)-3,5-diethyl-1*H*-pyrazol-1-yl]ethyl]-2-methoxyacetamide;
N-[2-[4-(3,5-dichlorophenoxy)-3,5-diethyl-1*H*-pyrazol-1-yl]ethyl]-2-pyridinecarboxamide;
N-[2-[4-(3,5-dichlorophenoxy)-3,5-diethyl-1*H*-pyrazol-1-yl]ethyl]-2-pyrazinecarboxamide;
3-[[3,5-Diethyl-1-(2-hydroxyethyl)-1*H*-pyrazol-4-yl]oxy}benzonitrile;
4-[[3,5-diethyl-1-(2-hydroxyethyl)-1*H*-pyrazol-4-yl]oxy]-3,5-dimethylbenzonitrile;
3-chloro-4-[[3,5-diethyl-1-(2-hydroxyethyl)-1*H*-pyrazol-4-yl]oxy}benzonitrile;
5-[[3,5-diethyl-1-(2-hydroxyethyl)-1*H*-pyrazol-4-yl]oxy}-2-fluorobenzonitrile;
2-[4-(4-chlorophenoxy)-3,5-diethyl-1*H*-pyrazol-1-yl]ethanol;
2-[4-(3-chlorophenoxy)-3,5-diethyl-1*H*-pyrazol-1-yl]ethanol;
2-[4-(2-chlorophenoxy)-3,5-diethyl-1*H*-pyrazol-1-yl]ethanol;
2-[4-(2,6-dichlorophenoxy)-3,5-diethyl-1*H*-pyrazol-1-yl]ethanol;
2-[4-(2,3-dichlorophenoxy)-3,5-diethyl-1*H*-pyrazol-1-yl]ethanol;
2-[4-(2,4-dichlorophenoxy)-3,5-diethyl-1*H*-pyrazol-1-yl]ethanol;
2-[3,5-diethyl-4-(2-fluorophenoxy)-1*H*-pyrazol-1-yl]ethanol;
2-[3,5-diethyl-4-(3-fluorophenoxy)-1*H*-pyrazol-1-yl]ethanol;
2-[4-(3,5-dimethylphenoxy)-3,5-diethyl-1*H*-pyrazol-1-yl]ethanol;
2-[3,5-diethyl-4-(4-fluoro-3-methylphenoxy)-1*H*-pyrazol-1-yl]ethanol;
2-[4-(2,5-dichlorophenoxy)-3,5-diethyl-1*H*-pyrazol-1-yl]ethanol;
2-[4-(2,5-dichlorophenoxy)-3,5-diethyl-1*H*-pyrazol-1-yl]ethanol;
2-[4-(3,4-dichlorophenoxy)-3,5-diethyl-1*H*-pyrazol-1-yl]ethanol;
2-[4-(2,6-difluorophenoxy)-3,5-diethyl-1*H*-pyrazol-1-yl]ethanol;
2-[4-(2,5-difluorophenoxy)-3,5-diethyl-1*H*-pyrazol-1-yl]ethanol;
2-[4-(3,5-difluorophenoxy)-3,5-diethyl-1*H*-pyrazol-1-yl]ethanol;
4-(3,5-Dichlorophenoxy)-3,5-diethyl-1-(2-methoxyethyl)-1*H*-pyrazole;
4-(3,5-dichlorophenoxy)-3,5-diethyl-1-(methoxymethyl)-1*H*-pyrazole;
4-(3,5-dichlorophenoxy)-3,5-diethyl-1-methyl-1*H*-pyrazole;
4-(3,5-Dichlorophenoxy)-3-ethyl-1*H*-pyrazole;
4-[2-[4-(3,5-Dichlorophenoxy)-3,5-diethyl-1*H*-pyrazol-1-yl]ethyl]morpholine;
N-[2-[4-(3,5-dichlorophenoxy)-3,5-diethyl-1*H*-pyrazol-1-yl]ethyl]-*N*-(2-methoxyethyl)amine;
1-(1-[2-[4-(3,5-dichlorophenoxy)-3,5-diethyl-1*H*-pyrazol-1-yl]ethyl]-4-piperidinyl)ethanone;
N-[2-[4-(3,5-dichlorophenoxy)-3,5-diethyl-1*H*-pyrazol-1-yl]ethyl]-*N*,*N*-dimethylamine;
N-[2-({2-[4-(3,5-dichlorophenoxy)-3,5-diethyl-1*H*-pyrazol-1-yl]ethyl}amino)ethyl]acetamide;

N-[2-[4-(3,5-dichlorophenoxy)-3,5-diethyl-1*H*-pyrazol-1-yl]ethyl]-*N*-methylamine;
N-[2-[4-(3,5-dichlorophenoxy)-3,5-diethyl-1*H*-pyrazol-1-yl]ethyl]-*N*-(tetrahydro-2-furanylmethyl)amine;
3-[[4-(3,5-Dichlorophenoxy)-3,5-diethyl-1*H*-pyrazol-1-yl]methyl]morpholine;
1-(3-Azetidinyl)-4-(3,5-dichlorophenoxy)-3,5-diethyl-1*H*-pyrazole;
7-(3,5-Dichlorophenoxy)-6-ethyl-2,3-dihydropyrazolo[5,1-*b*][1,3]oxazole;
4-(3,5-Dichlorophenoxy)-3,5-dimethyl-1*H*-pyrazole;
1-[4-(3,5-Dichlorophenoxy)-3,5-diethyl-1*H*-pyrazol-1-yl]-2-propanol;
2-[2-[4-(3,5-Dichlorophenxoy)-3,5-diethyl-1*H*-pyrazol-1-yl)ethoxy]ethanamine;
4-[[4-(3,5-Dichlorophenoxy)-3-methyl-1*H*-pyrazol-5-yl]methyl]morpholine;
4-(3,5-Dichlorophenoxy)-3-methyl-5-[(2-methyl-1*H*-imidazol-1-yl)methyl]-1*H*-pyrazole;
2-[4-(3,5-Dichlorophenoxy)-3-ethyl-5-methoxy-1*H*-pyrazol-1-yl]ethanol;
1-[[4-(3,5-Dichlorophenoxy)-3-methyl-1*H*-pyrazol-5-yl]methyl]-1*H*-1,2,4-triazole;
3-[(3,5-Diethyl-1*H*-pyrazol-4-yl)oxy]benzonitrile;
3-[[1-(2-Aminoethyl)-3,5-diethyl-1*H*-pyrazol-4-yl]oxy}benzonitrile;
2-[4-(3-Cyanophenoxy)-3,5-diethyl-1*H*-pyrazol-1-yl]acetamide;
Ethyl [4-(3-cyanophenoxy)-3,5-diethyl-1*H*-pyrazol-1-yl]acetate;
1-Allyl-4-(3,5-dichlorophenoxy)-3,5-diethyl-1*H*-pyrazole;
N-[[4-(3,5-Dichlorophenoxy)-3-methyl-1*H*-pyrazol-5-yl]methyl]-*N*-(4-methoxybenzyl)amine;
N-(cyclopropylmethyl)[4-(3,5-dichlorophenoxy)-3-methyl-1*H*-pyrazol-5-yl]methanamine;
[4-(3,5-dichlorophenoxy)-3-methyl-1*H*-pyrazol-5-yl]-*N*,*N*-dimethylmethanamine;
[4-(3,5-dichlorophenoxy)-3-methyl-1*H*-pyrazol-5-yl]-*N*-methylmethanamine;
1-[[4-(3,5-dichlorophenoxy)-3-methyl-1*H*-pyrazol-5-yl]methyl]-4-methylpiperazine;
1-[[4-(3,5-dichlorophenoxy)-3-methyl-1*H*-pyrazol-5-yl]methyl]-4-piperidinecarboxamide;
N-[[4-(3,5-dichlorophenoxy)-3-methyl-1*H*-pyrazol-5-yl]methyl]-2-methoxyethanamine;
1-acetyl-4-[[4-(3,5-dichlorophenoxy)-3-methyl-1*H*-pyrazol-5-yl]methyl]piperazine;
N-[2-([[4-(3,5-dichlorophenoxy)-3-methyl-1*H*-pyrazol-5-yl]methyl]amino)ethyl]acetamide;
N-(1-[[4-(3,5-dichlorophenoxy)-3-methyl-1*H*-pyrazol-5-yl]methyl]-4-piperidinyl)acetamide;
1-[[4-(3,5-dichlorophenoxy)-3-methyl-1*H*-pyrazol-5-yl]methyl]-4-methoxypiperidine;
3-Chloro-5-[(3,5-dimethyl-1*H*-pyrazol-4-yl)oxy]benzonitrile;
3-[[5-(Aminomethyl)-3-methyl-1*H*-pyrazol-4-yl]oxy]-5-chlorobenzonitrile;

3-Chloro-5-[[3-methyl-5-(1-piperazinylmethyl)-1*H*-pyrazol-4-yl]oxy]benzonitrile;
3-Chloro-5-[(5-[[(4-cyanobenzyl)amino]methyl}-3-methyl-1*H*-pyrazol-4-yl)oxy]benzonitrile;
3-Chloro-5-[(3-methyl-5-[[4-(methylsulfonyl)-1-piperazinyl]methyl}-1*H*-pyrazol-4-yl)oxy]benzonitrile;
3-Chloro-5-[(5-[[4-(methoxyacetyl)-1-piperazinyl]methyl}-3-methyl-1*H*-pyrazol-4-yl)oxy]benzonitrile;
Methyl 4-[[4-(3-chloro-5-cyanophenoxy)-3-methyl-1*H*-pyrazol-5-yl]methyl}-1-piperazinecarboxylate;
4-[({[4-(3-Chloro-5-cyanophenoxy)-3-methyl-1*H*-pyrazol-5-yl]methyl}amino)methyl]benzenesulfonamide;
4-(3,5-Dichlorophenoxy)-5-(methoxymethyl)-3-methyl-1*H*-pyrazole;
3-*tert*-Butyl-4-(3,5-dichlorophenoxy)-5-methyl-1*H*-pyrazole;
4-(3,5-Dichlorophenoxy)-3-ethyl-5-methyl-1*H*-pyrazole;
4-Cyano-*N*-[[4-(3,5-dichlorophenoxy)-3-methyl-1*H*-pyrazol-5-yl]methyl}benzamide;
3-Cyano-*N*-[[4-(3,5-dichlorophenoxy)-3-methyl-1*H*-pyrazol-5-yl]methyl}benzamide;
N-[[4-(3,5-Dichlorophenoxy)-3-methyl-1*H*-pyrazol-5-yl]methyl}-*N*-(3-pyridinylmethyl)amine;
3-({5-[(4-Acetyl-1-piperazinyl)methyl]-3-methyl-1*H*-pyrazol-4-yl}oxy)-5-chlorobenzonitrile;
3-Chloro-5-[(5-[[(4-cyanobenzyl)(methyl)amino]methyl}-3-methyl-1*H*-pyrazol-4-yl)oxy]benzonitrile;
3-Chloro-5-[(5-[[(4-cyanobenzyl)(2-hydroxyethyl)amino]methyl}-3-methyl-1*H*-pyrazol-4-yl)oxy]benzonitrile;
3-Chloro-5-({3-methyl-5-[(2-methyl-1*H*-imidazol-1-yl)methyl]-1*H*-pyrazol-4-yl}oxy)benzonitrile;
2-(4-(3,5-Dichlorophenoxy)-3-methyl-5-[[(3-pyridinylmethyl)amino]methyl}-1*H*-pyrazol-1-yl)ethanol;
5-[(3-Isopropyl-5-methyl-1*H*-pyrazol-4-yl)oxy]isophthalonitrile;
5-[[1-(2-Hydroxyethyl)-3-isopropyl-5-methyl-1*H*-pyrazol-4-yl]oxy}isophthalonitrile;
3-(3,5-Dichlorophenoxy)-2-ethyl-6,7-dihydropyrazolo[1,5-*a*]pyrazin-4(5*H*)-one;
3-(3,5-Dichlorophenoxy)-2-ethyl-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrazine;
3-(3,5-Dichlorophenoxy)-2-ethyl-5-methyl-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrazine;
4-[(3-(3,5-Dichlorophenoxy)-2-ethyl-6,7-dihydropyrazolo[1,5-*a*]pyrazin-5(4*H*)-yl)methyl]benzonitrile;

3-(3,5-Dichlorophenoxy)-2-ethyl-5-(4-methoxybenzyl)-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrazine;
[1-(2-Aminoethyl)-4-(3,5-dichlorophenoxy)-3-ethyl-1*H*-pyrazol-5-yl]methanol;
2-[4-(3,5-Dichlorophenoxy)-5-(ethoxymethyl)-3-ethyl-1*H*-pyrazol-1-yl]ethylamine;
2-[4-(3,5-dichlorophenoxy)-3-ethyl-5-(1*H*-pyrazol-1-ylmethyl)-1*H*-pyrazol-1-yl]ethylamine;
N-[[1-(2-aminoethyl)-4-(3,5-dichlorophenoxy)-3-ethyl-1*H*-pyrazol-5-yl]methyl]-*N*-(4-methoxybenzyl)amine;
4-[([[1-(2-aminoethyl)-4-(3,5-dichlorophenoxy)-3-ethyl-1*H*-pyrazol-5-yl]methyl}amino)methyl]benzonitrile;
2-[5-[(4-Acetyl-1-piperazinyl)methyl]-4-(3,5-dichlorophenoxy)-3-ethyl-1*H*-pyrazol-1-yl]ethylamine;
N-[2-({[1-(2-Aminoethyl)-4-(3,5-dichlorophenoxy)-3-ethyl-1*H*-pyrazol-5-yl]methyl}amino)ethyl]acetamide;
[4-(3,5-Dichlorophenoxy)-3-methyl-1*H*-pyrazol-5-yl]methanamine hydrobromide;
N-[[4-(3,5-Dichlorophenoxy)-3-methyl-1*H*-pyrazol-5-yl]methyl]-*N*-(4-fluorobenzyl)amine;
4-[([[4-(3,5-Dichlorophenoxy)-3-methyl-1*H*-pyrazol-5-yl]methyl}amino)methyl]benzonitrile;
3-Chloro-5-[(1,3,5-trimethyl-1*H*-pyrazol-4-yl)oxy]benzonitrile;
3-Chloro-5-[(5-[[(4-cyanobenzyl)amino]methyl}-1,3-dimethyl-1*H*-pyrazol-4-yl)oxy]benzonitrile;
3-Chloro-5-[[1-(2-hydroxyethyl)-3,5-dimethyl-1*H*-pyrazol-4-yl]oxy}benzonitrile;
3-Chloro-5-[[5-[[(4-cyanobenzyl)amino]methyl}-1-(2-hydroxyethyl)-3-methyl-1*H*-pyrazol-4-yl]oxy}benzonitrile;
4-[([[4-(3-Chloro-5-cyanophenoxy)-3-methyl-1*H*-pyrazol-5-yl]methyl}amino)methyl]benzamide;
3-[[3,5-diethyl-1-(2-hydroxyethyl)-1*H*-pyrazol-4-yl]oxy}-5-fluorobenzonitrile;
3-[[3,5-diethyl-1-(2-hydroxyethyl)-1*H*-pyrazol-4-yl]oxy}-5-methylbenzonitrile;
5-[[3,5-diethyl-1-(2-hydroxyethyl)-1*H*-pyrazol-4-yl]oxy}isophthalonitrile;
3-chloro-5-[[3,5-diethyl-1-(2-hydroxyethyl)-1*H*-pyrazol-4-yl]oxy}benzonitrile;
3-[(3,5-diethyl-1*H*-pyrazol-4-yl)oxy]-5-fluorobenzonitrile;
5-[(3,5-diethyl-1*H*-pyrazol-4-yl)oxy]isophthalonitrile;
3-[(3,5-diethyl-1*H*-pyrazol-4-yl)oxy]-5-methylbenzonitrile;
3-chloro-5-[(3,5-diethyl-1*H*-pyrazol-4-yl)oxy]benzonitrile;
3-[[1-(2-aminoethyl)-3,5-diethyl-1*H*-pyrazol-4-yl]oxy}-5-methylbenzonitrile;
3-[[1-(2-aminoethyl)-3,5-diethyl-1*H*-pyrazol-4-yl]oxy}-5-chlorobenzonitrile;
5-[[1-(2-aminoethyl)-3,5-diethyl-1*H*-pyrazol-4-yl]oxy}isophthalonitrile;
3-[[1-(2-aminoethyl)-3,5-diethyl-1*H*-pyrazol-4-yl]oxy}-5-fluorobenzonitrile;

5-[(3-cyclopropyl-5-ethyl-1*H*-pyrazol-4-yl)oxy]isophthalonitrile;
5-[(3-*tert*-butyl-5-methyl-1*H*-pyrazol-4-yl)oxy]isophthalonitrile;
5-[(5-ethyl-3-isopropyl-1*H*-pyrazol-4-yl)oxy]isophthalonitrile;
4-(3,5-Dichlorophenoxy)-3,5-diethyl-1-(1-methyl-3-azetidinyl)-1*H*-pyrazole;
2-[4-(3,5-Dichlorophenoxy)-3-ethyl-1*H*-pyrazol-1-yl]ethylamine;
2-[4-(3,5-Dichlorophenoxy)-5-ethyl-1*H*-pyrazol-1-yl]ethylamine;
tert-Butyl 2-[4-(3,5-dichlorophenoxy)-3-ethyl-5-(hydroxymethyl)-1*H*-pyrazol-1-yl]ethylcarbamate;
tert-Butyl 2-[4-(3,5-dichlorophenoxy)-5-(ethoxymethyl)-3-ethyl-1*H*-pyrazol-1-yl]ethylcarbamate;
tert-Butyl 2-[5-(bromomethyl)-4-(3,5-dichlorophenoxy)-3-ethyl-1*H*-pyrazol-1-yl]ethylcarbamate;
tert-Butyl 2-[5-(aminomethyl)-4-(3,5-dichlorophenoxy)-3-ethyl-1*H*-pyrazol-1-yl]ethylcarbamate;
tert-Butyl 2-[5-[(4-acetyl-1-piperazinyl)methyl]-4-(3,5-dichlorophenoxy)-3-ethyl-1*H*-pyrazol-1-yl]ethylcarbamate;
tert-Butyl 2-[4-(3,5-dichlorophenoxy)-3-ethyl-5-(1*H*-pyrazol-1-ylmethyl)-1*H*-pyrazol-1-yl]ethylcarbamate;
tert-Butyl 2-[5-({[2-(acetylamino)ethyl]amino}methyl)-4-(3,5-dichlorophenoxy)-3-ethyl-1*H*-pyrazol-1-yl]ethylcarbamate;
tert-Butyl 2-(4-(3,5-dichlorophenoxy)-3-ethyl-5-{[(4-methoxybenzyl)amino]methyl}-1*H*-pyrazol-1-yl)ethylcarbamate;
tert-Butyl 2-[5-{[(4-cyanobenzyl)amino]methyl}-4-(3,5-dichlorophenoxy)-3-ethyl-1*H*-pyrazol-1-yl]ethylcarbamate;
3-[[5-(Bromomethyl)-1,3-dimethyl-1*H*-pyrazol-4-yl]oxy}-5-chlorobenzonitrile;
3-[(3,5-Diethyl-1-methyl-1*H*-pyrazol-4-yl)oxy]benzonitrile;
3-[[3,5-Diethyl-1-(2-methoxyethyl)-1*H*-pyrazol-4-yl]oxy}benzonitrile;
3-({5-[2-(Benzyloxy)ethyl]-3-ethyl-1*H*-pyrazol-4-yl}oxy)-5-fluorobenzonitrile;
3-[[3-Ethyl-5-(2-hydroxyethyl)-1*H*-pyrazol-4-yl]oxy}-5-fluorobenzonitrile;
3-({5-[2-(4-Cyanophenoxy)ethyl]-3-ethyl-1*H*-pyrazol-4-yl}oxy)-5-fluorobenzonitrile;
3-[(3-Ethyl-5-{2-[(2-methyl-3-pyridinyl)oxy]ethyl}-1*H*-pyrazol-4-yl)oxy]-5-fluorobenzonitrile;
3-({3-Ethyl-5-[2-(3-pyridinyloxy)ethyl]-1*H*-pyrazol-4-yl}oxy)-5-fluorobenzonitrile;
3-[(5-{2-[(2-Amino-3-pyridinyl)oxy]ethyl}-3-ethyl-1*H*-pyrazol-4-yl)oxy]-5-fluorobenzonitrile;
5-({5-[2-(benzyloxy)ethyl]-3-ethyl-1*H*-pyrazol-4-yl}oxy)isophthalonitrile;
5-[[3-Ethyl-5-(2-hydroxyethyl)-1*H*-pyrazol-4-yl]oxy}isophthalonitrile;
3-[[5-(Aminomethyl)-1-(2-hydroxyethyl)-3-methyl-1*H*-pyrazol-4-yl]oxy}-5-chlorobenzonitrile;

5-[(1-Allyl-3-*tert*-butyl-5-methyl-1*H*-pyrazol-4-yl)oxy]isophthalonitrile;
5-[[3-*tert*-Butyl-1-(2-hydroxyethyl)-5-methyl-1*H*-pyrazol-4-yl]oxy}isophthalonitrile;
5-[[1-(2-Aminoethyl)-3-*tert*-butyl-5-methyl-1*H*-pyrazol-4-yl]oxy}isophthalonitrile;
3-[[3,5-Diethyl-1-(2-hydroxyethyl)-1*H*-pyrazol-4-yl]oxy}-5-(1*H*-1,2,4-triazol-1-yl)benzonitrile;
3-[[3,5-diethyl-1-(2-hydroxyethyl)-1*H*-pyrazol-4-yl]oxy}-5-(4-oxo-1(4*H*)-pyridinyl)benzonitrile;
3-[[3,5-diethyl-1-(2-hydroxyethyl)-1*H*-pyrazol-4-yl]oxy}-5-(1*H*-1,2,3-triazol-1-yl)benzonitrile;
3-[[3,5-diethyl-1-(2-hydroxyethyl)-1*H*-pyrazol-4-yl]oxy}-5-(2*H*-1,2,3-triazol-2-yl)benzonitrile;
3-[[3,5-Diethyl-1-(2-hydroxyethyl)-1*H*-pyrazol-4-yl]oxy}-5-fluorobenzamide;
3-[[3,5-Diethyl-1-(2-hydroxyethyl)-1*H*-pyrazol-4-yl]oxy}-5-(1*H*-pyrazol-1-yl)benzamide;
3-[[3,5-Diethyl-1-(2-hydroxyethyl)-1*H*-pyrazol-4-yl]oxy}-5-(2-oxo-1(2*H*)-pyridinyl)benzamide;
3-[[3,5-Diethyl-1-(2-hydroxyethyl)-1*H*-pyrazol-4-yl]oxy}-5-(6-oxo-1(6*H*)-pyridazinyl)benzamide;
3-[[3,5-Diethyl-1-(2-hydroxyethyl)-1*H*-pyrazol-4-yl]oxy}-5-(2,3-dimethyl-5-oxo-2,5-dihydro-1*H*-pyrazol-1-yl)benzamide;
5-[[3-Cyclopropyl-5-ethyl-1-(2-hydroxyethyl)-1*H*-pyrazol-4-yl]oxy}isophthalonitrile;
5-[[5-Cyclopropyl-3-ethyl-1-(2-hydroxyethyl)-1*H*-pyrazol-4-yl]oxy}isophthalonitrile;
5-[[5-Ethyl-1-(2-hydroxyethyl)-3-isopropyl-1*H*-pyrazol-4-yl]oxy}isophthalonitrile;
5-[[3-Ethyl-1-(2-hydroxyethyl)-5-isopropyl-1*H*-pyrazol-4-yl]oxy}isophthalonitrile;
2-[4-(3,5-Dicyanophenoxy)-3,5-diethyl-1*H*-pyrazol-1-yl]ethyl carbamate;
N-{2-[4-(3,5-Dicyanophenoxy)-3,5-diethyl-1*H*-pyrazol-1-yl]ethyl}sulfamide;
N-[2-[4-(3,5-Dicyanophenoxy)-3,5-diethyl-1*H*-pyrazol-1-yl]ethyl]-2-methoxyacetamide;
5-[[1-(3-Azetidinyl)-3,5-diethyl-1*H*-pyrazol-4-yl]oxy}isophthalonitrile;
5-[[3,5-Diethyl-1-(3-hydroxypropyl)-1*H*-pyrazol-4-yl]oxy}isophthalonitrile;
5-[(3,5-Diethyl-1-methyl-1*H*-pyrazol-4-yl)oxy]isophthalonitrile;
5-[[3,5-Diethyl-1-(2-methoxyethyl)-1*H*-pyrazol-4-yl]oxy}isophthalonitrile;
5-[[1-(3-Aminopropyl)-3,5-diethyl-1*H*-pyrazol-4-yl]oxy}isophthalonitrile;
methyl [4-(3,5-Dicyanophenoxy)-3,5-diethyl-1*H*-pyrazol-1-yl]acetate;
2-[4-(3,5-Dicyanophenoxy)-3,5-diethyl-1*H*-pyrazol-1-yl]acetamide;
5-[[3,5-Diethyl-1-(hydroxymethyl)-1*H*-pyrazol-4-yl]oxy}isophthalonitrile;
3-[([[4-(3-cyano-5-fluorophenoxy)-3-methyl-1*H*-pyrazol-5-yl]methyl}amino)methyl]benzamide;

4-[([[4-(3-Cyano-5-flu rophenoxy)-3-methyl-1*H*-pyrazol-5-yl]methyl}amino)methyl]benzamide;
4-[([[4-(3,5-Dicyanophenoxy)-3-methyl-1*H*-pyrazol-5-yl]methyl}amino)methyl]benzamide;
3-[([[4-(3-Chloro-5-cyanophenoxy)-3-methyl-1*H*-pyrazol-5-yl]methyl}amino)methyl]benzamide;
4-[([[4-(3-Cyano-5-methylphenoxy)-3-methyl-1*H*-pyrazol-5-yl]methyl}amino)methyl]benzamide;
4-[([[4-(3-Cyanophenoxy)-3-methyl-1*H*-pyrazol-5-yl]methyl}amino)methyl]benzamide;
5-[(3,5-Dicyclopropyl-1*H*-pyrazol-4-yl)oxy]isophthalonitrile;
5-[[3,5-Dicyclopropyl-1-(2-hydroxyethyl)-1*H*-pyrazol-4-yl]oxy}isophthalonitrile;
5-[[1-(2-Aminoethyl)-3,5-dicyclopropyl-1*H*-pyrazol-4-yl]oxy}isophthalonitrile;
3-[[3-cyclopropyl-1-(2-hydroxyethyl)-5-methyl-1*H*-pyrazol-4-yl]oxy}-5-methylbenzonitrile;
3-[[5-cyclopropyl-1-(2-hydroxyethyl)-3-methyl-1*H*-pyrazol-4-yl]oxy}-5-methylbenzonitrile;
3-[3-Cyclopropyl-1-(2-amino-ethyl)-5-methyl-1H-pyrazol-4-yloxy]-5-methyl-benzonitrile;
3-[(3-Cyclopropyl-5-methyl-1*H*-pyrazol-4-yl)oxy]-5-methylbenzonitrile;
3-[[1-(3-Aminopropyl)-3,5-diethyl-1*H*-pyrazol-4-yl]oxy}-5-methylbenzonitrile;
3-[[3,5-Diethyl-1-(2-hydroxyethyl)-1*H*-pyrazol-4-yl]oxy}-4-methoxybenzonitrile;
2-[3,5-Diethyl-4-(1-naphthyloxy)-1*H*-pyrazol-1-yl]ethanol;
2-[3,5-Diethyl-4-(2-naphthyloxy)-1*H*-pyrazol-1-yl]ethanol;
2-{4-[3,5-Di(1*H*-pyrazol-1-yl)phenoxy]-3,5-diethyl-1*H*-pyrazol-1-yl}ethanol;
2-{3,5-Diethyl-4-[3-fluoro-5-(1*H*-pyrazol-1-yl)phenoxy]-1*H*-pyrazol-1-yl}ethanol;
3-[[3,5-Diethyl-1-(2-hydroxyethyl)-1*H*-pyrazol-4-yl]oxy}-5-methoxybenzonitrile;
2-[4-(3,5-Difluorophenoxy)-3,5-diethyl-1*H*-pyrazol-1-yl]ethylamine;
3-[[1-(2-Aminoethyl)-3,5-diethyl-1*H*-pyrazol-4-yl]oxy}-5-fluorobenzamide;
3-[(3-Isopropyl-5-methyl-1*H*-pyrazol-4-yl)oxy]-5-methylbenzonitrile;
3-[[1-(2-Aminoethyl)-3-isopropyl-5-methyl-1*H*-pyrazol-4-yl]oxy}-5-methylbenzonitrile;
2-[4-(3,5-Dichlorophenoxy)-3,5-diethyl-1*H*-pyrazol-1-yl]-*N*-(2-pyridinylmethyl)acetamide;
[4-(3,5-Dichlorophenoxy)-3-methyl-1*H*-pyrazol-5-yl]acetonitrile;
1-[[4-(3,5-Dichlorophenoxy)-3-methyl-1*H*-pyrazol-5-yl]acetyl}piperidine;
(3*R*)-1-[[4-(3,5-Dichlorophenoxy)-3-methyl-1*H*-pyrazol-5-yl]acetyl]-3-piperidinol;
N-(2,4-Dichlorobenzyl)-2-[4-(3,5-dichlorophenoxy)-3-methyl-1*H*-pyrazol-5-yl]acetamide;

2-[4-(3,5-Dichlorophenoxy)-3-methyl-1*H*-pyrazol-5-yl]-*N*-(6-methyl-2-pyridinyl)acetamide;
2-[4-(3,5-Dichlorophenoxy)-3-methyl-1*H*-pyrazol-5-yl]-*N*-[4-(trifluoromethyl)benzyl]acetamide;
N-(3-Chlorobenzyl)-2-[4-(3,5-dichlorophenoxy)-3-methyl-1*H*-pyrazol-5-yl]acetamide;
2-[4-(3,5-Dichlorophenoxy)-3-methyl-1*H*-pyrazol-5-yl]-*N*-[2-(trifluoromethyl)benzyl]acetamide;
2-[4-(3,5-Dichlorophenoxy)-3-methyl-1*H*-pyrazol-5-yl]-*N*-(4-fluorobenzyl)acetamide;
N-Benzyl-2-[4-(3,5-dichlorophenoxy)-3-methyl-1*H*-pyrazol-5-yl]-*N*-methylacetamide;
3-chloro-5-[(5-[[(2-chlorobenzyl)amino]methyl}-3-methyl-1*H*-pyrazol-4-yl)oxy]benzonitrile;
3-({5-[(Benzylamino)methyl]-3-methyl-1*H*-pyrazol-4-yl}oxy)-5-chlorobenzonitrile;
3-[(5-[[Benzyl(methyl)amino]methyl}-3-methyl-1*H*-pyrazol-4-yl)oxy]-5-chlorobenzonitrile;
3-Chloro-5-[[5-({[(5-chloro-2-pyridinyl)methyl]amino}methyl)-3-methyl-1*H*-pyrazol-4-yl]oxy}benzonitrile;
3-Chloro-5-[(3-methyl-5-[[(4-pyridinylmethyl)amino]methyl}-1*H*-pyrazol-4-yl)oxy]benzonitrile;
3-Chloro-5-[(3-methyl-5-[[(4-methylbenzyl)amino]methyl}-1*H*-pyrazol-4-yl)oxy]benzonitrile;
3-Chloro-5-[(5-[[(3-methoxypropyl)amino]methyl}-3-methyl-1*H*-pyrazol-4-yl)oxy]benzonitrile;
4-[2-({[4-(3-Chloro-5-cyanophenoxy)-3-methyl-1*H*-pyrazol-5-yl]methyl}amino)ethyl]benzenesulfonamide;
3-Chloro-5-[[3-methyl-5-({[(1*S*)-1-phenylethyl]amino}methyl)-1*H*-pyrazol-4-yl]oxy}benzonitrile;
3-Chloro-5-[(5-[[(4-chlorobenzyl)amino]methyl}-3-methyl-1*H*-pyrazol-4-yl)oxy]benzonitrile;
3-Chloro-5-[(3-methyl-5-[[methyl(2-phenylethyl)amino]methyl}-1*H*-pyrazol-4-yl)oxy]benzonitrile;
3-Chloro-5-({3-methyl-5-[(1*H*-pyrazol-3-ylamino)methyl]-1*H*-pyrazol-4-yl}oxy)benzonitrile;
N-[2-({[4-(3-Chloro-5-cyanophenoxy)-3-methyl-1*H*-pyrazol-5-yl]methyl}amino)ethyl]acetamide;
3-Chloro-5-[(5-[[(3-chlorobenzyl)amino]methyl}-3-methyl-1*H*-pyrazol-4-yl)oxy]benzonitrile;

3-Chloro-5-[[5-({[3-fluoro-5-(trifluoromethyl)benzyl]amino}methyl)-3-methyl-1*H*-pyrazol-4-yl]oxy}benzonitrile;
3-Chloro-5-[(3-methyl-5-{[(6-methyl-2-pyridinyl)amino]methyl}-1*H*-pyrazol-4-yl)oxy]benzonitrile;
3-Chloro-5-[(5-{[(4-hydroxy-6-methyl-2-pyrimidinyl)amino]methyl}-3-methyl-1*H*-pyrazol-4-yl)oxy]benzonitrile;
3-Chloro-5-[(5-{[(4-fluorobenzyl)amino]methyl}-3-methyl-1*H*-pyrazol-4-yl)oxy]benzonitrile;
3-Chloro-5-[[5-({[(1*R*)-2-hydroxy-1-phenylethyl]amino}methyl)-3-methyl-1*H*-pyrazol-4-yl]oxy}benzonitrile;
3-({5-[(Benzylamino)methyl]-3-methyl-1*H*-pyrazol-4-yl}oxy)-5-chlorobenzonitrile;
3-Chloro-5-[(5-{[(3-methoxybenzyl)amino]methyl}-3-methyl-1*H*-pyrazol-4-yl)oxy]benzonitrile;
3-Chloro-5-[[3-methyl-5-({[4-(trifluoromethyl)benzyl]amino}methyl)-1*H*-pyrazol-4-yl]oxy}benzonitrile;
3-Chloro-5-[[5-({[(1*R*)-1-(hydroxymethyl)-2-methylpropyl]amino}methyl)-3-methyl-1*H*-pyrazol-4-yl]oxy}benzonitrile;
3-Chloro-5-[(5-{[(2-methoxybenzyl)amino]methyl}-3-methyl-1*H*-pyrazol-4-yl)oxy]benzonitrile;
3-Chloro-5-[[3-methyl-5-({[2-(2-thienyl)ethyl]amino}methyl)-1*H*-pyrazol-4-yl]oxy}benzonitrile;
3-Chloro-5-[(3-methyl-5-{[(3-pyridinylmethyl)amino]methyl}-1*H*-pyrazol-4-yl)oxy]benzonitrile;
3-Chloro-5-[[3-methyl-5-({[2-(trifluoromethyl)benzyl]amino}methyl)-1*H*-pyrazol-4-yl]oxy}benzonitrile;
3-Chloro-5-[(5-{[(2,4-dichlorobenzyl)amino]methyl}-3-methyl-1*H*-pyrazol-4-yl)oxy]benzonitrile;
3-Chloro-5-[(3-methyl-5-{[(2-pyridinylmethyl)amino]methyl}-1*H*-pyrazol-4-yl)oxy]benzonitrile;
3-Chloro-5-[(5-{[(3,4-dichlorobenzyl)amino]methyl}-3-methyl-1*H*-pyrazol-4-yl)oxy]benzonitrile;
3-Chloro-5-[(3-methyl-5-{[(3-phenylpropyl)amino]methyl}-1*H*-pyrazol-4-yl)oxy]benzonitrile;
3-Chloro-5-[(5-{[(4-methoxybenzyl)amino]methyl}-3-methyl-1*H*-pyrazol-4-yl)oxy]benzonitrile;
3-{[3,5-Diethyl-1-(2-hydroxyethyl)-1*H*-pyrazol-4-yl]oxy}-5-(methylsulfanyl)benzonitrile;
3-{[3,5-Diethyl-1-(2-hydroxyethyl)-1*H*-pyrazol-4-yl]oxy}-5-(methylsulfinyl)benzonitrile;

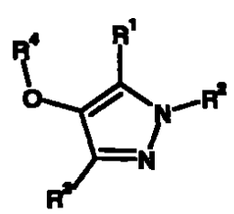
3-[[3,5-Diethyl-1-(2-hydroxyethyl)-1*H*-pyrazol-4-yl]oxy]-5-(methylsulfonyl)benzonitrile;
3-[[3,5-Diethyl-1-(2-hydroxyethyl)-1*H*-pyrazol-4-yl]oxy]-5-[2-(dimethylamino)ethoxy]benzonitrile;
3-[[3,5-Diethyl-1-(2-hydroxyethyl)-1*H*-pyrazol-4-yl]oxy]-5-[2-(methylamino)ethoxy]benzonitrile;
2-(3-Cyano-5-[[3,5-diethyl-1-(2-hydroxyethyl)-1*H*-pyrazol-4-yl]oxy]phenoxy)acetamide;
3-[[3,5-Diethyl-1-(2-hydroxyethyl)-1*H*-pyrazol-4-yl]oxy]-5-(2-methoxyethoxy)benzonitrile;
3-[[1-(2-Aminoethyl)-3,5-diethyl-1*H*-pyrazol-4-yl]oxy]-5-methoxybenzonitrile;
3-[[1-(2-Aminoethyl)-3,5-diethyl-1*H*-pyrazol-4-yl]oxy]-5-(1*H*-pyrazol-1-yl)benzonitrile;
3,5-Dichlorophenyl-3-methyl-5-[(3-methyl-1,2,4-oxadiazol-5-yl)methyl]-1*H*-pyrazol-4-yl ether;
3-Fluoro-5-[[1-(2-hydroxyethyl)-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl]oxy]benzonitrile;
5-[(3,5-Diethyl-1-[2-[(2-methoxyethoxy)methoxy]ethyl]-1*H*-pyrazol-4-yl)oxy]isophthalonitrile;
3-Cyano-5-[[3,5-diethyl-1-(2-hydroxyethyl)-1*H*-pyrazol-4-yl]oxy]benzamide;
5-[[5-Ethyl-3-(1-hydroxyethyl)-1*H*-pyrazol-4-yl]oxy]isophthalonitrile;
5-[[5-Ethyl-3-(1-hydroxyethyl)-1-(2-hydroxyethyl)-1*H*-pyrazol-4-yl]oxy]isophthalonitrile;
3-[[3,5-Diethyl-1-(2-hydroxyethyl)-1*H*-pyrazol-4-yl]oxy]-5-(5-trifluoromethyl-1,2,4-oxadiazol-3-yl)benzonitrile;
3-[[3,5-Diethyl-1-(2-hydroxyethyl)-1*H*-pyrazol-4-yl]oxy]-5-(5-methyl-1,2,4-oxadiazol-3-yl)benzonitrile;
3-[[3,5-Diethyl-1-(2-hydroxyethyl)-1*H*-pyrazol-4-yl]oxy]-5-(5-ethyl-1,2,4-oxadiazol-3-yl)benzonitrile;
3-[[3,5-Diethyl-1-(2-hydroxyethyl)-1*H*-pyrazol-4-yl]oxy]-5-(5-isopropyl-1,2,4-oxadiazol-3-yl)benzonitrile;
5-[([[4-(3-Chloro-5-cyanophenoxy)-3-methyl-1*H*-pyrazol-5-yl]methyl]amino)methyl]nicotinamide;
2-[([[4-(3-Chloro-5-cyanophenoxy)-3-methyl-1*H*-pyrazol-5-yl]methyl]amino)methyl]isonicotinamide;
Di(*tert*-butyl) 2-[4-(3,5-dicyanophenoxy)-3,5-diethyl-1*H*-pyrazol-1-yl]ethyl phosphate;
2-[4-(3,5-Dicyanophenoxy)-3,5-diethyl-1*H*-pyrazol-1-yl]ethyl dihydrogen phosphate;

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5-[[3,5-Diethyl-1-(2-hydroxyethyl)-1*H*-pyrazol-4-yl]oxy]isophthalonitrile sulfate salt;
5-[[3,5-Diethyl-1-(2-hydroxyethyl)-1*H*-pyrazol-4-yl]oxy]isophthalonitrile ;
5-[[3,5-Diethyl-1-(2-hydroxyethyl)-1*H*-pyrazol-4-yl]oxy]isophthalonitrile tosylate salt;
5-[[3,5-Diethyl-1-(2-hydroxyethyl)-1*H*-pyrazol-4-yl]oxy]isophthalonitrile mesylate salt;
3-[[1-(2-Aminoethyl)-3,5-diethyl-1*H*-pyrazol-4-yl]oxy]-5-methylbenzonitrile bis-mesylate salt;
3-[[1-(2-Aminoethyl)-3,5-diethyl-1*H*-pyrazol-4-yl]oxy]-5-methylbenzonitrile phosphate salt;
3-[[1-(2-Aminoethyl)-3,5-diethyl-1*H*-pyrazol-4-yl]oxy]-5-methylbenzonitrile (L) tartrate salt;
3-[[1-(2-Aminoethyl)-3,5-diethyl-1*H*-pyrazol-4-yl]oxy]-5-methylbenzonitrile succinate salt;
3-[[1-(2-Aminoethyl)-3,5-diethyl-1*H*-pyrazol-4-yl]oxy]-5-methylbenzonitrile (L) citrate salt;
or a pharmaceutically acceptable salt, solvate or derivative thereof.

29. 3-[[3,5-diethyl-1-(2-hydroxyethyl)-1*H*-pyrazol-4-yl]oxy]-5-fluorobenzonitrile;
3-[[3,5-diethyl-1-(2-hydroxyethyl)-1*H*-pyrazol-4-yl]oxy]-5-methylbenzonitrile;
5-[[3,5-diethyl-1-(2-hydroxyethyl)-1*H*-pyrazol-4-yl]oxy]isophthalonitrile;
3-chloro-5-[[3,5-diethyl-1-(2-hydroxyethyl)-1*H*-pyrazol-4-yl]oxy]benzonitrile;
5-[(3,5-diethyl-1*H*-pyrazol-4-yl)oxy]isophthalonitrile;
3-[(3,5-diethyl-1*H*-pyrazol-4-yl)oxy]-5-methylbenzonitrile;
3-chloro-5-[(3,5-diethyl-1*H*-pyrazol-4-yl)oxy]benzonitrile;
3-[[1-(2-aminoethyl)-3,5-diethyl-1*H*-pyrazol-4-yl]oxy]-5-methylbenzonitrile;
3-[[1-(2-aminoethyl)-3,5-diethyl-1*H*-pyrazol-4-yl]oxy]-5-chlorobenzonitrile;
5-[[1-(2-aminoethyl)-3,5-diethyl-1*H*-pyrazol-4-yl]oxy]isophthalonitrile;
or a pharmaceutically acceptable salt, solvate or derivative thereof

30. A compound of the formula (I)



(I)

or a pharmaceutically acceptable salt or solvate thereof, wherein:

R^1 is H, C_1-C_8 alkyl, -OC_1-C_8 alkyl, -OC_3-C_7 cycloalkyl, said C_1-C_8 alkyl being optionally substituted by R^{15};

R^2 is H, C_1-C_3 alkyl, propenyl or C-linked R^{15}, said C_1-C_3 alkyl being optionally substituted by -OH, -OCH_3, -$OCH_2CH_2NH_2$, -CN, -CO_2CH_3, -$CONH_2$, -C(=NH)NH_2, -$CONHNH_2$, -NH_2, -$NHCH_3$, -$N(CH_3)_2$, -$NHCH_2CH_2NHCOCH_3$, -$NHCH_2CH_2OCH_3$, -$NHCH_2R^{15}$, -$NHCOR^{15}$, -$NHCOCH_2OCH_3$, or R^{15}

R^3 is C_1-C_8 alkyl;

R^4 is phenyl optionally substituted by halo, -CN, C_1-C_8 alkyl, C_1-C_8 haloalkyl, C_3-C_7 cycloalkyl or C_1-C_8 alkoxy; and

R^{15} is azetidinyl, tetrahydrofuranyl, morpholinyl, piperazinyl, pyrazolyl, oxadiazolyl, pyridinyl or pyrimidinyl each being optionally substituted by -OH, -NH_2, oxo or C_1-C_8 alkyl or -CO(C_1-C_8 alkyl).

31. A pharmaceutical composition including a compound of the formula (I) or a pharmaceutically acceptable salt, solvate or derivative thereof, according to any preceding claim, together with one or more pharmaceutically acceptable excipients, diluents or carriers.

32. A pharmaceutical composition according to claim 31 including one or more additional therapeutic agents.

33. A compound of the formula (I) or a pharmaceutically acceptable salt, solvate or derivative thereof according to any of claims 1 to 30, or a pharmaceutical composition according to claim 31 or 32, for use as a medicament.

34. A compound of the formula (I) or a pharmaceutically acceptable salt, solvate or derivative thereof according to any of claims 1 to 30, or a pharmaceutical composition according to claim 31 or 32, for use as a reverse transcriptase inhibitor or modulator.

35. A compound of the formula (I) or a pharmaceutically acceptable salt, solvate or derivative thereof according to any of claims 1 to 30, or a pharmaceutical composition according to claim 31 or 32, for use in the treatment

of an HIV, or genetically-related retroviral, infection or a resulting acquired immune deficiency syndrome (AIDS).

36. The use of a compound of the formula (I) or a pharmaceutically acceptable salt, solvate or derivative thereof according to any of claims 1 to 30, or a pharmaceutical composition according to claim 31 or 32, for the manufacture of a medicament having reverse transcriptase inhibitory or modulating activity.

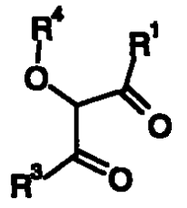
37. The use of a compound of the formula (I) or a pharmaceutically acceptable salt, solvate or derivative thereof according to any of claims 1 to 30, or a pharmaceutical composition according to claim 31 or 32, for the manufacture of a medicament for the treatment of an HIV, or genetically-related retroviral, infection or a resulting acquired immune deficiency syndrome (AIDS).

38. A method of treatment of a mammal, including a human being, with a reverse transcriptase inhibitor or modulator including treating said mammal with an effective amount of a compound of the formula (I) or a pharmaceutically acceptable salt, solvate or derivative thereof according to any of claims 1 to 30, or a pharmaceutical composition according to claim 31 or 32.

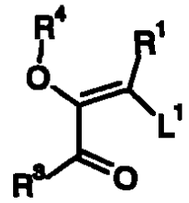
39. A method of treatment of a mammal, including a human being, with an HIV, or genetically-related retroviral, infection or a resulting acquired immune deficiency syndrome (AIDS), including treating said mammal with an effective amount of a compound of the formula (I) or a pharmaceutically acceptable salt, solvate or derivative thereof according to any of claims 1 to 30, or a pharmaceutical composition according to claim 31 or 32.

40. A process for preparing a compound of the formula (I) or a salt, solvate or pharmaceutically acceptable derivative thereof according to any of claims 1 to 30, which comprises:

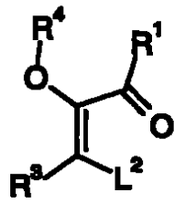
(A) except where either R^1 or R^3 is halo, $-OR^8$ or –CN, condensation of a compound of the formula (II), (VI) or (VII)



(II),



(VI) or



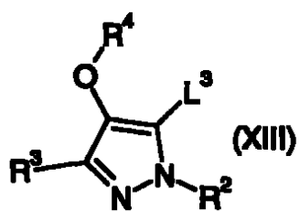
(VII)

with a compound of the formula

$$H_2NNHR^2 \text{ (V)}$$

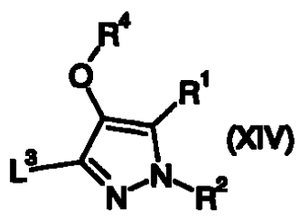
or a salt or hydrate thereof;

(B) for the preparation of a compound of the formula (I) in which R^1 or R^3 is $-OR^8$, reaction of, respectively, a compound of the formulae (XIII) or (XIV)



(XIII)

or



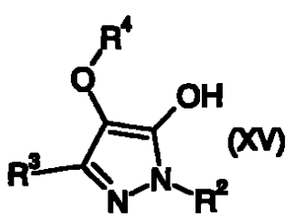
(XIV)

with an alcohol of the formula (XXI)

$$R^8OH \text{ (XXI)}$$

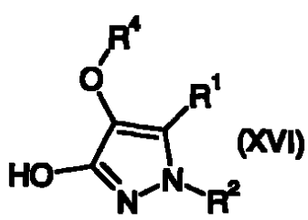
in the presence of a suitable palladium catalyst and carbon monoxide;

(C) for the preparation of a compound of the formula (I) in which R^1 or R^3 is $-OR^8$, reaction of, respectively, a compound of the formulae (XV) or (XVI),



(XV)

or



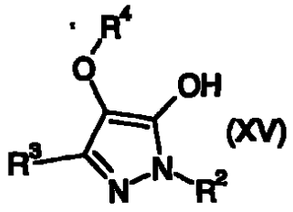
(XVI)

with a compound of the formula (XXI)

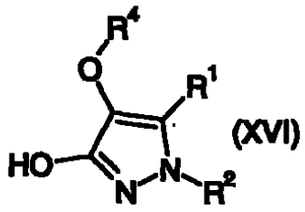
$$R^8OH \quad (XXI)$$

under dehydrating conditions; or

(D) for the preparation of a compound of the formula (I) in which R^1 or R^3 is halo, reaction of, respectively, a compound of the formulae (XV) or (XVI)


(XV)

or


(XVI)

with a halogenating agent; or

(E) interconversion of a compound of formula (I) into another compound of formula (I); or

(F) deprotecting a protected derivative of compound of formula (I); and

optionally converting a compound of formula (I) prepared by any one of processes (A) to (F) into pharmaceutically acceptable salt, solvate or derivative thereof.

41. A compound of the formulae (II), (VI), (VII), (XIII) or (XIV).

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DERIVADOS DE PIRAZOL

Esta invención se refiere a derivados de pirazol y a procedimientos para la preparación de los mismos, a intermedios usados en su preparación, a composiciones que los contienen y usos de tales derivados.

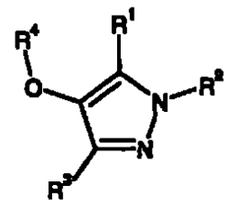
Los compuestos de la presente invención se unen a la enzima transcriptasa inversa y son moduladores, especialmente inhibidores de la misma. La transcriptasa inversa está implicada en el ciclo de vida infeccioso de VIH, y los compuestos que interfieren con la función de esta enzima han mostrado utilidad en el tratamiento de afecciones, incluyendo el SIDA. Existe una necesidad constante de proporcionar moduladores nuevos y mejores, especialmente inhibidores, de la transcriptasa inversa de VIH, ya que el virus puede mutar, volviéndose resistente a los efectos de los moduladores conocidos.

Los compuestos de la presente invención son útiles en el tratamiento de una diversidad de trastornos, incluyendo aquellos en los que está implicada la inhibición de la transcriptasa inversa. Los trastornos de interés incluyen los causados por el Virus de la Inmunodeficiencia Humana (VIH) y retrovirus relacionados genéticamente, tales como el Síndrome de Inmunodeficiencia Adquirida (SIDA).

La solicitud de patente europea EP 0 786 455 A1 describe una clase de compuestos de imidazol que inhiben el

crecimiento de VIH. En *J. Med. Chem.*, 2000, 43, 1034 se describe una clase de N-fenilpirazoles que actúan como inhibidores de la transcriptasa inversa. En la patente de Estados Unidos número 3.303.200 se atribuye actividad antiviral a una clase de derivados de N-(hidroxietil)pirazol.

De acuerdo con la presente invención, se proporciona un compuesto de fórmula



(I)

o una sal, solvato o derivado farmacéuticamente aceptable del mismo, en la que:

R^1 es H, alquilo C_1-C_6, cicloalquilo C_3-C_7, fenilo, bencilo, halo, -CN, $-OR^7$, $-CO_2R^{10}$, $-CONR^5R^{10}$, R^8 o R^9, estando dichos alquilo C_1-C_6, cicloalquilo C_3-C_7, fenilo y bencilo opcionalmente sustituidos con halo, -CN, $-OR^{10}$, $S(O)_xR^{10}$, $-CO_2R^{10}$, $-CONR^5R^{10}$, $-OCONR^5R^{10}$, $-NR^5CO_2R^{10}$, $-NR^{10}R^{11}$, $-NR^5COR^{10}$, $-SO_2NR^5R^{10}$, $-NR^5CONR^5R^{10}$, $-NR^5SO_2R^{10}$ o R^{10}; y

R^2 es H, alquilo C_1-C_6, alquenilo C_3-C_6, alquinilo C_3-C_6, cicloalquilo C_3-C_7, cicloalquenilo C_3-C_7, fenilo, bencilo, R^8 o R^9, estando dichos alquilo C_1-C_6, cicloalquilo C_3-C_7, fenilo y bencilo opcionalmente sustituidos con halo, $-OR^5$, OR^{12}, -CN, $-CO_2R^7$, $-OCONR^5R^5$, $-CONR^5R^5$, $-C(=NR^5)NR^5OR^5$, $-CONR^5NR^5R^5$, $-NR^6R^6$,

$-NR^5R^{12}$, $-NR^5COR^5$, $-NR^5COR^8$, $-NR^5COR^{12}$, $-NR^5CO_2R^5$, $-NR^5CONR^5R^5$, $-SO_2NR^5R^5$, $-NR^5SO_2R^5$, $-NR^5SO_2NR^5R^5$, R^8 o R^9;

o, R^1 y R^2, cuando se toman conjuntamente, representan alquileno C_3-C_4 lineal, opcionalmente sustituido con oxo, estando un grupo metileno de dicho alquileno C_3-C_4 opcionalmente reemplazado por un átomo de oxígeno o un átomo de nitrógeno, estando opcionalmente sustituido dicho átomo de nitrógeno por R^{10};

R^3 es H, alquilo C_1-C_6, cicloalquilo C_3-C_7, fenilo, bencilo, halo, -CN, $-OR^7$, $-CO_2R^5$, $-CONR^5R^5$, R^8 o R^9, estando dichos alquilo C_1-C_6, cicloalquilo C_3-C_7, fenilo y bencilo opcionalmente sustituidos con halo, -CN, $-OR^5$, $-CO_2R^5$, $-CONR^5R^5$, $-OCONR^5R^5$, $-NR^5CO_2R^5$, $-NR^6R^6$, $-NR^5COR^5$, $-SO_2NR^5R^5$, $-NR^5CONR^5R^5$, $-NR^5SO_2R^5$, R^8 o R^9;

R^4 es fenilo, naftilo o piridilo, estando cada uno opcionalmente sustituido con R^8, halo, -CN, alquilo C_1-C_6, haloalquilo C_1-C_6, cicloalquilo C_3-C_7, alcoxi C_1-C_6, $-CONR^5R^5$, OR^{13}, SO_2R^6, O-(alquileno C_1-C_6)-$CONR^5R^5$, O-(alquileno C_1-C_6)-NR^5R^5 o O-(alquileno C_1-C_6)-OR^6;

cada R^5 es independientemente H, alquilo C_1-C_6 o cicloalquilo C_3-C_7 o, cuando dos grupos R^5 están unidos al mismo átomo de nitrógeno, estos dos grupos, tomados conjuntamente con el átomo de nitrógeno al que están unidos, representan azetidinilo, pirrolidinilo, piperidinilo, homopiperidinilo, piperazinilo, homopiperazinilo o morfolinilo, estando dichos

azetidinilo, pirrolidinilo, piperidinilo, homopiperidinilo, piperazinilo, homopiperazinilo y morfolinilo opcionalmente sustituidos con alquilo C_1-C_6 o cicloalquilo C_3-C_7;

cada R^6 es independientemente H, alquilo C_1-C_6 o cicloalquilo C_3-C_7;

R^7 es alquilo C_1-C_6 o cicloalquilo C_3-C_7;

R^8 es un grupo heterocíclico aromático de cinco o seis miembros que contiene (i) de 1 a 4 heteroátomos de nitrógeno o (ii) 1 ó 2 heteroátomos de nitrógeno y 1 heteroátomo de oxígeno o azufre o (iii) 1 ó 2 heteroátomos de oxígeno o azufre, estando dicho grupo heterocíclico opcionalmente sustituido con halo, oxo, -CN, $-COR^5$, $-CONR^5R^5$, $-SO_2NR^5R^5$, $-NR^5SO_2R^5$, $-OR^5$, $-NR^5R^5$, -(alquileno C_1-C_6)-NR^5R^5, alquilo C_1-C_6, fluoroalquilo (C_1-C_6) o cicloalquilo C_3-C_7;

R^9 es un grupo heterocíclico de cuatro a siete miembros, saturado o parcialmente insaturado, que contiene (i) 1 ó 2 heteroátomos de nitrógeno o (ii) 1 heteroátomo de nitrógeno y 1 heteroátomo de oxígeno o 1 heteroátomo de azufre o (iii) 1 heteroátomo de oxígeno o azufre, estando dicho grupo heterocíclico opcionalmente sustituido con oxo, alquilo C_1-C_6, cicloalquilo C_3-C_7, $-SO_2R^5$, $-CONR^5R^5$, $-COOR^5$, -CO-(alquileno C_1-C_6)-OR^5 o $-COR^5$ y opcionalmente sustituido en un átomo de carbono que no es adyacente a un heteroátomo con halo, $-OR^5$, $-NR^5R^5$, $-NR^5COR^5$, $-NR^5COOR^5$, $-NR^5CONR^5R^5$, $-NR^5SO_2R^5$ o -CN;

R^{10} es H, R^8, R^9, R^{13}, alquilo C_1-C_6, cicloalquilo C_3-C_7 o

-(alquil C_1-C_6)-(cicloalquilo C_3-C_7), estando dichos alquilo C_1-C_6 y cicloalquilo C_3-C_7 opcionalmente sustituidos con $-OR^5$, $-OR^{13}$, R^8, R^9, R^{13} o $-COR^{13}$;

R^{11} es H, alquilo C_1-C_6 o cicloalquilo C_3-C_7, estando dichos alquilo C_1-C_6 y cicloalquilo C_3-C_7 opcionalmente sustituidos con $-OR^5$, $-NR^5R^5$, $-NR^5COR^5$, $-CONR^5R^5$, R^8 o R^9;

R^{12} es alquilo C_1-C_6 sustituido con R^8, R^9, $-OR^5$, $-CONR^5R^5$, $-NR^5COR^5$ o $-NR^5R^5$;

R^{13} es fenilo opcionalmente sustituido con halo, -CN, $-COR^5$, $-CONR^5R^5$, $-SO_2NR^5R^5$, $-NR^5SO_2R^5$, $-OR^5$, $-NR^5R^5$, -(alquileno C_1-C_6)-NR^5R^5, alquilo C_1-C_6, haloalquilo (C_1-C_6) o cicloalquilo C_3-C_7; y

x es 0, 1 ó 2;

con la condición de que (a) cuando tanto R^1 como R^3 son fenilo, R^2 no es metilo; y (b) cuando R^1 es etoxi y R^3 es etoxicarbonilo, R^2 no es fenilo.

En las definiciones anteriores, halo significa fluoro, cloro, bromo o yodo. A menos que se indique otra cosa, los grupos alquilo, alquenilo, alquinilo, alquileno y alcoxi que contienen el número requerido de átomos de carbono pueden ser de cadena lineal o ramificada. Los ejemplos de alquilo incluyen metilo, etilo, n-propilo, i-propilo, n-butilo, i-butilo, sec-butilo y t-butilo. Los ejemplos de alquenilo incluyen etenilo, propen-1-ilo, propen-2-ilo, propen-3-ilo, 1-buten-1-ilo, 1-buten-2-ilo, 1-buten-3-ilo, 1-buten-4-ilo,

2-buten-1-ilo, 2-buten-2-ilo, 2-metilpropen-1-ilo o 2-metilpropen-3-ilo. Los ejemplos de alquinilo incluyen etinilo, propin-1-ilo, propin-3-ilo, 1-butin-1-ilo, 1-butin-3-ilo, 1-butin-4-ilo o 2-butin-1-ilo. Los ejemplos de alquileno incluyen metileno, 1,1-etileno, 1,2-etileno, 1,1-propileno, 1,2-propileno, 2,2-propileno y 1,3-propileno. Los ejemplos de alcoxi incluyen metoxi, etoxi, n-propoxi, i-propoxi, n-butoxi, i-butoxi, sec-butoxi y t-butoxi. Los ejemplos de cicloalquilo incluyen ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo y cicloheptilo. Cuando R^1 y R^2 se toman conjuntamente, forman, junto con el átomo de nitrógeno y el átomo de carbono del anillo de pirazol al que están unidos, un anillo de 5 ó 6 miembros. Cuando un grupo heterocíclico R^8 o R^9 está unido a un heteroátomo de oxígeno, azufre o nitrógeno, el grupo heterocíclico R^8 o R^9 tiene que estar unido a través de un átomo de carbono del anillo. Además, cuando un grupo heterocíclico R^9 está unido a un heteroátomo de oxígeno, azufre o nitrógeno, el grupo heterocíclico R^9 tiene que estar unido a través de un átomo de carbono del anillo que no sea adyacente a un heteroátomo del anillo.

Las sales farmacéuticamente aceptables de los compuestos de fórmula (I) incluyen las sales de adición de ácidos y las sales de bases de los mismos.

Las sales de adición de ácidos adecuadas se forman a

partir de ácidos que forman sales no tóxicas, y son ejemplos las sales clorhidrato, bromhidrato, yodhidrato, sulfato, bisulfato, nitrato, fosfato, fosfato ácido, acetato, maleato, fumarato, lactato, tartrato, citrato, gluconato, succinato, sacarato, benzoato, metanosulfonato, etanosulfonato, bencenosulfonato, paratoluenosulfonato y pamoato.

Las sales de bases adecuadas se forman a partir de bases que forman sales no tóxicas y son ejemplos las sales de sodio, potasio, aluminio, calcio, magnesio, cinc y dietanolamina.

Como revisión de sales adecuadas, véase Berge y col., *J. Pharm. Sci.*, 66, 1-19, 1977.

Los solvatos farmacéuticamente aceptables de los compuestos de fórmula (I) incluyen los hidratos de los mismos.

Dentro del presente alcance de los compuestos de fórmula (I) se encuentran polimorfos de los mismos.

Los compuestos de fórmula (I) pueden modificarse para proporcionar derivados farmacéuticamente aceptables de los mismos en cualquiera de los grupos funcionales de los compuestos. Se describen ejemplos de tales derivados en: Drugs of Today, Volumen 19, Número 9, 1983, páginas 499-538; Topics in Chemistry, Capítulo 31, páginas 306-316; y en "Design of Prodrugs" de H. Bundgaard, Elsevier, 1985, Capítulo 1 (cuyas descripciones se incorporan en este

documento como referencia) e incluyen: ésteres, ésteres de carbonato, hemiésteres, ésteres de fosfato, nitroésteres, ésteres de sulfato, sulfóxidos, amidas, sulfonamidas, carbamatos, azocompuestos, fosfamidas, glicósidos, éteres, acetales y cetales.

Un compuesto de fórmula (I) puede contener uno o más átomos de carbono asimétricos y, por lo tanto, puede existir en dos o más formas estereoisoméricas. La presente invención incluye los estereoisómeros individuales de los compuestos de fórmula (I) junto con, cuando sea apropiado, los tautómeros individuales de los mismos, y mezclas de los mismos.

La separación de diastereoisómeros puede conseguirse por técnicas convencionales, por ejemplo, por cristalización fraccionada, cromatografía o cromatografía líquida de alta resolución (HPLC) de una mezcla estereoisomérica de un compuesto de fórmula (I) o una sal o derivado adecuado del mismo. Un enantiómero individual de un compuesto de fórmula (I) también puede prepararse a partir de un intermedio correspondiente ópticamente puro o por resolución, tal como HPLC del correspondiente racemato usando un soporte quiral adecuado o por cristalización fraccionada de las sales diastereoisoméricas formadas por reacción del correspondiente racemato con un ácido o base ópticamente activo adecuado, según sea apropiado.

Preferiblemente, R^1, cuando se toma por separado, es H, alquilo C_1-C_6, cicloalquilo C_3-C_7 o $-OR^7$, estando dichos alquilo C_1-C_6 y cicloalquilo C_3-C_7 opcionalmente sustituidos con halo, $-CN$, $-OR^{10}$, $S(O)_xR^{10}$, $-CO_2R^{10}$, $-CONR^5R^{10}$, $-OCONR^5R^{10}$, $-NR^5CO_2R^{10}$, $-NR^{10}R^{11}$, $-NR^5COR^{10}$, $-SO_2NR^5R^{10}$, $-NR^5CONR^5R^{10}$, $-NR^5SO_2R^{10}$ o R^{10}.

Preferiblemente, R^1, cuando se toma por separado, es H, alquilo C_1-C_6, cicloalquilo C_3-C_7 o $-OR^7$, estando dicho alquilo C_1-C_6 opcionalmente sustituido con halo, $-OR^{10}$, $-NR^{10}R^{11}$, $-NR^5COR^{10}$ o R^{10}.

Preferiblemente, R^1, cuando se toma por separado, es H, alquilo C_1-C_4, ciclopropilo o $-OCH_3$, estando dicho alquilo C_1-C_4 opcionalmente sustituido con bromo, -OH, -O(alquilo C_1-C_2), $-NR^{10}R^{11}$, $-NHCOR^{13}$ o R^{10}.

Preferiblemente, R^1, cuando se toma por separado, es H, $-CH_3$, $-CH_2CH_3$, $-CH(CH_3)_2$, $-C(CH_3)_3$, ciclopropilo, $-OCH_3$, $-CH_2OH$, $-CH_2OCH_3$, $-CH_2OCH_2CH_3$, $-CH_2Br$, $-CH_2NH_2$, $-CH_2NHCH_3$, $-CH_2N(CH_3)_2$, $-CH_2NHCH_2$(ciclopropilo), $-CH_2NHCH_2CH_2OCH_3$, $-CH_2NHCH_2CH_2NHCOCH_3$, $-CH_2NHCO$(4-cianofenilo), $-CH_2NHCO$(3-cianofenilo), $-CH_2NHCH_2$(4-cianofenilo), $-CH_2NHCH_2$(4-fluorofenilo), $-CH_2NHCH_2$(4-metoxifenilo), $-CH_2NHCH_2$(4-aminosulfonilfenilo), $-CH_2NHCH_2$(4-aminocarbonilfenilo), $-CH_2NHCH_2$(pirid-3-ilo), $-CH_2N(CH_3)$(4-cianofenilmetilo), $-CH_2N(CH_2CH_2OH)$(4-cianofenilmetilo), 4-metoxipiperidin-1-ilmetilo, 4-aminocarbonilpiperidin-1-ilmetilo, 4-metilcarbonilaminopiperidin-1-ilmetilo,

piperazin-1-ilmetilo, 4-metilpiperazin-1-ilmetilo, 4-metilcarbonilpiperazin-1-ilmetilo, 4-metoximetilcarbonil-piperazin-1-ilmetilo, 4-metoxicarbonilpiperazin-1-ilmetilo, 4-metilsulfonilpiperazin-1-ilmetilo, morfolin-4-ilmetilo, 2-metilimidazol-1-ilmetilo, pirazol-1-ilmetilo o 1,2,4-triazol-1-ilmetilo.

Preferiblemente, R^1, cuando se toma por separado, es $-CH_3$, $-CH_2CH_3$, ciclopropilo, $-CH_2NHCH_2$(4-cianofenilo), $-CH_2NHCH_2$(4-fluorofenilo), $-CH_2NHCH_2$(4-metoxifenilo), $-CH_2NHCH_2$(4-aminosulfonilfenilo) o $-CH_2NHCH_2$(4-aminocarbonil-fenilo).

Preferiblemente, R^2, cuando se toma por separado, es H, alquilo C_1-C_6, alquenilo C_3-C_6 o R^9, estando dicho alquilo C_1-C_6 opcionalmente sustituido con halo, $-OR^5$, OR^{12}, $-CN$, $-CO_2R^7$, $-OCONR^5R^5$, $-CONR^5R^5$, $-C(=NR^5)NR^5OR^5$, $-CONR^5NR^5R^5$, $-NR^6R^6$, $-NR^5R^{12}$, $-NR^5COR^5$, $-NR^5COR^8$, $-NR^5COR^{12}$, $-NR^5CO_2R^5$, $-NR^5CONR^5R^5$, $-SO_2NR^5R^5$, $-NR^5SO_2R^5$, R^8 o R^9.

Preferiblemente, R^2, cuando se toma por separado, es H, alquilo C_1-C_6, alquenilo C_3-C_6 o R^9, estando dicho alquilo C_1-C_6 opcionalmente sustituido con $-OR^5$, OR^{12}, $-CN$, $-CO_2R^7$, $-CONR^5R^5$, $-C(=NR^5)NR^5OR^5$, $-CONR^5NR^5R^5$, $-NR^6R^6$, $-NR^5R^{12}$, $-NR^5COR^8$, $-NR^5COR^{12}$, $-NR^5CO_2R^5$, R^8 o R^9.

Preferiblemente, R^2, cuando se toma por separado, es H, alquilo C_1-C_3, propenilo o R^9, estando dicho alquilo C_1-C_3 opcionalmente sustituido con $-OH$, $-OCH_3$, $-OCH_2CH_2NH_2$, $-CN$,

$-CO_2CH_3$, $-CO_2CH_2CH_3$, $-CONH_2$, $-C(=NH)NHOH$, $-CONHNH_2$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-NHCH_2CH_2NHCOCH_3$, $-NHCH_2CH_2OCH_3$, $-NHCH_2R^9$, $-NHCOR^8$, $-NHCOCH_2OCH_3$, $-NHCO_2C(CH_3)_3$, R^8 o R^9.

Preferiblemente, R^2, cuando se toma por separado, es H, metilo, $-CH_2CH=CH_2$, $-CH_2CN$, $-CH_2OCH_3$, $-CH_2CONH_2$, $-CH_2CONHNH_2$, $-CH_2CO_2CH_3$, $-CH_2CO_2CH_2CH_3$, $-CH_2C(=NH)NHOH$, $-CH_2CH_2OH$, $-CH_2CH_2OCH_3$, $-CH_2CH_2NH_2$, $-CH_2CH_2NHCOCH_2OCH_3$, $-CH_2CH_2NHCO_2C(CH_3)_3$, 2-(pirid-2-ilcarbonilamino)et-1-ilo, 2-(pirazin-2-ilcarbonilamino)et-1-ilo, $-CH_2CH_2OCH_2CH_2NH_2$, $-CH_2CH_2NHCH_3$, $-CH_2CH_2N(CH_3)_2$, $-CH_2CH_2NHCH_2CH_2NHCOCH_3$, $-CH_2CH_2NHCH_2CH_2OCH_3$, $-CH_2CH(OH)CH_3$, (3-hidroxipirazol-5-il)metilo, 2-hidroxi-1,3,4-oxadiazol-5-ilmetilo, 2-amino-1,3,4-oxadiazol-5-ilo, 5-hidroxi-1,2,4-oxadiazol-3-ilmetilo, 6-hidroxi-2-metilpirimidin-4-ilmetilo, 6-hidroxi-2-aminopirimidin-4-ilmetilo, 2-(morfolin-4-il)et-1-ilo, 2-(4-metilcarbonilpiperazin-1-il)et-1-ilo, morfolin-3-ilmetilo, (2-(tetrahidrofuran-2-ilmetilamino)et-1-ilo, 1-metilazetidin-3-ilo o azetidin-3-ilo.

Preferiblemente, R^2, cuando se toma por separado, es H, $-CH_2CH_2OH$ o $-CH_2CH_2NH_2$.

Preferiblemente, R^1 y R^2, cuando se toman conjuntamente, representan alquileno C_3-C_4 lineal, opcionalmente sustituido con oxo, reemplazándose un grupo metileno de dicho alquileno C_3-C_4 por un átomo de oxígeno o un átomo de nitrógeno, estando dicho átomo de nitrógeno opcionalmente sustituido con R^{10}.

Preferiblemente, R^1 y R^2, cuando se toman conjuntamente,

representan propileno lineal, reemplazándose un grupo metileno por un átomo de oxígeno, o butileno lineal, reemplazándose un grupo metileno por un átomo de nitrógeno, estando dichos propileno y butileno opcionalmente sustituidos con oxo y estando dicho átomo de nitrógeno opcionalmente sustituido con R^{10}.

Preferiblemente, R^1 y R^2, cuando se toman conjuntamente, representan ^{x}-OCH_2CH_2-^{y}, ^{x}-$CONHCH_2CH_2$-^{y}, ^{x}-$CH_2NHCH_2CH_2$-^{y}, ^{x}-$CH_2N(CH_3)CH_2CH_2$-^{y}, ^{x}-$CH_2N(4\text{-cianofenilmetil})CH_2CH_2$-^{y} o ^{x}-$CH_2N(4\text{-metoxifenilmetil})CH_2CH_2$-^{y}, representando "x" el punto de unión al átomo de carbono del anillo de pirazol y representando "y" el punto de unión al átomo de nitrógeno del anillo de pirazol.

Preferiblemente, R^3 es H o alquilo C_1-C_6, estando dicho alquilo C_1-C_6 opcionalmente sustituido con halo, -CN, $-OR^5$, $-CO_2R^5$, $-CONR^5R^5$, $-OCONR^5R^5$, $-NR^5CO_2R^5$, $-NR^6R^6$, $-NR^5COR^5$, $-SO_2NR^5R^5$, $-NR^5CONR^5R^5$, $-NR^5SO_2R^5$, R^8 o R^9.

Preferiblemente, R^3 es H o alquilo C_1-C_6.

Preferiblemente, R^3 es H o alquilo C_1-C_4.

Preferiblemente, R^3 es H, $-CH_3$, $-CH_2CH_3$, $-CH(CH_3)_2$ o $-C(CH_3)_3$.

Preferiblemente, R^3 es $-CH_3$, $-CH_2CH_3$, $-CH(CH_3)_2$ o ciclopropilo.

Preferiblemente, R^4 es fenilo opcionalmente sustituido con R^8, halo, -CN, alquilo C_1-C_6, haloalquilo C_1-C_6,

cicloalquilo C_3-C_7 o alcoxi C_1-C_6.

Preferiblemente, R^4 es fenilo sustituido con R^8, halo, -CN, alquilo C_1-C_6, haloalquilo C_1-C_6, cicloalquilo C_3-C_7 o alcoxi C_1-C_6.

Preferiblemente, R^4 es fenilo sustituido con halo, -CN o alquilo C_1-C_6.

Preferiblemente, R^4 es fenilo sustituido con fluoro, cloro, -CN o metilo.

Preferiblemente, R^4 es 3-cianofenilo, 4-clorofenilo, 3-clorofenilo, 2-clorofenilo, 3-fluorofenilo, 2-fluorofenilo, 3,5-diclorofenilo, 2,6-diclorofenilo, 2,3-diclorofenilo, 2,4-diclorofenilo, 3,4-diclorofenilo, 2,5-diclorofenilo, 2,6-difluorofenilo, 2,3-difluorofenilo, 3,5-difluorofenilo, 2,5-difluorofenilo, 3,5-dicianofenilo, 3,5-dimetilfenilo, 4-fluoro-3-metilfenilo, 3-ciano-4-fluorofenilo, 3-ciano-5-fluorofenilo, 2-cloro-4-cianofenilo, 3-cloro-5-cianofenilo, 3-ciano-5-metilfenilo o 4-ciano-2,6-dimetilfenilo.

Preferiblemente, R^4 es 3,5-dicianofenilo, 3-ciano-5-fluorofenilo, 3-cloro-5-cianofenilo o 3-ciano-5-metilfenilo.

En una serie alternativa de preferencias:

Preferiblemente, R^4 es fenilo opcionalmente sustituido con R^8, halo, -CN, alquilo C_1-C_6, haloalquilo C_1-C_6, cicloalquilo C_3-C_7, alcoxi C_1-C_6, $-CONR^5R^5$, OR^{13}, SO_xR^6, O-(alquileno C_1-C_6)-$CONR^5R^5$, O-(alquileno C_1-C_6)-NR^5R^5 o O-(alquileno C_1-C_6)-OR^6; o naftilo.

Preferiblemente, R^4 es fenilo sustituido con R^8, halo, -CN, alquilo C_1-C_6, haloalquilo C_1-C_6, cicloalquilo C_3-C_7, alcoxi C_1-C_6, $-CONR^5R^5$, OR^{13}, SO_xR^6, O-(alquileno C_1-C_6)-$CONR^5R^5$, O-(alquileno C_1-C_6)-NR^5R^5 o O-(alquileno C_1-C_6)-OR^6.

Preferiblemente, R^8 es pirrolilo, imidazolilo, pirazolilo, 1,2,3-triazolilo, 1,2,4-triazolilo, tetrazolilo, oxazolilo, isoxazolilo, tiazolilo, isotiazolilo, 1,2,4-oxadiazolilo, 1,3,4-oxadiazolilo, furanilo, tienilo, piridinilo, piridazinilo, pirimidinilo o pirazinilo, estando cada uno opcionalmente sustituido con halo, -CN, $-COR^5$, $-CONR^5R^5$, $-SO_2NR^5R^5$, $-NR^5SO_2R^5$, $-OR^5$, $-NR^5R^5$, -(alquileno C_1-C_6)-NR^5R^5, alquilo C_1-C_6, fluoro(alquilo C_1-C_6) o cicloalquilo C_3-C_7.

Preferiblemente, R^8 es imidazolilo, pirazolilo, 1,2,4-triazolilo, 1,2,4-oxadiazolilo, 1,3,4-oxadiazolilo, piridinilo, pirazinilo o pirimidinilo, estando cada uno opcionalmente sustituido con halo, -CN, $-COR^5$, $-CONR^5R^5$, $-SO_2NR^5R^5$, $-NR^5SO_2R^5$, $-OR^5$, $-NR^5R^5$, -(alquileno C_1-C_6)-NR^5R^5, alquilo C_1-C_6, fluoroalquilo (C_1-C_6) o cicloalquilo C_3-C_7.

Preferiblemente, R^8 es imidazolilo, pirazolilo, 1,2,4-triazolilo, 1,2,4-oxadiazolilo, 1,3,4-oxadiazolilo, piridinilo, pirazinilo o pirimidinilo, estando cada uno opcionalmente sustituido con $-OR^5$, $-NR^5R^5$ o alquilo C_1-C_6.

Preferiblemente, R^8 es imidazolilo, pirazolilo, 1,2,4-triazolilo, 1,2,4-oxadiazolilo, 1,3,4-oxadiazolilo, piridinilo, pirazinilo o pirimidinilo, estando cada uno

opcionalmente sustituido con -OH, $-NH_2$ o metilo.

Preferiblemente, R^8 es pirazol-1-ilo, 2-metilimidazol-1-ilo, 1,2,4-triazol-1-ilo, 3-hidroxipirazol-5-ilo, 2-hidroxi-1,3,4-oxadiazol-5-ilo, 2-amino-1,3,4-oxadiazol-5-ilo, 5-hidroxi-1,2,4-oxadiazol-3-ilo,2-metil-4-hidroxipirimidin-6-ilo, 2-amino-4-hidroxipirimidin-6-ilo, piridin-3-ilo, piridin-2-ilo o pirazin-2-ilo.

Preferiblemente, R^9 es azetidinilo, tetrahidropirrolilo, piperidinilo, azepinilo, oxetanilo, tetrahidrofuranilo, tetrahidropiranilo, oxepinilo, morfolinilo, piperazinilo o diazepinilo, estando cada uno opcionalmente sustituido con oxo, alquilo C_1-C_6, cicloalquilo C_3-C_7, $-SO_2R^5$, $-CONR^5R^5$, $-COOR^5$, -CO-(alquileno C_1-C_6)-OR^5 o $-COR^5$ y opcionalmente sustituido en un átomo de carbono que no es adyacente a un heteroátomo con halo, $-OR^5$, $-NR^5R^5$, $-NR^5COR^5$, $-NR^5COOR^5$, $-NR^5CONR^5R^5$, $-NR^5SO_2R^5$ o -CN.

Preferiblemente, R^9 es azetidinilo, piperidinilo, tetrahidrofuranilo, piperazinilo o morfolinilo, estando cada uno opcionalmente sustituido con oxo, alquilo C_1-C_6, cicloalquilo C_3-C_7, $-SO_2R^5$, $-CONR^5R^5$, $-COOR^5$, -CO-(alquileno C_1-C_6)-OR^5 o $-COR^5$ y opcionalmente sustituido en un átomo de carbono que no es adyacente a un heteroátomo con halo, $-OR^5$, $-NR^5R^5$, $-NR^5COR^5$, $-NR^5COOR^5$, $-NR^5CONR^5R^5$, $-NR^5SO_2R^5$ o -CN.

Preferiblemente, R^9 es azetidinilo, piperidinilo, tetrahidrofuranilo, piperazinilo o morfolinilo, estando cada

uno opcionalmente sustituido con alquilo C_1-C_6, $-SO_2R^5$, $-CONR^5R^5$, $-COOR^5$, $-CO-$(alquileno C_1-C_6)$-OR^5$ o $-COR^5$ y opcionalmente sustituido en un átomo de carbono que no es adyacente a un heteroátomo con $-OR^5$ o $-NR^5COR^5$.

Preferiblemente, R^9 es azetidinilo, piperidinilo, tetrahidrofuranilo, piperazinilo o morfolinilo, estando cada uno opcionalmente sustituido con $-CH_3$, $-SO_2CH_3$, $-CONH_2$, $-COOCH_3$, $-COCH_2OCH_3$ o $-COCH_3$ y opcionalmente sustituido en un átomo de carbono que no es adyacente a un heteroátomo con $-OCH_3$ o $-NHCOCH_3$.

Preferiblemente, R^9 es 4-metoxipiperidin-1-ilo, 4-aminocarbonilpiperidin-1-ilo,4-metilcarbonilaminopiperidin-1-ilo, piperazin-1-ilo, 4-metilpiperazin-1-ilo, 4-metilcarbonilpiperazin-1-ilo, 4-metoximetilcarbonilpiperazin-1-ilo, 4-metoxicarbonilpiperazin-1-ilo, 4-metilsulfonil-piperazin-1-ilo, morfolin-4-ilo, tetrahidrofuran-2-ilo, morfolin-3-ilo, azetidin-3-ilo o 1-metilazetidin-3-ilo.

Preferiblemente, R^{10} es H, R^8, R^9, R^{13}, alquilo C_1-C_6 o -(alquil C_1-C_6)-(cicloalquilo C_3-C_7), estando dicho alquilo C_1-C_6 opcionalmente sustituido con $-OR^5$, $-OR^{13}$, R^8, R^9, R^{13} o $-COR^{13}$.

Preferiblemente, R^{10} es H, R^8, R^9, R^{13}, alquilo C_1-C_6 o -(alquil C_1-C_6)-(cicloalquilo C_3-C_7), estando dicho alquilo C_1-C_6 opcionalmente sustituido con $-OR^5$ o R^{13}.

Preferiblemente, R^{10} es H, R^8, R^9, R^{13}, $-CH_3$, $-CH_2CH_3$ o $-CH_2$(ciclopropilo), estando dicho $-CH_3$ y $-CH_2CH_3$ opcionalmente

sustituido con $-OCH_3$ o R^{13}.

Preferiblemente, R^{10} es H, R^8, R^9, R^{13}, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2OCH_3$, $-CH_2$(ciclopropilo), 4-cianofenilmetilo, 4-fluorofenilmetilo, 4-metoxifenilmetilo, 4-aminosulfonil-fenilmetilo o 4-aminocarbonilfenilmetilo.

Preferiblemente, R^{11} es H o alquilo C_1-C_6, estando dicho alquilo C_1-C_6 opcionalmente sustituido con $-OR^5$, $-NR^5R^5$, $-NR^5COR^5$, $-CONR^5R^5$, R^8 o R^9.

Preferiblemente, R^{11} es H o alquilo C_1-C_6, estando dicho alquilo C_1-C_6 opcionalmente sustituido con $-OR^5$ o $-NR^5COR^5$.

Preferiblemente, R^{11} es H, $-CH_3$ o $-CH_2CH_3$, estando dichos $-CH_3$ o $-CH_2CH_3$ opcionalmente sustituidos con $-OH$ o $-NHCOCH_3$.

Preferiblemente, R^{11} es H, $-CH_3$, $CH_2CH_2NHCOCH_3$ o $-CH_2CH_2OH$.

Preferiblemente, R^{12} es alquilo C_1-C_4 sustituido con R^8, R^9, $-OR^5$, $-CONR^5R^5$, $-NR^5COR^5$ o $-NR^5R^5$.

Preferiblemente, R^{12} es alquilo C_1-C_4 sustituido con R^9, $-OR^5$, $-NR^5COR^5$ o $-NR^5R^5$.

Preferiblemente, R^{12} es alquilo C_1-C_2 sustituido con tetrahidrofuranilo, $-OCH_3$, $-NHCOCH_3$ o $-NH_2$.

Preferiblemente, R^{12} es $-CH_2CH_2NH_2$, $-CH_2CH_2OCH_3$, tetrahidrofuran-2-ilmetilo, $-CH_2CH_2NHCOCH_3$ o $-CH_2OCH_3$.

Preferiblemente, R^{13} es fenilo sustituido con halo, $-CN$, $-COR^5$, $-CONR^5R^5$, $-SO_2NR^5R^5$, $-NR^5SO_2R^5$, $-OR^5$, $-NR^5R^5$, -(alquileno C_1-C_6)-NR^5R^5, alquilo C_1-C_6, haloalquilo(C_1-C_6) o cicloalquilo C_3-C_7.

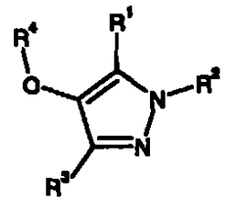
Preferiblemente, R^{13} es fenilo sustituido con halo, -CN, $-CONR^5R^5$, $-SO_2NR^5R^5$ o $-OR^5$.

Preferiblemente, R^{13} es fenilo sustituido con fluoro, -CN, $-CONH_2$, $-SO_2NH_2$ o $-OCH_3$.

Preferiblemente, R^{13} es 4-cianofenilo, 3-cianofenilo, 4-fluorofenilo, 4-metoxifenilo, 4-aminocarbonilfenilo o 4-aminosulfonilfenilo.

Los grupos preferidos de compuestos de acuerdo con la invención incluyen todas las combinaciones de las definiciones preferidas de sustituyentes individuales proporcionados anteriormente.

De acuerdo con la invención, también se prefieren los compuestos de fórmula (I)



(I)

o una sal, solvato o derivado farmacéuticamente aceptable de los mismos, en la que:

R^1 es H, alquilo C_1-C_6, -Oalquilo C_1-C_6, -Ocicloalquilo C_3-C_7, estando dicho alquilo C_1-C_6 opcionalmente sustituido con R^{15};

R^2 es H, alquilo C_1-C_3, propenilo o R^{15} unido a C, estando dicho alquilo C_1-C_3 opcionalmente sustituido con -OH, $-OCH_3$,

$-OCH_2CH_2NH_2$, $-CN$, $-CO_2CH_3$, $-CONH_2$, $-C(=NH)NH_2$, $-CONHNH_2$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-NHCH_2CH_2NHCOCH_3$, $-NHCH_2CH_2OCH_3$, $-NHCH_2R^{15}$, $-NHCOR^{15}$, $-NHCOCH_2OCH_3$ o R^{15};

R^3 es alquilo C_1-C_6;

R^4 es fenilo opcionalmente sustituido con halo, -CN, alquilo C_1-C_6, haloalquilo C_1-C_6, cicloalquilo C_3-C_7 o alcoxi C_1-C_6; y

R^{15} es azetidinilo, tetrahidrofuranilo, morfolinilo, piperazinilo, pirazolilo, oxadiazolilo, piridinilo o pirimidinilo, estando cada uno opcionalmente sustituido con $-OH$, $-NH_2$, oxo o alquilo C_1-C_6 o -CO(alquilo C_1-C_6).

Los compuestos individuales preferidos de acuerdo con la invención incluyen los Ejemplos presentados más adelante, particularmente los Ejemplos 117, 118, 119, 120, 122, 123, 124, 125, 126, 127 y 128, y las sales y solvatos farmacéuticamente aceptables de los mismos.

Todos los compuestos de fórmula (I) pueden prepararse por rutas convencionales tales como los procedimientos descritos en los procedimientos generales presentados más adelante, por los procedimientos específicos descritos en la sección de Ejemplos, o por procedimientos similares a los mismos. La presente invención también incluye uno cualquiera o más de estos procedimientos para preparar los compuestos de fórmula (I), además de cualquier nuevo intermedio usado en estos procedimientos.

En los siguientes procedimientos generales, R^1, R^2, R^3 y R^4 son como se han definido previamente para un compuesto de fórmula (I), a menos que se indique otra cosa.

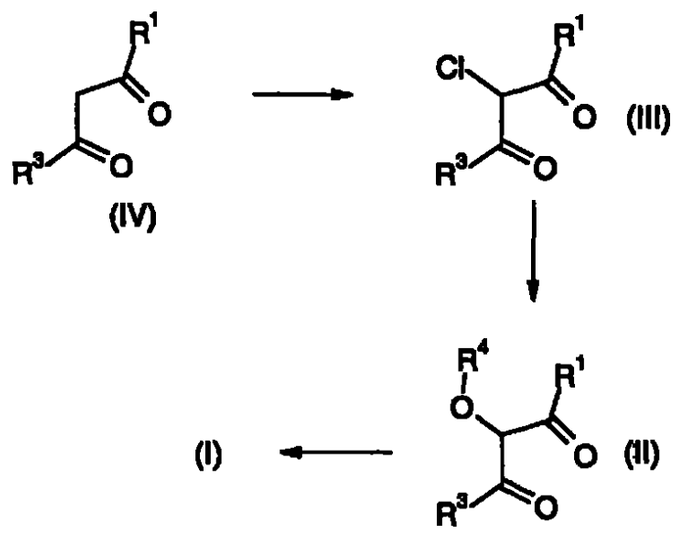
Excepto cuando R^1 o R^3 es halo, $-OR^8$ o -CN, los compuestos de fórmula (I) pueden prepararse usando la ruta mostrada en el Esquema 1 que se presenta a continuación.

En el Esquema 1, los compuestos de fórmula (I) pueden prepararse por la condensación de un compuesto de fórmula (II) con un compuesto de fórmula

$$H_2NNHR^2 \quad (V),$$

o una sal o hidrato del mismo, opcionalmente en presencia de un ácido o una base, siendo la base preferiblemente una base de amina terciaria, tal como trietilamina, y siendo el ácido preferiblemente ácido acético. En un procedimiento típico, una solución del compuesto de fórmula (II) en un disolvente adecuado, tal como etanol, se trata con el compuesto de fórmula (V), o la sal o hidrato del mismo, y, si se usa, el ácido o base apropiado, a una temperatura de la temperatura ambiente a la temperatura de reflujo del disolvente. En un procedimiento preferido, la mezcla de reacción se calienta a reflujo.

Esquema 1



También pueden usarse equivalentes funcionales de compuestos de fórmula (II) en esta reacción. Éstos incluyen compuestos de fórmula (VI) o (VII), en las que L^1 y L^2, respectivamente, son grupos salientes adecuados, preferiblemente -N(alquilo C_1-C_6)$_2$, más preferiblemente -N$(CH_3)_2$.

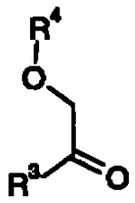


De esta forma, un compuesto de fórmula (I) puede

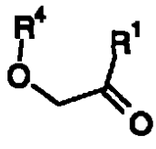
prepararse por la condensación de un compuesto de fórmula (VI) o (VII) con un compuesto de fórmula (V), o una sal o hidrato del mismo, opcionalmente en presencia de un ácido o una base, siendo la base preferiblemente una base de amina terciaria, tal como trietilamina, y siendo el ácido preferiblemente ácido acético. En un procedimiento típico, una solución del compuesto de fórmula (VI) o (VII) en un disolvente adecuado, tal como etanol, se trata con el compuesto de fórmula (V), o la sal o hidrato del mismo, y, si se usa, el ácido o base apropiado, a una temperatura de la temperatura ambiente a la temperatura de reflujo del disolvente. En un procedimiento preferido, la mezcla de reacción se calienta a reflujo. Los compuestos de fórmula (VI) o (VII) son particularmente adecuados para la síntesis de compuestos de fórmula (I) en la que R^1 o R^3 es, respectivamente, H.

Los compuestos de fórmula (VI) en la que R^1 es H y L^1 es dimetilamino pueden prepararse por la reacción de un compuesto de fórmula (VIII) con dimetilacetal de dimetilformamida a una temperatura elevada, preferiblemente a aproximadamente 100°C. Los compuestos de fórmula (VII) en la que R^1 es H y L^1 es dimetilamino pueden prepararse por la reacción de un compuesto de fórmula (IX) en las mismas condiciones. Otros compuestos de fórmula (VI) o (VII) en las que L^1 o L^2 es dimetilamino pueden prepararse por

procedimientos análogos.



(VIII)



(IX)

Los compuestos de fórmula (VIII) están disponibles en el mercado o pueden prepararse por la reacción de un compuesto de fórmula

$$R^3COCH_2Br \quad (X)$$

con un compuesto de fórmula

$$R^4OH \quad (XI).$$

En un procedimiento típico, una solución del compuesto de fórmula (XI) en un disolvente adecuado, tal como acetona, se trata con una base adecuada, tal como carbonato de cesio, y el compuesto de fórmula (X). En un procedimiento preferido, la mezcla de reacción se calienta, por ejemplo, a reflujo. Opcionalmente, puede añadirse un catalizador nucleófilo, tal como yoduro sódico o yoduro de tetrabutilamonio.

Los compuestos de fórmula (IX) están disponibles en el mercado o pueden prepararse a partir de un compuesto de fórmula

$$R^1COCH_2Br \quad (XII)$$

y un compuesto de fórmula (XI) de la misma forma que un

compuesto de fórmula (VIII) puede prepararse a partir de un compuesto de fórmula (X).

Los compuestos de fórmula (II) pueden prepararse por la reacción de un compuesto de fórmula (III) con un compuesto de fórmula (XI).

En un procedimiento típico, una solución del compuesto de fórmula (III) en un disolvente adecuado, tal como acetona, se trata con un compuesto de fórmula (XI) y una base adecuada, tal como carbonato potásico o de cesio, y se calienta, preferiblemente a reflujo. Opcionalmente, puede añadirse un catalizador nucleófilo, tal como yoduro sódico o yoduro de tetrabutilamonio.

Los compuestos de fórmula (III) están disponibles en el mercado o pueden prepararse por la reacción de un compuesto de fórmula (IV) con un reactivo de cloración. En un procedimiento típico, una solución enfriada del compuesto de fórmula (IV) en un disolvente adecuado tal como acetonitrilo se trata primero con bromuro de tetrabutilamonio y clorotrimetilsilano y después con dimetilsulfóxido seco. En otro procedimiento típico, el compuesto de fórmula (IV) se trata con cloruro de sulfurilo, opcionalmente en presencia de un disolvente adecuado tal como diclorometano.

Los compuestos de fórmula (I) en la que R^1 o R^3 es $-OR^8$ pueden prepararse usando la ruta mostrada en el Esquema 2 que se indica a continuación, en el que R^8 es alquilo C_1-C_6 y L^3

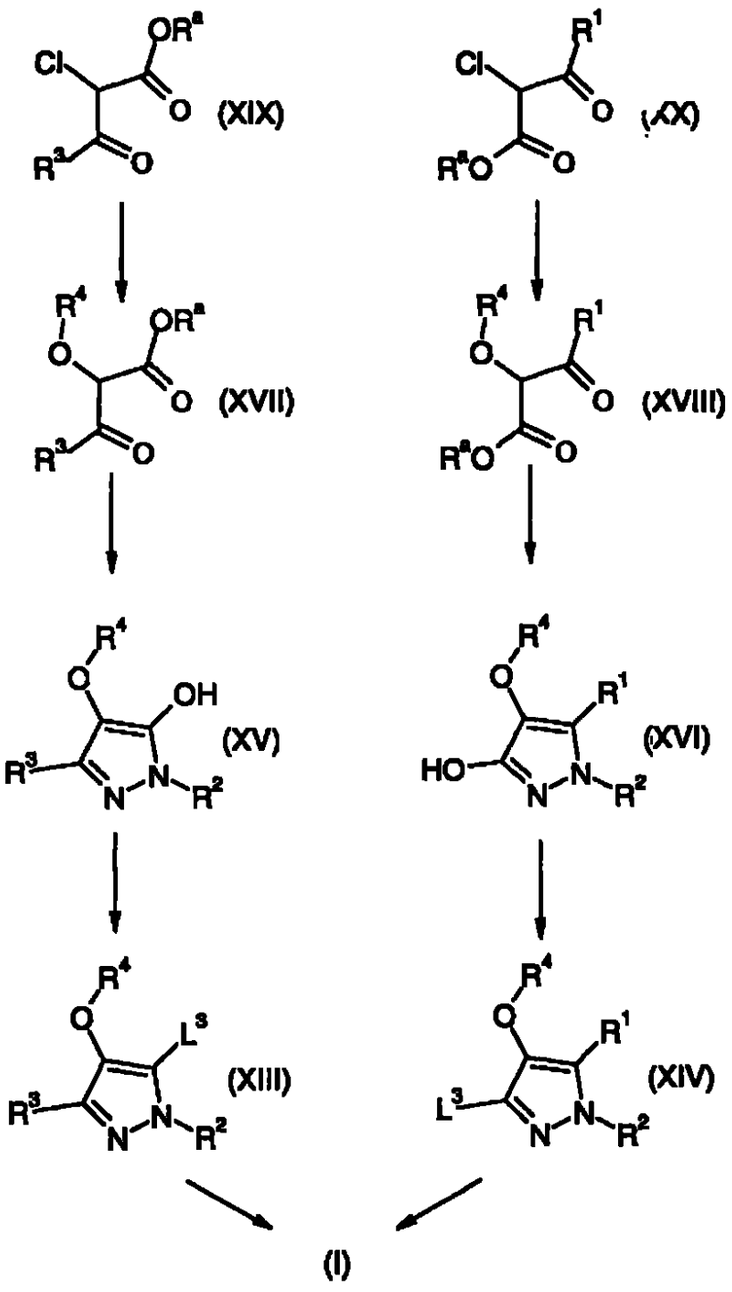
es un grupo saliente adecuado, preferiblemente trifluorometanosulfonato.

En el Esquema 2, los compuestos de fórmula (I) en la que R^1 es $-OR^8$ pueden prepararse por la reacción de un compuesto de fórmula (XIII) con un alcohol de fórmula

$$R^8OH \quad (XXI)$$

en presencia de un catalizador de paladio adecuado y monóxido de carbono. En un procedimiento típico, una mezcla del compuesto de fórmula (XIII), un catalizador de paladio adecuado tal como cloruro de 1,1'-bis(difenilfosfino) ferrocenopaladio(II), el alcohol de fórmula (XXI) y, opcionalmente, un disolvente adecuado tal como N,N-dimetilformamida, se calienta, preferiblemente a aproximadamente 50°C, en una atmósfera de monóxido de carbono, preferiblemente a una presión de 345 kPa.

Esquema 2



Los compuestos de fórmula (XIII) pueden prepararse por la modificación de un compuesto de fórmula (XV). En el caso en el que L^3 es trifluorometanosulfonato, un agente de modificación adecuado es feniltriflamida. En un procedimiento típico, en el que L^3 es trifluorometanosulfonato, una solución del compuesto de fórmula (XV) y una base adecuada, preferiblemente una base de trialquilamina tal como trietilamina, en un disolvente adecuado tal como diclorometano, se trata con feniltriflamida.

El compuesto de fórmula (XV) puede prepararse por la reacción de un compuesto de fórmula (XVII) con un compuesto de fórmula (V), o una sal o hidrato del mismo, opcionalmente en presencia de un ácido o una base, siendo la base preferiblemente una base de amina terciaria tal como trietilamina y siendo el ácido preferiblemente ácido acético. En un procedimiento típico, una solución del compuesto de fórmula (XVII) en un disolvente adecuado, tal como etanol, se trata con el compuesto de fórmula (V), o la sal o hidrato del mismo, y, si se usa, el ácido o base apropiado, a una temperatura de aproximadamente la temperatura ambiente a la temperatura de reflujo del disolvente. En un procedimiento preferido, la mezcla de reacción se calienta a reflujo.

Los compuestos de fórmula (XVII) pueden prepararse por la reacción de un compuesto de fórmula (XIX) con un compuesto de fórmula (XI). En un procedimiento típico, una solución del

compuesto de fórmula (XVII) en un disolvente adecuado tal como acetona se trata con un compuesto de fórmula (XI) y una base adecuada, tal como carbonato de cesio o potásico, y se calienta, preferiblemente a reflujo. Opcionalmente, puede añadirse un catalizador nucleófilo tal como yoduro sódico o yoduro de tetrabutilamonio.

En el Esquema 2, los compuestos de fórmula (I) en la que R^3 es $-OR^8$ pueden prepararse a partir de un compuesto de fórmula (XX) de la misma forma que un compuesto de fórmula (I) en la que R^1 es $-OR^8$ se prepara a partir de un compuesto de fórmula (XIX) como se ha indicado anteriormente, *mutatis mutandis*.

Los clorocetoésteres de fórmula (XIX) y (XX) están disponibles en el mercado o pueden prepararse por la cloración de los correspondientes cetoésteres, por ejemplo, usando cloruro de sulfonilo.

Como alternativa, los compuestos de fórmula (I) en la que R^1 o R^3 es $-OR^8$ pueden prepararse a partir de compuestos de fórmula (XV) o (XVI), respectivamente, por reacción con un compuesto de fórmula (XXI) en condiciones de deshidratación, por ejemplo, usando la reacción de Mitsunobu. En un procedimiento típico, una solución del compuesto de fórmula (XV) o (XVI) en un disolvente adecuado, tal como tetrahidrofurano, se trata con azodicarboxilato de dietilo, trifenilfosfina y un compuesto de fórmula (XXI).

Los compuestos de fórmula (I) en la que R^1 o R^3 es halo pueden prepararse por la reacción, respectivamente, de un compuesto de fórmula (XV) o un compuesto de fórmula (XVI) con un agente de halogenación adecuado. En un procedimiento típico, el compuesto de fórmula (XV) o (XVI) se trata con $POCl_3$, opcionalmente en presencia de un disolvente adecuado tal como dimetilformamida, para dar un compuesto de fórmula (I) en la que R^1 o R^3, respectivamente, es cloro.

Los especialistas en la técnica apreciarán que, en muchos casos, los compuestos de fórmula (I) pueden convertirse en otros compuestos de fórmula (I) por transformaciones de grupos funcionales. Por ejemplo:

(a) los compuestos de fórmula (I) en la que R^2 es H, pueden convertirse en compuestos de fórmula (I) en la que R^2 es alquilo C_1-C_6 opcionalmente sustituido, por reacción con un agente alquilante apropiado. En un procedimiento típico, una solución de un compuesto de fórmula (I) en la que R^2 es H en un disolvente adecuado tal como etanol o N,N-dimetilformamida, se trata con bromuro de alquilo y una base tal como etóxido sódico o hidruro sódico y se calienta a una temperatura de la temperatura ambiente a la temperatura de reflujo del disolvente. Una combinación preferida es N,N-dimetilformamida como disolvente, hidruro sódico como base y la temperatura ambiente como la temperatura. Los ejemplos de agentes alquilantes específicos incluyen

bromoacetonitrilo, 4-cloroacetoacetato de etilo, bromoacetato de metilo y clorhidrato de cloroetilamina. El uso de otros agentes alquilantes específicos se ilustra en los Ejemplos proporcionados más adelante;

(b) los compuestos de fórmula (I) en la que R^1, R^2 o R^3 contiene una funcionalidad éster, pueden reducirse con un agente reductor adecuado, tal como hidruro de litio y aluminio, para dar los correspondientes compuestos de fórmula (I) en la que R^1, R^2 o R^3 contiene un grupo hidroxi. En un procedimiento típico, una solución del compuesto de fórmula (I) en la que R^1, R^2 o R^3 contiene un grupo éster, en un disolvente adecuado tal como éter dietílico, se trata con hidruro de litio y aluminio, preferiblemente con refrigeración a una temperatura de -78°C a 0°C;

(c) los compuestos de fórmula (I) en la que R^1, R^2 o R^3 están sustituidos con un heterociclo de fórmula R^6, pueden prepararse por reacciones convencionales de formación de heterociclos bien conocidas para los especialistas (véase, por ejemplo, Advanced Organic Chemistry, 3ª Edición, de Gerry March o Comprehensive Heterocyclic Chemistry, A.R. Katritzky, C.W. Rees, E.F.V. Scriven, Volúmenes 1-11). Por ejemplo, los compuestos de fórmula (I) en la que R^2 es (2-amino-6-hidroxipirimidin-4-il)metilo pueden prepararse por la reacción secuencial de un compuesto de fórmula (I) en la que R^2 es H con cloroacetoacetato y después clorhidrato de

guanidina. Estas y otras reacciones de formación de heterociclos similares se ilustran por los Ejemplos proporcionados más adelante; y

(d) los compuestos de fórmula (I) en la que R^1 o R^3 es $-CO_2R^5$, siendo R^5 distinto de H, pueden convertirse en compuestos de fórmula (I) en la que R^1 o R^3, respectivamente, es $-CO_2H$, por hidrólisis. Típicamente, la reacción se realizará en un disolvente adecuado, tal como etanol acuoso o 1,4-dioxano acuoso, y en presencia de una base tal como hidróxido sódico. Tal ácido puede convertirse en una amida primaria por reacción con amoniaco y un agente de acoplamiento adecuado, tal como una carbodiimida, por ejemplo, diciclohexilcarbodiimida. Tal amida primaria después puede convertirse en un nitrilo por deshidratación con un agente deshidratante adecuado, tal como cloruro de fosforilo.

(e) los compuestos de fórmula (I) en la que R^1 o R^3 es alquilo C_1-C_6 pueden convertirse en compuestos de fórmula (I) en la que R^1 o R^3, respectivamente, es alquilo C_1-C_6 sustituido con halo (tal como bromo), por halogenación, usando un agente de halogenación adecuado. Convenientemente, la reacción se realiza en presencia de un disolvente, tal como un haloalcano (por ejemplo, diclorometano) y a temperatura ambiente. Los agentes de halogenación adecuados incluyen halógenos (por ejemplo, bromo) o N-halosuccinimidas (por ejemplo, N-bromosuccinimida).

Los compuestos de fórmula (I) que contienen un grupo -OH, -NH- o $-NH_2$ pueden prepararse por desprotección del correspondiente compuesto que lleva un grupo $-OP^1$, $-NP^1-$ o $-NHP^1$, respectivamente, siendo el grupo P^1 un grupo protector adecuado. Los ejemplos de grupos protectores adecuados serán evidentes para los especialistas [véase, por ejemplo, "Protecting Groups in Organic Synthesis (Second Edition)" de Theodora W. Green y Peter G.M. Wuts, 1991, John Wiley and Sons]. Tales compuestos que llevan un grupo $-OP^1$, $-NP^1-$ o $-NHP^1$ pueden prepararse usando las rutas descritas anteriormente, *mutatis mutandis*.

Los compuestos de fórmula (IV), (V) y (XXI) están disponibles en el mercado o se preparan fácilmente por procedimientos bien conocidos por los especialistas en la técnica.

Los compuestos de fórmula (I) pueden administrarse solos, pero generalmente se administrarán en mezcla con un excipiente, diluyente o vehículo farmacéutico adecuado seleccionado en relación con la vía de administración para la que están destinados y la práctica farmacéutica convencional.

Por ejemplo, los compuestos de fórmula (I) pueden administrarse por vía oral, bucal o sublingual, en forma de comprimidos, cápsulas, multiparticulados, geles, películas, óvulos, elixires, soluciones o suspensiones, que pueden

contener agentes aromatizantes o colorantes, para aplicaciones de liberación inmediata, retrasada, modificada, sostenida, pulsátil o controlada. Los compuestos de fórmula (I) también pueden administrarse como formas de dosificación de dispersión rápida o de disolución rápida, en forma de una dispersión de alta energía, o como partículas recubiertas. Las formulaciones adecuadas de los compuestos de fórmula (I) pueden estar en forma recubierta o no recubierta, según se desee.

Tales composiciones farmacéuticas sólidas, por ejemplo, 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 almidón glicolato sódico, croscarmelosa sódica y ciertos silicatos complejos, y aglutinantes de granulación tales como polivinilpirrolidona, hidroxipropilmetilcelulosa (HPMC), hidroxipropilcelulosa (HPC), sacarosa, gelatina y goma arábiga. Además, pueden incluirse agentes lubricantes tales como estearato de magnesio, ácido esteárico, behenato de glicerilo y talco.

Ejemplo General

Una formulación del comprimido típicamente puede contener de 0,01 mg a 500 mg de compuesto activo, mientras que los pesos de relleno de los comprimidos pueden variar de

50 mg a 1000 mg. A continuación se ilustra un ejemplo de una formulación para un comprimido de 10 mg:

Ingrediente	% p/p
Compuesto de fórmula (I) o sal	10,000*
Lactosa	64,125
Almidón	21,375
Croscarmelosa sódica	3,000
Estearato de Magnesio	1,500

* Cantidad ajustada de acuerdo con la actividad del fármaco.

Los comprimidos se fabrican por un procedimiento convencional, por ejemplo, por compresión directa o por un procedimiento de granulación en húmedo o en seco. Los núcleos de los comprimidos pueden recubrirse con recubrimientos apropiados.

También pueden emplearse composiciones sólidas de tipo similar como cargas en cápsulas de gelatina o de HPMC. Los excipientes preferidos a este respecto incluyen lactosa, almidón, una celulosa, azúcar de la leche o polietilenglicoles de alto peso molecular. Para las suspensiones acuosas y/o elixires, los compuestos de fórmula (I) pueden combinarse con diversos agentes edulcorantes o aromatizantes, materiales colorantes o tintes, con agentes emulsionantes y/o de suspensión, y con diluyentes tales como agua, etanol, propilenglicol y glicerina, y combinaciones de los mismos.

Los compuestos de fórmula (I) también pueden administrarse por vía parenteral, por ejemplo, intravenosa, intraarterial, intraperitoneal, intratecal, intraventricular, intrauretral, intraesternal, intracraneal, intramuscular subcutánea, o pueden administrarse por infusión o por técnicas de inyección sin aguja. Para tal administración parenteral, se usan de la mejor manera en forma de una solución acuosa estéril que puede contener otras sustancias, por ejemplo, suficientes sales o glucosa como para hacer que la solución sea isotónica con la sangre. Las soluciones acuosas deben tamponarse convenientemente (preferiblemente a un pH de 3 a 9), si es necesario. La preparación de formulaciones parenterales adecuadas en condiciones estériles se realiza fácilmente por técnicas farmacéuticas convencionales bien conocidas para los especialistas en la técnica.

Para la administración oral y parenteral a pacientes humanos, el nivel de dosificación diario de los compuestos de fórmula (I) normalmente será de 0,01 a 30 mg/kg, preferiblemente de 0,01 a 5 mg/kg (en una sola dosis o en dosis divididas).

De esta forma, los comprimidos o cápsulas del compuesto de fórmula (I) pueden contener de 1 a 500 mg de compuesto activo para la administración de una sola unidad o de dos o más de una vez, según sea apropiado. En cualquier caso, el

médico determinará la dosis real más adecuada para cualquier paciente individual, y ésta variará con la edad, peso y respuesta del paciente particular. Las dosis anteriores son ejemplos del caso medio. Por supuesto, puede haber casos particulares en los que se requieran intervalos de dosificación superiores o inferiores, y tales casos están dentro del alcance de esta invención. La persona especialista apreciará que, en el tratamiento de ciertas afecciones, los compuestos de fórmula (I) pueden tomarse como una sola dosis cuando sea necesario o se desee.

Los compuestos de fórmula (I) también pueden administrarse por vía intranasal o por inhalación y convenientemente se liberan en forma de un inhalador de polvo seco o una presentación de pulverización de aerosol desde un recipiente a presión, bomba, pulverización, atomizador o nebulizador, con o sin el uso de un propulsor adecuado, por ejemplo, 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 a presión, la unidad de dosificación puede determinarse proporcionando una válvula para liberar una cantidad medida. El recipiente a presión, bomba, pulverizador, atomizador o nebulizador puede contener una

solución o suspensión del compuesto activo, por ejemplo, usando una mezcla de etanol y el propulsor como disolvente, y puede contener además un lubricante, por ejemplo, trioleato de sorbitán. Pueden formularse cápsulas y cartuchos (fabricados, por ejemplo, con gelatina) para uso en un inhalador o insuflador para que contengan una mezcla en polvo de un compuesto de fórmula (I) y una base en polvo adecuada, tal como lactosa o almidón.

Como alternativa, los compuestos de fórmula (I) pueden administrarse en forma de un supositorio o pesario, o pueden aplicarse tópicamente en forma de un gel, hidrogel, loción, solución, crema, pomada o polvo fino. Los compuestos de fórmula (I) también pueden administrarse dérmica o transdérmicamente, por ejemplo, por medio del uso de un parche cutáneo. También pueden administrarse por vía pulmonar o rectal.

También pueden administrarse por vía ocular. Para uso oftálmico, los compuestos pueden formularse en forma de suspensiones micronizadas en solución salina isotónica, con el pH ajustado, o preferiblemente, como soluciones en solución salina isotónica con el pH ajustado, opcionalmente en combinación con un conservante tal como cloruro de benzalconio. Como alternativa, pueden formularse en una pomada tal como vaselina.

Para aplicación tópica a la piel, los compuestos de

fórmula (I) pueden formularse como una pomada adecuada que contiene el compuesto activo suspendido o disuelto en, por ejemplo, una mezcla con uno o más de los siguientes: aceite mineral, vaselina líquida, vaselina blanca, propilenglicol, compuesto de polioxietileno y polioxipropileno, cera emulsionante y agua. Como alternativa, pueden formularse en forma de una loción o crema adecuada, suspendidos o disueltos en, por ejemplo, una mezcla de uno o más de los siguientes: aceite mineral, monoestearato de sorbitán, un polietilenglicol, parafina líquida, polisorbato 60, cera de ésteres cetílicos, alcohol cetearílico, 2-octildodecanol, alcohol bencílico y agua.

Los compuestos de fórmula (I) también pueden usarse en combinación con una ciclodextrina. Se sabe que las ciclodextrinas forman complejos de inclusión y complejos que no son de inclusión con moléculas de fármaco. La formación de un complejo de fármaco-ciclodextrina puede modificar la solubilidad, la velocidad de disolución, la biodisponibilidad y/o la propiedad de estabilidad de una molécula de fármaco. Los complejos de fármaco-ciclodextrina generalmente son útiles para la mayoría de las formas de dosificación y vías de administración. Como alternativa a la formación directa de complejos con el fármaco, la ciclodextrina puede usarse como aditivo auxiliar, por ejemplo, como vehículo, diluyente o solubilizante. Las alfa-, beta- y gamma-ciclodextrinas son

las usadas más comúnmente y se describen ejemplos adecuados en los documentos WO-A-91/11172, WO-A-94/02518 y WO-A-98/55148.

Se apreciará que todas las referencias en este documento al tratamiento incluyen el tratamiento curativo, paliativo y profiláctico.

Se prefiere la administración oral.

Dentro del alcance de la presente invención se incluyen realizaciones que comprenden la coadministración de un compuesto de la presente invención con uno o más agentes terapéuticos adicionales, y composiciones que contienen un compuesto de la presente invención junto con uno o más agentes terapéuticos adicionales. Tal terapia de combinación es especialmente útil para la prevención y/o tratamiento de la infección por VIH y retrovirus relacionados que pueden producir rápidamente cepas resistentes a cualquier monoterapia. Como alternativa, pueden ser deseables agentes terapéuticos adicionales para tratar enfermedades y afecciones que resultan o acompañan a la enfermedad que se está tratando con el compuesto de la presente invención. Por ejemplo, en el tratamiento de una infección por VIH o por retrovirus relacionados, puede ser deseable tratar adicionalmente infecciones oportunistas, neoplasmas y otras afecciones que se producen como resultado del estado inmunocomprometido del paciente que se está tratando.

Las combinaciones preferidas de la presente invención incluyen el tratamiento simultáneo o secuencial con un compuesto de fórmula (I), como se ha definido anteriormente, o una sal farmacéuticamente aceptable del mismo, y:

(a) uno o más inhibidores de la transcriptasa inversa, tales como zidovudina, didanosina, zalcitabina, estavudina, lamivudina, abacavir y adefovir;

(b) uno o más inhibidores de transcriptasa inversa no nucleosídicos tales como nevirapina, delavirdina y efavirenz;

(c) uno o más inhibidores de la proteasa de VIH tales como indanivir, ritonavir, saquinavir y nelfinavir;

(d) uno o más antagonistas de CCR5 tales como TAK-779;

(e) uno o más antagonistas de CXCR4 tales como AMD-3100;

(f) uno o más inhibidores de integrasa;

(g) uno o más inhibidores de la fusión viral, tales como T-20;

(h) uno o más fármacos de investigación tales como trizivir, KNI-272, amprenavir, GW-33908, FTC, PMPA, S-1153, MKC-442, MSC-204, MSH-372, DMP450, PNU-140690, ABT-378, KNI-764, DPC-083, TMC-120 o TMC-125; o

(i) uno o más agentes antifúngicos o antibacterianos, tales como fluconazol.

La actividad de los compuestos de la invención como inhibidores de la transcriptasa inversa y como agentes para tratar las infecciones por VIH puede medirse usando los

siguientes ensayos.

A. Inhibición de la enzima transcriptasa inversa de VIH-1

La actividad sobre la transcriptasa inversa de los compuestos de la invención puede ensayarse como se indica a continuación. Usando la transcriptasa inversa de VIH-1 recombinante purificada (RT, EC, 2.7.7.49) obtenida por expresión en Escherichia coli, se estableció un sistema de ensayo en una placa de 96 pocillos para ensayar un gran número de muestras usando el sistema de ensayo de enzima Poly(rA)-oligo(dT) Reverse Transcriptase [3H]-SPA (Amersham NK9020) o el sistema de ensayo de enzima [3H]-flashplate (NEN-SMP 103) y siguiendo las recomendaciones del fabricante. Los compuestos se disolvieron en DMSO al 100% y se diluyeron con el tampón apropiado hasta una concentración final de DMSO del 5%. La actividad inhibidora se expresó en porcentaje de inhibición con respecto al control de DMSO. La concentración a la que el compuesto inhibía la transcriptasa inversa en un 50% se expresó como CI_{50} del compuesto. Los compuestos de los ejemplos 7, 20 y 51, cuando se ensayaron de acuerdo con el procedimiento anterior, tuvieron valores de CI_{50} de, respectivamente, 39000, 3200 y 248 nanomolar.

B. Ensayo en cultivo de células de la actividad contra el Virus de la Inmunodeficiencia Humana (VIH-1)

La actividad anti-VIH de Ejemplos seleccionados de la invención se ensayó por los siguientes procedimientos.

1) Se cultivaron células SupT1 en un medio RPMI-1640 suplementado con un 10% de suero de ternero fetal y se dividieron de forma que estuvieran en la fase de crecimiento en el día de uso.

2) Los compuestos se disolvieron en DMSO al 100% y se diluyeron con el medio de cultivo anterior a concentraciones predeterminadas y se distribuyeron en alícuotas de 20 µl en una placa de 96 pocillos (concentración final de DMSO 0,1%).

3) Para preparar las células infectadas, se añadieron 100 µl de virus RF (TCID50 de 10^7/ml) a 10^6 células y se incubaron durante 1 hora a 37°C. Las células después se lavaron dos veces en PBS y se resuspendieron en el medio de cultivo a una densidad de 2,2 x 10^5 células/ml. 180 µl de estas células infectadas se transfirieron a pocillos de la placa de 96 pocillos que contenían los compuestos.

4) La placa se incubó en un incubador de CO_2 a 37°C durante 4 días. Los porcentajes de supervivencia de las células se midieron siguiendo las recomendaciones del fabricante (CellTiter 96® AQ_{ueous} Non-Radioactive Assay - Promega (n° de catálogo: G5430)). La concentración a la que el compuesto inhibía el efecto citotóxico del virus en un 50% se expresó como la CE_{50}.

De esta forma, la invención proporciona:

(i) un compuesto de fórmula (I) o una sal, solvato o derivado farmacéuticamente aceptable del mismo;

(ii) un procedimiento para la preparación de un compuesto de fórmula (I) o una sal, solvato o derivado farmacéuticamente aceptable del mismo;

(iii) una composición farmacéutica que incluye un compuesto de fórmula (I) o una sal, solvato o derivado farmacéuticamente aceptable del mismo, junto con un excipiente, diluyente o vehículo farmacéuticamente aceptable;

(iv) un compuesto de fórmula (I) o una sal, solvato o composición farmacéuticamente aceptable del mismo, para uso como un medicamento;

(v) un compuesto de fórmula (I) o una sal, solvato o composición farmacéuticamente aceptable del mismo, para uso como un inhibidor o modulador de la transcriptasa inversa;

(vi) un compuesto de fórmula (I) o una sal, solvato o composición farmacéuticamente aceptable del mismo, para uso en el tratamiento de una infección por VIH o por un retrovirus relacionado genéticamente, o del síndrome de inmunodeficiencia adquirida resultante (SIDA);

(vii) el uso de un compuesto de fórmula (I) o de una sal, solvato o composición farmacéuticamente aceptable del mismo, para la fabricación de un medicamento que tenga actividad inhibidora o

moduladora de la transcriptasa inversa;

(viii) el uso de un compuesto de fórmula (I) o de una sal, solvato o composición farmacéuticamente aceptable del mismo, para la fabricación de un medicamento para el tratamiento de una infección por VIH o por un retrovirus relacionado genéticamente, o del síndrome de inmunodeficiencia adquirida resultante (SIDA);

(ix) un procedimiento de tratamiento de un mamífero, incluyendo un ser humano, con un inhibidor o modulador de la transcriptasa inversa, que incluye tratar a dicho mamífero con una cantidad eficaz de un compuesto de fórmula (I), o con una sal, solvato o composición farmacéuticamente aceptable del mismo;

(x) un procedimiento de tratamiento de un mamífero, incluyendo un ser humano, para tratar una infección por VIH o por un retrovirus relacionado genéticamente o el síndrome de inmunodeficiencia adquirida resultante (SIDA), que incluye tratar a dicho mamífero con una cantidad eficaz de un compuesto de fórmula (I), o con una sal, solvato o composición farmacéuticamente aceptable del mismo;

(xi) ciertos nuevos intermedios descritos en este

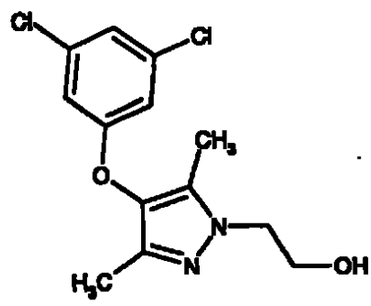
documento.

Los siguientes Ejemplos ilustran la preparación de los compuestos de fórmula (I). La síntesis de ciertos intermedios usados en este documento se describe en la sección de Preparaciones que sigue a los Ejemplos.

En todos los casos, los espectros de resonancia magnética nuclear (RMN) de H^1 fueron coherentes con las estructuras propuestas. Los desplazamientos químicos (δ) característicos se proporcionan en partes por millón campo abajo de tetrametilsilano usando abreviaturas convencionales para designar a los picos principales: por ejemplo, s, singlete; d, doblete; t, triplete; q, cuadruplete; m, multiplete; a, ancho. Se han usado las siguientes abreviaturas: HRMS, espectrometría de masas de alta resolución; hplc, cromatografía líquida de alta resolución; nOe, efecto nuclear de Overhauser; p.f., punto de fusión; $CDCl_3$, deuterocloroformo: D_6-DMSO, deuterodimetilsulfóxido; CD_3OD, deuterometanol. Cuando se ha usado la cromatografía de capa fina (TLC), se refiere a TLC de gel de sílice usando placas 60 F_{254} de gel de sílice, R_f es la distancia recorrida por un compuesto dividida por la distancia recorrida por el frente de disolvente en una placa de TLC.

EJEMPLO 1

2-[4-(3,5-Diclorofenoxi)-3,5-dimetil-1*H*-pirazol-1-il]etanol



Se añadió 2-hidroxietil hidrazina (21,5 µl, 0,316 mmol) a una solución agitada de la β-dicetona de la Preparación 1 (75 mg, 0,287 mmol) en etanol (2,9 ml) a temperatura ambiente en una atmósfera de nitrógeno y la solución naranja resultante se calentó a reflujo durante 18 horas. Después de la refrigeración, la mezcla se concentró a presión reducida. El residuo se disolvió en diclorometano (20 ml) y se lavó con ácido clorhídrico 2 M (10 ml) y salmuera (10 ml) y después se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida, dando un aceite viscoso naranja. El producto bruto se purificó por cromatografía ultrarrápida sobre gel de sílice, eluyendo con pentano:acetato de etilo (10:1, en volumen) y después con diclorometano, proporcionando el compuesto del título (32 mg) en forma de un polvo blanco, p.f. 114-115°C.

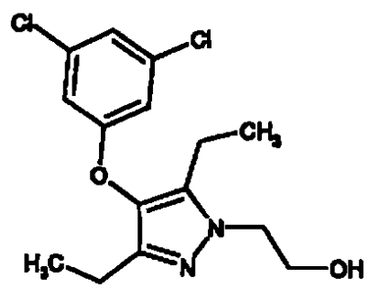
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 2,08 (s, 3H), 2,10 (s, 3H), 3,30 (t, 1H), 4,06 (m, 4H), 6,79 (s, 2H), 7,01 (s, 1H),

LRMS (Espectro de Masas de Baja Resolución) (termonebulización): m/z [MH^+] 301.

Microanálisis: Encontrado: C, 51,76; H, 4,64; N, 9,20, $C_{13}H_{14}Cl_2N_2O_2$ requiere C, 51,85; H, 4,69; N, 9,30%.

EJEMPLO 2

2-[4-(3,5-Diclorofenoxi)-3,5-dietil-1*H*-pirazol-1-il]etanol



Se añadieron secuencialmente 3,5-diclorofenol (501 mg, 3,07 mmol), carbonato potásico (467 mg, 3,38 mmol) y finalmente yoduro sódico (461 mg, 3,07 mmol) a una solución agitada de la clorocetona de la Preparación 2 (500 mg, 3,07 mmol) en acetona (15 ml), a temperatura ambiente y en una atmósfera de nitrógeno, produciendo una suspensión naranja/roja. La mezcla se calentó a reflujo durante 22,5 horas, produciendo una suspensión amarilla. Después de la refrigeración, la mezcla se diluyó con agua (10 ml) y la acetona se retiró a presión reducida en una campana de ventilación (precaución: posible resto de gas lacrimógeno). El residuo se diluyó con ácido clorhídrico 2 M y se extrajo con diclorometano (1x20 ml, 2x10 ml). Las capas orgánicas reunidas se lavaron con salmuera (20 ml), se secaron sobre sulfato de magnesio, se filtraron y se concentraron a presión

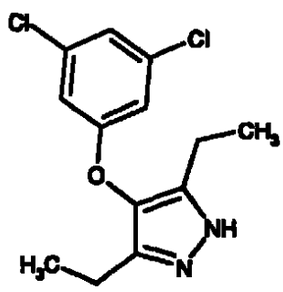
reducida, dando 4-(3,5-diclorofenoxi)-3,5-heptanodiona en forma de un aceite naranja bruto (777 mg). Una porción de la 4-(3,5-diclorofenoxi)-3,5-heptanodiona bruta (250 mg, aprox. 0,865 mmol) se disolvió en etanol (8,6 ml) y se trató con 2-hidroxietil hidrazina (65 µl, 0,951 mmol). La solución resultante se calentó a reflujo durante 16 horas produciendo una solución roja. Después de la refrigeración, la mezcla se concentró a presión reducida y el residuo se disolvió en diclorometano (20 ml). La solución resultante se lavó con ácido clorhídrico 2 M (10 ml), una solución 1 N de hidróxido sódico (10 ml) y salmuera (10 ml), se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida, dando un aceite naranja (102 mg). El producto bruto se purificó por cromatografía ultrarrápida sobre gel de sílice, eluyendo con metanol:diclorometano (5:95, en volumen), proporcionando el compuesto del título (23 mg) en forma de un aceite naranja que solidificó hasta un sólido céreo tras reposo.

^{1}H-RMN (400 MHz, $CDCl_3$) δ = 1,08 (t, 3H), 1,12 (t, 3H), 2,38 (q, 2H), 2,48 (q, 2H), 3,69 (s a, 1H), 4,02 (m, 4H), 6,76 (s, 2H), 6,97 (s, 1H).

LRMS (termonebulización): m/z [MH^+] 329.

EJEMPLO 3

4-(3,5-Diclorofenoxi)-3,5-dietil-1*H*-pirazol



Una mezcla de la clorocetona de la Preparación 2 (5 g, 30,8 mmol), 3,5-diclorofenol (5 g, 30,8 mmol), carbonato de cesio (10 g, 30,8 mmol) y acetona (40 ml) se calentó a reflujo durante 18 horas. Después de la refrigeración, se retiró un sólido por filtración y se lavó con diclorometano (100 ml). Los filtrados reunidos se concentraron a presión reducida. El producto bruto se disolvió en etanol (20 ml), se añadió hidrato de hidrazina (1,5 ml, 30,8 mmol) y la mezcla se calentó a 60°C durante 30 minutos en una atmósfera de nitrógeno. Después de la refrigeración, la mezcla se concentró a presión reducida y el residuo se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con éter:pentano (1:1, en volumen), proporcionando el compuesto del título (5,5 g) en forma de un aceite amarillo que solidificó tras reposo, dando un sólido amarillo, p.f. 114-115°C.

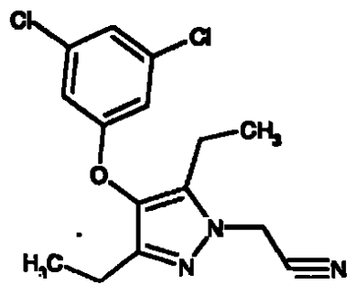
^{1}H-RMN (300 MHz, $CDCl_3$) δ = 1,15 (6H, t), 2,48 (4H, q), 6,78 (2H, s), 6,95 (1H, s).

LRMS (termonebulización): m/z [MH^+] 285.

Microanálisis: Encontrado: C, 54,93; H, 5,05; N, 9,94, $C_{13}H_{14}Cl_2N_2O$ requiere C, 54,75; H, 4,95; N, 9,82%.

EJEMPLO 4

[4-(3,5-Diclorofenoxi)-3,5-dietil-1*H*-pirazol-1-il]acetonitrilo

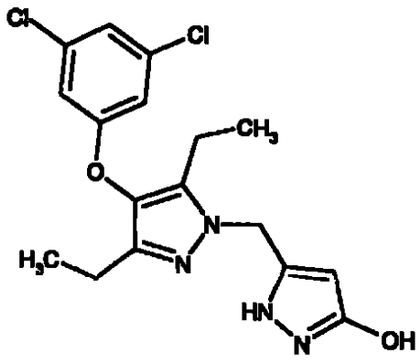


Se añadió hidruro sódico (dispersión en aceite al 60%, 470 mg, 11,8 mmol) a una solución agitada de 4-(3,5-diclorofenoxi)-3,5-dietil-1*H*-pirazol (3 g, 10,5 mmol, Ejemplo 3) en N,N-dimetilformamida seca (20 ml) a 0°C en una atmósfera de nitrógeno. La mezcla se agitó durante 5 minutos, tiempo durante el cual se desprendió hidrógeno y después se añadió bromoacetonitrilo (0,81 ml, 11,6 mmol). La solución amarilla se volvió parda oscura y se formó un precipitado. Se añadió más N,N-dimetilformamida seca (5 ml) para ayudar a la disolución y después de 45 minutos la mezcla de reacción se inactivo por la adición de agua (1 ml). La mezcla se repartió entre agua (150 ml) y dietil éter (2x150 ml). Las capas orgánicas reunidas se lavaron con agua (50 ml) y salmuera (100 ml), se secaron sobre sulfato de magnesio y se

concentraron a presión reducida. El producto bruto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano, proporcionando el compuesto del título (3,2 g) en forma de un polvo amarillo, p.f. 70-72°C. ^{1}H-RMN (400 MHz, $CDCl_3$) δ = 1,14 (6H, m), 2,38 (2H, q), 2,56 (2H, q), 4,92 (2H, s), 6,75 (2H, s), 7,00 (1H, s). Microanálisis: Encontrado: C, 55,43; H, 4,69; N, 12,71. $C_{15}H_{15}Cl_2N_3O$ requiere C, 55,57; H, 4,60; N, 12,96%.

EJEMPLO 5

5-{[4-(3,5-Diclorofenoxi)-3,5-dietil-1*H*-pirazol-1-il]metil}-1*H*-pirazol-3-ol



Una mezcla del éster (120 mg, 0,29 mmol) de la Preparación 3, hidrato de hidrazina (16 mg, 0,29 mmol) y etanol (5 ml) se agitó y se calentó a 60°C durante 2 horas en una atmósfera de nitrógeno. Después de la refrigeración, la mezcla se concentró a presión reducida y el sólido blanco resultante se agitó en acetato de etilo y después se recogió por filtración, dando el compuesto del título (60 mg) en

forma de un sólido blanco, p.f. 142-144°C.

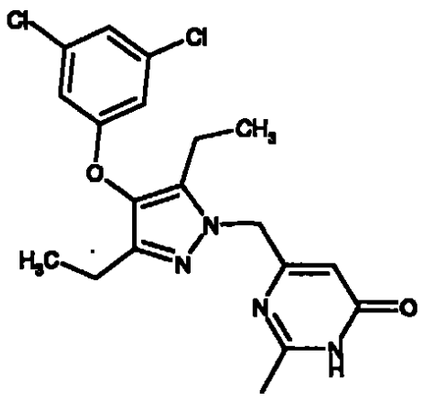
^{1}H-RMN (300 MHz, DMSO-d_6) δ = 0,89 (3H, t), 0,99 (3H, t), 2,26 (2H, q), 2,45 (2H, q), 5,01 (2H, s), 5,19 (1H, s), 6,88 (2H, s), 7,21 (1H, s).

LRMS (electronebulización): m/z [M-H$^+$] 379.

Microanálisis: Encontrado: C, 55,39; H, 4,72; N, 14,69. $C_{17}H_{18}Cl_2N_4O_2$ requiere C, 53,56; H, 4,76; N, 14,69%.

EJEMPLO 6

6-{[4-(3,5-Diclorofenoxi)-3,5-dietil-1*H*-pirazol-1-il]metil}-2-metil-4(3*H*)-pirimidinona



Una mezcla del éster (140 mg, 0,34 mmol) de la Preparación 3, clorhidrato de acetamidina (95 mg, 1,0 mmol), etóxido sódico (68 mg, 1,0 mmol) y etanol (5 ml) se agitó y se calentó a 70°C durante 1 hora en una atmósfera de nitrógeno. Después de la refrigeración, la mezcla se concentró a presión reducida. El aceite resultante se disolvió en diclorometano (50 ml), se lavó con agua (20 ml),

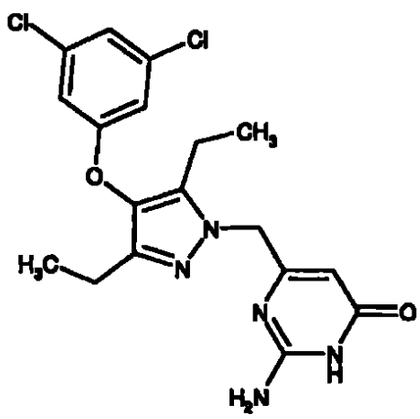
se secó sobre sulfato de magnesio y se concentró a presión reducida, dando el compuesto del título en forma de una espuma blanca (100 mg),

^{1}H-RMN (300 MHz, $CDCl_3$) δ = 1,10 (3H, t), 1,19 (3H, t), 2,48 (7H, m), 5,08 (2H, s), 5,72 (1H, s), 6,82 (2H, s), 7,03 (1H, s).

LRMS (termonebulización): m/z [MH^+] 407.

EJEMPLO 7

2-Amino-6-{[4-(3,5-diclorofenoxi)-3,5-dietil-1*H*-pirazol-1-il]metil}-4(3*H*)-pirimidinona



Una mezcla del éster (150 mg, 0,365 mmol) de la Preparación 3 y clorhidrato de guanidina (104 mg, 1,08 mmol) y etóxido sódico (73 mg, 1,08 mmol) en etanol (5 ml) se agitó y se calentó a 70°C durante 3 horas en una atmósfera de nitrógeno. Después de la refrigeración, la mezcla se concentró a presión reducida y el aceite resultante se

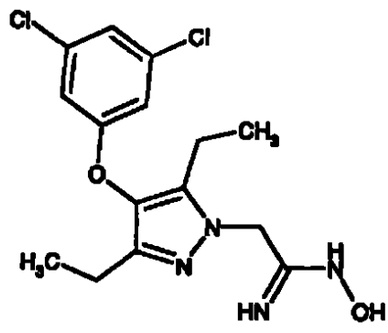
disolvió en diclorometano (50 ml), se lavó con agua (20 ml), se secó sobre sulfato de magnesio y se concentró a presión reducida. El producto bruto se purificó por cromatografía sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco (90:10:1, en volumen), dando el compuesto del título en forma de un sólido blanco (30 mg), p.f. 238-240°C.

^{1}H-RMN (400 MHz, DMSO-d_6) δ = 0,91 (3H, t), 0,99 (3H, t), 2,29 (2H, q), 2,44 (2H, q), 4,75 (1H, s), 4,81 (2H, s), 6,58 (2H, s a), 6,87 (2H, s), 7,22 (1H, s).

LRMS (termonebulización): m/z [MH^+] 408.

EJEMPLO 8

2-[4-(3,5-Diclorofenoxi)-3,5-dietil-1*H*-pirazol-1-il]-*N*-hidroxietanimidamida



Se añadieron clorhidrato de hidroxilamina (1,1 g, 15,8 mmol) y carbonato potásico (2,1 g, 15,2 mmol) a una suspensión del nitrilo (1 g, 3,1 mmol) del Ejemplo 4 en una mezcla de metanol (25 ml) y agua (10 ml), que después se

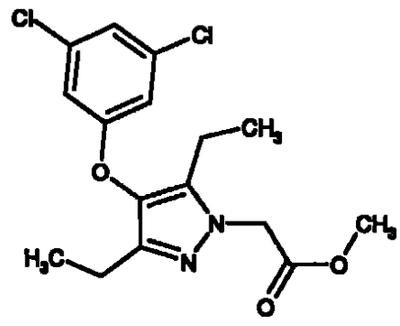
calentó a reflujo durante 3 días. Después de la refrigeración, la mezcla se extrajo con diclorometano (2x250 ml) y las capas orgánicas reunidas se lavaron con salmuera (100 ml), se secaron sobre sulfato de magnesio, se filtraron y se concentraron a presión reducida, produciendo el producto en forma de un sólido blanco (1,1 g), p.f. 128-130°C.

^{1}H-RMN (300 MHz, CD_3OD) δ = 1,10 (6H, m), 2,40 (2H, q), 2,60 (2H, q), 4,65 (2H, s), 6,90 (2H, s), 7,10 (1H, s).

LRMS (electronebulización): m/z [MH^+] 357.

EJEMPLO 9

[4-(3,5-Diclorofenoxi)-3,5-dietil-1*H*-pirazol-1-il]acetatode metilo



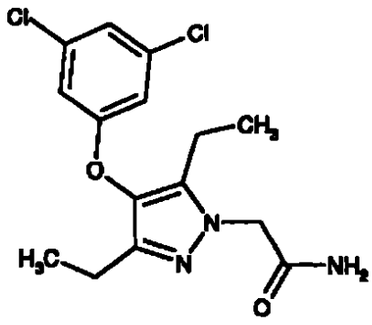
Se añadieron bromoacetato de metilo (984 µl, 10 mmol) y después hidruro sódico (dispersión en aceite al 60%, 801 mg, 20,1 mmol) a una solución agitada del pirazol (2,6 g, 9,12 mmol) del Ejemplo 3 en N,N'-dimetilformamida seca (25 ml) a 0°C en una atmósfera de nitrógeno. Después de agitar durante 1 hora, se añadió agua enfriada con hielo (100 ml)

y la mezcla se extrajo con éter (3x50 ml). Las capas de éter reunidas se secaron sobre sulfato de magnesio, se filtraron y se concentraron a presión reducida. El residuo se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con acetato de etilo:pentano (20:80, en volumen), proporcionando el compuesto del título (780 mg) en forma de un aceite amarillo que cristalizó parcialmente tras reposo. ^{1}H-RMN (400 MHz, $CDCl_3$) δ = 1,10 (6H, m), 2,44 (4H, m), 3,78 (3H, s), 4,80 (2H, s), 6,69 (2H, s), 6,99 (1H, s).

LRMS (termonebulización): m/z [MH^+] 357.

EJEMPLO 10

2-[4-(3,5-Diclorofenoxi)-3,5-dietil-1*H*-pirazol-1-il]acetamida



Se añadió 1,1'-carbonil diimidazol (71 mg, 0,44 mmol) a una solución agitada del ácido (125 mg, 0,36 mmol) de la Preparación 4 en N,N-dimetilformamida seca a temperatura ambiente y la mezcla de reacción se agitó durante 30 minutos. Se añadió amoniaco acuoso concentrado (d = 0,880 g/cm^3, aprox., 0,1 ml, aprox., 11,8 mmol) y se continuó agitando

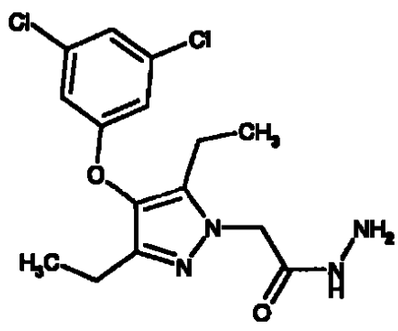
durante 10 minutos. El disolvente se retiró a presión reducida y el residuo se repartió entre agua (10 ml) y acetato de etilo (10 ml). La capa orgánica se concentró a presión reducida y el residuo se purificó por cromatografía sobre gel de sílice, eluyendo con acetato de etilo, dando el compuesto del título en forma de un sólido blanco (60 mg), p.f. 164-166°C.

^{1}H-RMN (300 MHz, $CDCl_3$) δ = 1,15 (6H, m), 2,50 (,4H, m), 4,70 (2H, s), 5,50 (1H, s a), 6,21 (1H, s a), 6,78 (2H, s), 7,04 (1H, s).

LRMS (termonebulización): m/z [MH^+] 342.

EJEMPLO 11

2-[4-(3,5-Diclorofenoxi)-3,5-dietil-1*H*-pirazol-1-il]acetohidrazida



Se añadió hidrato de hidrazina (520 µl, 10,9 mmol) a una solución del éster (780 mg, 2,18 mmol) del Ejemplo 9 en etanol (25 ml) y la mezcla resultante se calentó a reflujo durante 18 horas. Después de la refrigeración, el precipitado

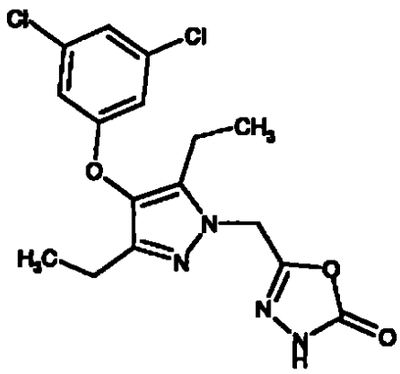
se recogió por filtración y se lavó con éter (50 ml), produciendo el compuesto del título (550 g) en forma de un sólido blanco, p.f. >250°C.

^{1}H-RMN (300 MHz, CD_3OD) δ = 1,10 (6H, m), 2,39 (2H, q), 2,55 (2H, q), 4,72 (2H, s), 6,93 (2H, s), 7,09 (1H, s).

LRMS (electronebulización): m/z [MH^+] 357.

EJEMPLO 12

5-[4-(3,5-Diclorofenoxi)-3,5-dietil-1*H*-pirazol-1-il]metil}-1,3,4-oxadiazol-2(3*H*)-ona



Una solución agitada de la hidrazida (275 mg, 0,77 mmol) del Ejemplo 11 y 1,1'-carbonil diimidazol (187 mg, 1,16 mmol) en dioxano (50 ml) se calentó a reflujo durante 18 horas. Después de la refrigeración, la mezcla se concentró a presión reducida y el residuo se disolvió en diclorometano (50 ml) y se lavó con agua (25 ml). La capa orgánica se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida. El residuo se purificó por cromatografía

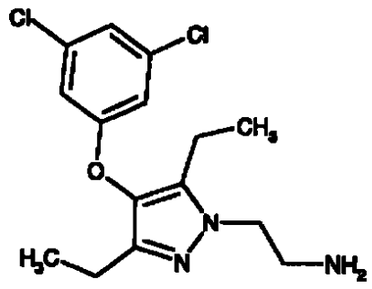
ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol (95:5, en volumen), produciendo el compuesto del título (112 mg) en forma de un sólido blanco, p.f. 138-142°C.

^{1}H-RMN (400 MHz, $CDCl_3$) δ = 1,10 (6H, m), 2,40 (2H, q), 2,55 (2H, q), 5,07 (2H, s), 6,76 (2H, s), 6,98 (1H, s), 10,45 (1H, s a).

LRMS (electronebulización): m/z [MH^+] 383.

EJEMPLO 13

2-[4-(3,5-Diclorofenoxi)-3,5-dietil-1*H*-pirazol-1-il]etilamina



Una mezcla del pirazol (390 mg, 1,37 mmol) del Ejemplo 3 y clorhidrato de cloroetilamina (238 mg, 2,05 mmol) se agitó y se calentó a 150°C durante 24 horas. Después de la refrigeración, la mezcla se repartió entre una solución acuosa saturada de bicarbonato sódico (100 ml) y diclorometano (2x50 ml). Las capas orgánicas reunidas se lavaron con salmuera (30 ml), se secaron sobre sulfato de magnesio, se filtraron y se concentraron a presión reducida. El aceite pardo resultante se purificó por cromatografía

ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol (90:10, en volumen), produciendo el compuesto del título (244 mg) en forma de un aceite pardo.

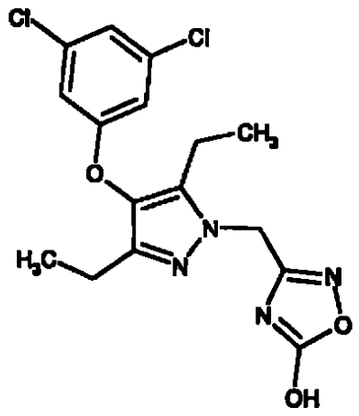
^{1}H-RMN (400 MHz, $CDCl_3$) δ = 1,09 (6H, m), 2,41 (2H, q), 2,52 (2H, q), 3,18 (2H, t), 4,02 (2H, t), 6,78 (2H, s), 6,99 (1H, s).

LRMS (electronebulización): m/z [MH^+] 330.

Microanálisis: Encontrado: C, 52,28; H, 5,70; N, 11,75. $C_{15}H_{19}Cl_2N_3O.H_2O$ requiere C, 52,03; H, 6,11; N, 12,14%.

EJEMPLO 14

3-{[4-(3,5-Diclorofenoxi)-3,5-dietil-1*H*-pirazol-1-il]metil}-1,2,4-oxadiazol-5-ol



Se añadió cloroformiato de etilo (0,30 ml, 3,08 mmol) a una solución agitada de la amidoxima del Ejemplo 8 (500 mg, 1,39 mmol) en piridina (8 ml) a 0°C en una atmósfera de nitrógeno y la solución resultante se agitó durante 10 minutos. La mezcla se concentró a presión reducida y el

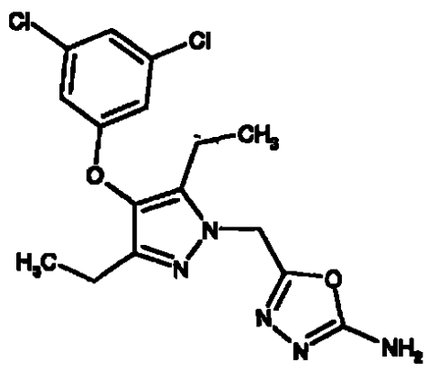
residuo se disolvió en una mezcla de agua (4 ml), tetrahidrofurano (4 ml) y una solución acuosa 1 M de hidróxido sódico (2 ml). La mezcla se calentó a reflujo durante 1 hora, se enfrió a temperatura ambiente y se agitó durante 2 días más. La solución resultante se diluyó con ácido clorhídrico acuoso 2 M (20 ml) y se extrajo con acetato de etilo (2x50 ml). Las capas orgánicas reunidas se lavaron con salmuera (50 ml), se secaron sobre sulfato de magnesio, se filtraron y se evaporaron a presión reducida, dando un aceite amarillo. El aceite se purificó por cromatografía en columna ultrarrápida sobre gel de sílice eluyendo con pentano:acetato de etilo (50:50, en volumen), produciendo un sólido blanco. El sólido se disolvió en una mezcla de tetrahidrofurano (1 ml) y una solución acuosa 1 M de hidróxido sódico (10 ml) y después se calentó a reflujo durante 24 horas. La solución resultante se diluyó con ácido clorhídrico 2 M (20 ml) y se extrajo con diclorometano (2x50 ml). Las capas orgánicas reunidas se lavaron con salmuera (50 ml), se secaron sobre sulfato de magnesio, se filtraron y se evaporaron a presión reducida, dando el compuesto del título (113 mg) en forma de un sólido blanco, p.f. 94-96°C.

^{1}H-RMN (400 MHz, $CDCl_3$) δ = 1,14 (m, 6H), 2,56 (m, 4H), 5,06 (s, 2H), 6,75 (s, 2H), 7,03 (s, 1H).

LRMS (electronebulización): m/z [M-(H^+)] 381.

EJEMPLO 15

5-{[4-(3,5-Diclorofenoxi)-3,5-dietil-1*H*-pirazol-1-il]metil}-1,3,4-oxadiazol-2-amina



Se añadió bromuro de cianógeno (49 mg, 0,462 mmol) a una solución agitada de la hidrazida del Ejemplo 11 (150 mg, 0,420 mmol) en etanol (30 ml), a temperatura ambiente, en una atmósfera de nitrógeno y la solución resultante se calentó a reflujo durante 2,5 horas. Después de la refrigeración, la mezcla se concentró a presión reducida, dando un aceite pardo. El producto bruto se purificó por cromatografía en columna ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco (98:1,75:0,25, en volumen), proporcionando el compuesto del título (71 mg) en forma de un polvo blanco, p.f. 226-228°C.

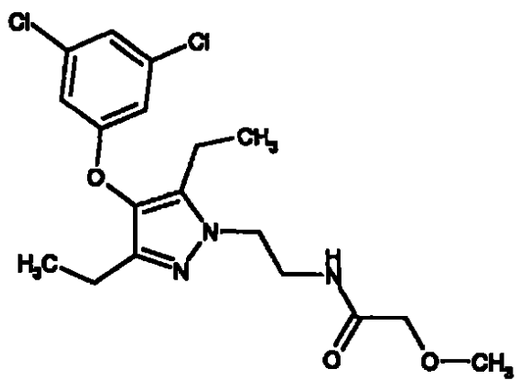
^{1}H-RMN (400 MHz, $CDCl_3$) δ = 1,00 (m, 6H), 2,29 (m, 2H), 2,55 (m, 2H), 5,34 (s, 2H), 6,90 (s, 2H), 7,07 (s, 2H), 7,24 (s, 1H).

LRMS (electronebulización): m/z [MH^+] 382.

Microanálisis: Encontrado: C, 49,82; H, 4,52; N, 17,81. $C_{16}H_{17}Cl_2N_3O_2.0,25H_2O$ requiere C, 49,69; H, 4,56; N, 18,11 %.

EJEMPLO 16

N-{2-[4-(3,5-Diclorofenoxi)-3,5-dietil-1*H*-pirazol-1-il]etil}-2-metoxiacetamida



Una solución del pirazol del Ejemplo 13 (53 mg, 0,161 mmol), clorhidrato de 1-(3-(dimetilamino)propil)-3-etilcarbodiimida (34 mg, 0,178 mmol) y 4-(dimetilamino)-piridina (22 mg, 0,178 mmol) en diclorometano (1 ml) se añadió a una solución agitada de ácido metoxiacético (14,2 µl, 0,178 mmol) en diclorometano (1 ml) a temperatura ambiente. La reacción se agitó durante 12 horas y después se concentró en una corriente de nitrógeno, dando un sólido amarillo. El producto bruto se purificó por cromatografía en columna ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol (98:2, en volumen), proporcionando el compuesto del título (54 mg) en forma de un sólido pardo,

p.f. 75-76°C.

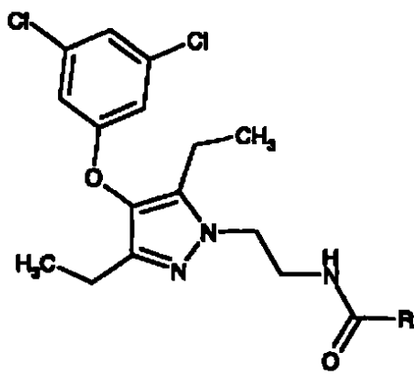
^{1}H-RMN (400 MHz, $CDCl_3$) δ = 1,08 (t, 3H), 1,18 (t, 3H), 2,42 (q, 2H), 2,52 (q, 2H), 3,39 (s, 3H), 3,75 (m, 2H), 3,90 (s, 2H), 4,13 (t, 2H), 6,79 (s, 2H), 6,99 (s, 1H), 7,21 (s a, 1H).

LRMS (electronebulización): m/z [MH^+] 400; [M-(H^+)] 398.

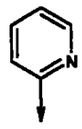
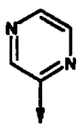
Microanálisis: Encontrado: C, 54,09; H, 5,79; N, 10,39. $C_{18}H_{23}Cl_2N_3O_3$ requiere C, 54,01; H, 5,79; N, 10,50%.

EJEMPLOS 17 Y 18

Los compuestos de los siguientes Ejemplos indicados en la tabla, de formula general:

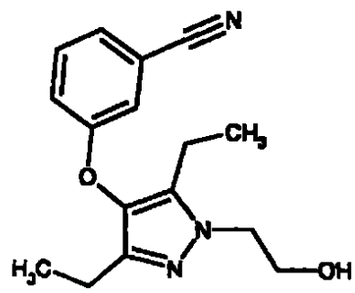


se prepararon por un procedimiento similar al del Ejemplo 16, usando el apropiado material de partida ácido y el pirazol del Ejemplo 13.

Ejemplo No.	R	LRMS (termonebulización)	Datos Analíticos
17		m/z [MH] 433	^{1}H RMN (400 MHz, $CDCl_3$) δ = 1,06 (t, 3H) 1 18 (t, 3H) 2,44 (q 2H) 2,52 (q 2H) 3 92 (m, 2H) 4,24 (t 2H) 6.79 (s 2H) 6,99 (s 1H) 7,40 (m, 1H) 7,82 (m, 1H) 8 19 (m 1H) 8,52 (s a, 2H) 8,55 (m 1H) Microanálisis Encontrado C 57 01 H 5.08 N 11 94 $C_{21}H_{20}Cl_2N_4O_3$ requiere C 58 21 H 5 12 N 12,03%
18		m/z [MH] 434	^{1}H RMN (400 MHz, $CDCl_3$) δ = 1,08 (t 3H) 1 18 (t 3H) 2,42 (q 2H) 2,52 (q 2H) 3 96 (m 2H) 4 24 (t, 2H) 6 79 (s 2H) 7,01 (s 1H) 8,22 (s a 1H) 8,54 (d 1H) 8 78 (d 1H) 9,40 (s 1H)

EJEMPLO 19

3-{[3,5-Dietil-1-(2-hidroxietil)-1*H*-pirazol-4-il]oxi}benzonitrilo



Una mezcla de la clorocetona de la Preparación 2 (243 mg, 1,50 mmol), 3- cianofenol (155 mg, 1,50 mmol), carbonato de cesio (488 mg, 1,50 mmol) y acetona (10 ml) se calentó a reflujo durante 2 horas. Después de la refrigeración, el sólido se retiró por filtración y el filtrado se concentró a presión reducida, dando un aceite pardo. El aceite se disolvió en etanol (10 ml), se añadió hidroxietilhidrazina (114 mg, 1,50 mmol) y la mezcla se calentó a 60°C durante 18 horas. Después de la refrigeración, la mezcla se concentró a presión reducida. Se lavó una solución del residuo en diclorometano (10 ml) se lavó con ácido clorhídrico acuoso 2 M (5 ml) y agua (5 ml), se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida, dando un aceite amarillo. El producto bruto se purificó por cromatografía en columna ultrarrápida sobre gel de sílice eluyendo con acetato de etilo, proporcionando el compuesto del título (80 mg) en

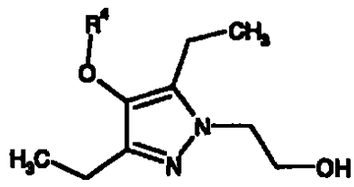
forma de un aceite incoloro.

^{1}H-RMN (400 MHz, $CDCl_3$) δ = 1,10 (m, 6H), 2,40 (q, 2H), 2,50 (q, 2H), 3,68 (s a, 1H), 4,07 (m, 4H), 7,12 (s, 1H), 7,14 (d, 1H), 7,28 (d, 2H).

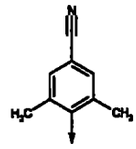
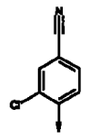
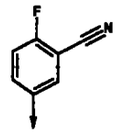
LRMS (electronebulización): m/z [MH^+] 286; [MNa^+] 308.

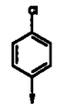
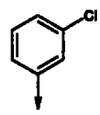
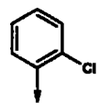
EJEMPLOS 20 A 38

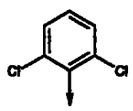
Los compuestos de los siguientes Ejemplos indicados en la tabla, de formula general:

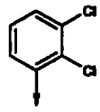
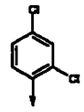


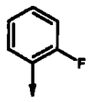
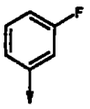
se prepararon por un procedimiento similar al del Ejemplo 19, usando los apropiados fenoles y la clorocetona de la Preparación 2.

Ejemplo No.	R^1	LRMS (electronebulización)	Datos Analíticos
20		m/z [MH$^+$] 314	^{1}H RMN (400 MHz, $CDCl_3$) δ = 0 99 (t 3H) 1,09 (t 3H) 2 18 (s 6H) 2,25 (q 2H) 2,40 (q 2H) 3 78 (s a 1H) 4,00 (m 4H) 7 34 (s 2H)
21		m/z [MH] 320	^{1}H RMN (400 MHz, $CDCl_3$) δ 1 10 (m 6H) 2,40 (q 2H) 2,53 (q 2H) 3,56 (s a, 1H) 4,04 (m 2H) 4,08 (m, 2H) 6,80 (d 1H) 7,44 (d 1H) 7 72 (s 1H) Masa Exacta Encontrada 320 1165 [MH$^+$] $C_{20}H_{19}ClN_2O_2$ requiere 320 1161 [MH]
22		m/z [MH$^+$] 304	^{1}H RMN (400 MHz, $CDCl_3$) δ = 1 10 (m, 6H) 2,39 (q 2H) 2,50 (q 2H) 4,60 (m 4H) 7 05 (m 1H) 7 14 (m 2H)

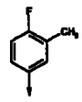
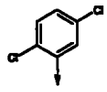
Ejemplo No.	R^1	LRMS (electronebulización)	Datos Analíticos
23		m/z [MH] 295	^{1}H RMN (400 MHz, $CDCl_3$) δ = 1,09 (m, 6H) 2,41 (m, 2H) 2,51 (m 2H) 3 78 (s a, 1H) 4,06 (m 4H) 6,81 (m 2H) 7,21 (m 2H) Microanálisis encontrado C 60,88, H 6,49 N 9,40 $C_{15}H_{19}ClN_2O_2$ requiere C 61 12 H 6,50 N 9,50%
24		m/z [MH] 295	^{1}H RMN (400 MHz, $CDCl_3$) δ 1,09 (t, 3H) 1 14 (t 3H) 2,41 (q 2H) 2,52 (q 2H) 3 79 (s a 1H) 4 05 (m, 4H) 6,78 (d 1H) 6,88 (s 1H) 6,98 (d 1H) 7 19 (t 1H)
25		m/z [MH] 295	^{1}H RMN (400 MHz, $CDCl_3$) δ = 1,08 (t 3H) 1 15 (t 3H) 2,44 (q 2H) 2,54 (q 2H) 4 02 (m 2H) 4,09 (m 2H) 6,69 (d 1H) 6 94 (t 1H) 7 10 (t 1H) 7,40 (d 1H)

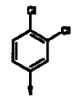
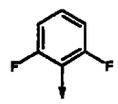
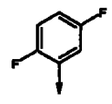
26		m/z [MH] 329	^{1}H RMN (400 MHz, $CDCl_3$)δ = 1.01 (t, 3H) 1 10 (t, 3H) 2,38 (q 2H) 2,49 (q 2H) 3 84 (s a 1H) 3 99 (m 4H) 7,01 (t, 1H) 7,30 (d 2H) Masa Exacta Encontrada 329,0822 [MH$^+$] $C_{20}H_{22}Cl_2N_2O_2$ requiere 329,0818 [MH]

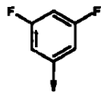
Ejemplo No	R^1	LRMS (electronebulización)	Datos Analíticos
27		m/z [MH] 328	^{1}H RMN (400 MHz, $CDCl_3$) δ = 1,09 (t, 3H) 1 14 (t 3H) 2,41 (q 2H) 2 51 (q 2H) 4,03 (m 2H) 4 07 (m 2H) 6,60 (d 1H) 7,04 (t, 1H) 7 10 (t 1H)
28		m/z [MH] 329	^{1}H RMN (400 MHz, $CDCl_3$) δ 1,08 (t 3H) 1 14 (t, 3H) 2 41 (q 2H) 2,51 (q 2H) 4,03 (m, 2H) 4,08 (m 2H) 6,62 (d 1H) 7 09 (d 1H) Microanálisis Encontrado: C 54,66, H 5,54 N 8 12 $C_{19}H_{18}Cl_2N_2O_2$ requiere C 54 72 H 5,51 N 8,51%

29		m/z [MH] 279	^{1}H RMN (400 MHz, $CDCl_3$) δ = 1 10 (t 3H) 1 14 (t 3H) 2,44 (q 2H) 2,55 (q 2H) 3 79 (s a, 2H) 4,06 (m 4H) 6,71 (m 1H) 6 98 (m 2H) 7 12 (m 1H)
30		m/z [MH] 279	^{1}H RMN (400 MHz, $CDCl_3$) δ = 1,09 (t 3H) 1 12 (t 3H) 2 43 (q 2H), 2,52 (q 2H) 3 78 (s a, 1H) 4,04 (m 4H) 6,59 (m 1H) 6,75 (m 2H) 7,20 (m 2H)

Ejemplo No	R^1	LRMS (electronch)	Datos Analiticos
31		m/z [MH] 289	^{1}H RMN (400 MHz $CDCl_3$) δ = 1 10 (t 3H) 1 17 (t 3H) 2,25 (s 6H) 2,42 (q 2H) 2,52 (q 2H) 3 90 (s a 1H) 4,05 (m, 4H) 6 49 (s 2H) 6 62 (s 1H)

32		m/z [MH] 293	^{1}H RMN (400 MHz, $CDCl_3$) δ 1,09 (t 3H) 1 14 (t 3H) 2,22 (s 3H) 2,42 (q 2H) 2,31 (q 2H) 3 83 (s a 1H) 4,03 (m, 4H) 6 60 (m 1H) 6 70 (m 1H) 6 88 (m 1H)
33		m/z [MH] 329	^{1}H RMN (400 MHz $CDCl_3$) δ = 1 11 (t, 3H) 1 17 (t 3H) 2,42 (q 2H) 2,54 (q 2H) 4,06 (m, 4H) 6,69 (s 1H) 6 94 (d 1H) 7,34 (d 1H) Microanálisis Encontrado: C 54,84 H 5,67 N,8 48 $C_{15}H_{18}Cl_2N_2O_2$ requiere C 54 72 H 5,51 N 8,51%
34		m/z [MH] 297	^{1}H RMN (400 MHz, $CDCl_3$) δ = 1,09 (3 3H) 1 12 (t 3H) 2,42 (q 2H) 2,50 (q 2H) 3 68 (s a 1H) 4,01 (m 4H) 6 47 (m 1H) 6 77 (m 1H) 6,86 (m 1H) Microanálisis Encontrado C 60,57 H 6,23 N 9,52 $C_{15}H_{18}F_2N_2O_2$ requiere C 60 80 H 6,12 N 9,45%

Ejemplo No	R^4	LRMS (electronebulización)	Datos Analíticos
35		m/z [MH] 329	^{1}H RMN (400 MHz, $CDCl_3$) δ = 1,08 (t 3H) 1 12 (t 3H), 2 41 (q 2H) 2,51 (q 2H) 3 73 (a a 1H) 4,08 (m 4H) 6,75 (d 1H) 6 98 (a 1H) 7 31 (a 1H) Microanálisis Encontrado C 54 70 H 5,54 N 8,50 $C_{19}H_{18}Cl_2N_2O_3$ requiere C 54 72 H 5,51 N 8,51%
36		m/z [MH] 297	^{1}H RMN (400 MHz, $CDCl_3$) δ 1,08 (t 3H) 1 12 (t, 3H) 2,49 (q 2H) 2 60 (q 2H) 3 81 (a a, 1H) 3 99 (m 4H) 6,91 (m 2H) 6 99 (m 1H)
37		m/z [MH] 297	^{1}H RMN (400 MHz, $CDCl_3$) δ = 1,09 (t 3H) 1 15 (t, 3H) 2 45 (q 2H) 2,55 (q 2H) 3 70 (a a, 1H) 4,06 (m 4H) 6,46 (m 1H) 6,62 (m 1H) 7,08 (m 1H)

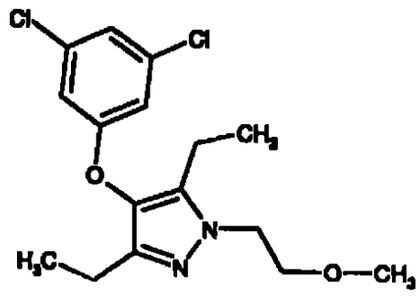
38		m/z [MH] 297	^{1}H RMN (400 MHz, $CDCl_3$) δ = 1,08 (t, 3H) 1 14 (t 3H) 2,41 (q 2H) 2,53 (q 2H) 3 72 (s a, 1H) 4,05 (m 4H) 6 43 (m 3H)

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2° parte ufp PCT 03-7961 7 BB

EJEMPLO 39

4-(3,5-Diclorofenoxi)-3,5-dietil-1-(2-metoxietil)-1*H*-pirazol



Se añadió hidruro sódico (dispersión en aceite al 60%, 34 mg, 0,850 mmol) a una solución agitada del 4-(3,5-diclorofenoxi)-3,5-dietil-1*H*-pirazol del Ejemplo 3 (200 mg, 0,701 mmol) y bromuro de metoxietilo (117 mg, 0,850 mmol) en N,N- dimetilformamida seca (2 ml) a 0°C en una atmósfera de nitrógeno. La mezcla se agitó a 0°C durante 45 minutos, tiempo durante el cual se desprendió hidrógeno y la solución amarilla se volvió parda oscura. La mezcla de reacción se inactivo por la adición de agua (5 ml) y la mezcla se concentró a presión reducida. El residuo se disolvió en acetato de etilo (20 ml) y se lavó con agua (10 ml) y salmuera (10 ml) y después se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida, dando un aceite pardo. El producto bruto se purificó por cromatografía en columna ultrarrápida sobre gel de sílice eluyendo con pentano:dietil éter (80:20, en volumen), proporcionando el compuesto del título (140 mg) en forma de un aceite incoloro.

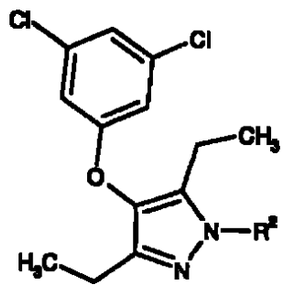
^{1}H-RMN (300 MHz, $CDCl_3$) δ = 1,09-1,15 (m, 6H), 2,41-2,49 (q, 2H), 2,51-2,57 (q, 2H), 3,34 (s, 3H), 3,74-3,78 (t, 2H), 4,15-4,17 (t, 2H), 6,81 (s, 2H), 7,01 (s, 1H).

LRMS (termonebulización): m/z [MH^+] 343.

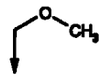
Microanálisis: Encontrado: C, 56,25; H, 5,94; N, 7,95. $C_{16}H_{20}Cl_2N_2O_2$ requiere C, 55,99; H, 5,87; N, 8,16%.

EJEMPLOS 40 Y 41

Los compuestos de los siguientes Ejemplos indicados en la tabla, de formula general:

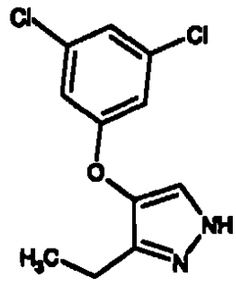


se prepararon por un procedimiento similar al del Ejemplo 39, usando los apropiados haluros y el pirazol del Ejemplo 3.

Ejemplo No	R^1	LRMS (termonebulización)	Datos Analíticos
40		m/z [MH] 329	^{1}H RMN (300 MHz, $CDCl_3$) δ = 1 13-1 18 (m 6H) 2,45 (q 2H) 2,60 (q 2H) 3,37 (s 3H) 5,34 (s 2H) 6,80 (s, 2H) 7,02 (s 1H) Microanálisis Encontrado C 54,72 H 5,46, N 8 40 $C_{19}H_{18}Cl_2N_2O_2$ requiere C 54 72 H 5,51 N 8,51%
41		m/z [MH] 299	^{1}H RMN (300 MHz, $CDCl_3$) δ = 1 15 (m 6H) 2,48 (m 4H) 3 79 (s 3H) 6,82 (s 2H) 7,01 (s 1H) Microanálisis Encontrado: C 56,08 H 5 37 N 9,29 $C_{16}H_{20}Cl_2N_2O$ requiere C 56,20 H 5 39 N 9 36%

EJEMPLO 42

4-(3,5-Diclorofenoxi)-3-etil-1*H*-pirazol



Una solución de la enamina de la Preparación 6 (2,88g, 10,0 mmol) e hidrato de hidrazina (0,49 ml, 10,0 mmol) en etanol (10 ml) se calentó a reflujo durante 12 horas. Después de la refrigeración, se añadió más hidrato de hidrazina (0,49 ml, 10,0 mmol) y la reacción se calentó a reflujo durante 3 horas. Después de la refrigeración la mezcla se concentró a presión reducida y el residuo se purificó por cromatografía en columna ultrarrápida sobre gel de sílice eluyendo con ciclohexano:acetato de etilo (80:20, en volumen) y después con ciclohexano:acetato de etilo (60:40, en volumen), proporcionando el compuesto del título (620 mg) en forma de un aceite amarillo.

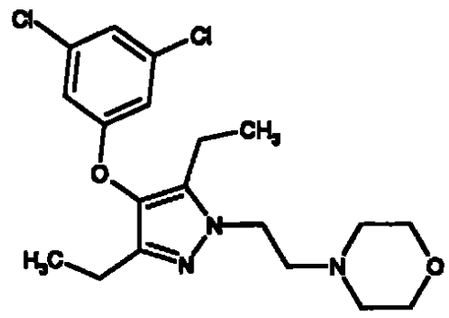
^{1}H-RMN (400 MHz, $CDCl_3$) δ = 1,23 (t, 3H), 2,66 (q, 2H), 6,87 (s, 2H), 7,02 (s, 1H), 7,40 (s, 1H).

LRMS (electronebulización): m/z [MH^+] 257; [M-(H^+)] 255.

EJEMPLO 43

4-{2-[4-(3,5-Diclorofenoxi)-3,5-dietil-1*H*-pirazol-1-

il]etil}morfolina



Se añadió gota a gota tetróxido de osmio (1,00 ml de una solución al 2,5% p/v en *terc*-butanol) a una solución agitada del pirazol del Ejemplo 64 (3,00 g, 9,23 mmol) y peryodato sódico (4,93 g, 23,1 mmol) en acetona (90 ml) y agua (30 ml) a temperatura ambiente. Después de 5 minutos se formó un precipitado blanco y la suspensión se agitó durante 3 horas más. El sólido se retiró por filtración y el filtrado se concentró a presión reducida. El residuo se repartió entre acetato de etilo (300 ml) y agua (100 ml) y la fase orgánica se separó, se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida, produciendo un aldehído intermedio. Se disolvió una alícuota del aldehído (100 mg, 0,305 mmol) en diclorometano (5 ml) y se añadieron morfolina (30 mg, 0,344 mmol) y ácido acético glacial (17,1 µl, 0,305 mmol). Después de agitar a temperatura ambiente durante 5 minutos, se añadió en una porción triacetoxiborohidruro sódico (95 mg, 0,451 mmol) y la reacción se agitó durante 1

hora. Después de este tiempo, la mezcla resultante se diluyó con diclorometano (20 ml) y se repartió entre agua (30 ml) y diclorometano (20 ml). La fase orgánica se lavó con una solución acuosa 2 M de hidróxido sódico (10 ml), se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida. El producto bruto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco (95:4:1, en volumen), proporcionando el compuesto del título (125 mg) en forma de un aceite incoloro.

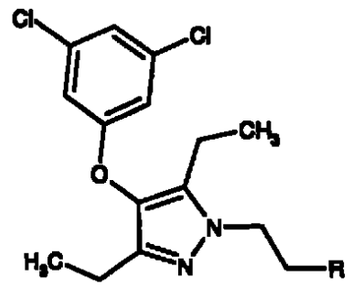
^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,06 (m, 6H), 2,12 (m, 8H), 2,75 (t, 2H), 3,64 (m, 4H), 4,04 (t, 2H), 6,73 (s, 2H), 6,95 (s, 1H).

LRMS (termonebulización): m/z [MH^+] 398.

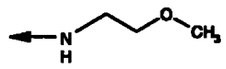
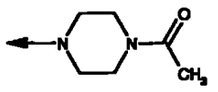
Microanálisis: Encontrado: C, 57,18; H, 6,31; N, 10,36. $C_{19}H_{25}Cl_2N_3O_2$ requiere C, 57,29; H, 6,33; N, 10,55%.

EJEMPLOS 44 A 49

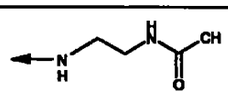
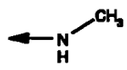
Los compuestos de los siguientes Ejemplos indicados en la tabla, de formula general:

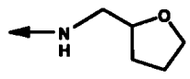


se prepararon por un procedimiento similar al del Ejemplo 43, usando el apropiado material de partida de amina y el pirazol del Ejemplo 64.

Ejemplo No	R	LRMS (termonebulización)	Datos Analíticos
44		m/z [MH] 386.	^{1}H RMN (300 MHz, $CDCl_3$) δ = 1,09-1 17 (m 6H) 2,40-2,47 (q 2H) 2,50-2,56 (q 2H) 2 80-2,82 (t, 2H) 3,07-3 11 (t 2H) 3,36 (s 3H) 3,47 3,51 (t 2H) 4,09-4 11 (t 2H) 6,81 (s 2H) 7,01 (s 1H)
45		m/z [MH] 439	^{1}H RMN (400 MHz, $CDCl_3$) δ = 1,04 (m 6H) 2,00 (s 3H) 2,38 (m 6H) 2 44 (q 2H) 2 77 (q 2H) 3 38 (m 2H) 3,55 (m, 2H) 4,05 (m 2H) 6,71 (s 2H) 6 92 (s 1H)
46		m/z [MH] 356	^{1}H RMN (400 MHz, $CDCl_3$) δ = 1,05 (m 6H) 2 23 (s 6H) 2 38 (q 2H) 2,45 (q 2H) 2,69 (m, 2H) 4,03 (m 2H) 6 75 (s 2H) 6,95 (s 1H)

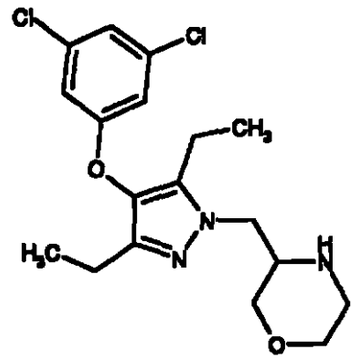
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Ejemplo No	R	LRMS (termonebulizado)	Datos Analíticos
47		m/z [MH] 413	^{1}H RMN (400 MHz, $CDCl_3$) δ = 1,08 (m 6H) 1,59 (s a, 1H) 1 91 (s 3H) 2,38 (q 2H) 2,48 (q 2H) 2 71 (m, 2H) 2 99 (m, 2H) 3 28 (m 2H) 4,02 (m 2H) 6,09 (s a, 1H) 6 71 (s 2H) 6,95 (s 1H) Microanálisis Encontrado C 54,86, H 6,32 N 13,33 $C_{20}H_{20}Cl_3N_3O_2$ requiere C 55,21 H 6,34 N 13,55% p f 69-70°C
48		m/z [MH] 342	^{1}H RMN (400 MHz, $CDCl_3$) δ = 1,08 (m, 7H) 2,39 (m, 2H) 2,42 (s 3H) 2,49 (q 2H) 3 00 (m 2H) 4,05 (m 2H) 6,78 (s 2H) 6,96 (s 1H)

Ejemplo No	R	LRMS (termonebulización)	Datos Analíticos
49		m/z [MH] 412	^{1}H RMN (400 MHz, $CDCl_3$) δ = 1,05 (m 6H) 1,49 (m 1H) 1,81 (m 4H) 2,42 (q 2H) 2,52 (q 2H) 2,64 (m 2H) 3,08 (t 2H) 3 76 (m 1H) 3 79 (m 1H) 4,00 (m 1H) 6,78 (s, 2H) 6 98 (s, 1H) Microanálisis Encontrado: C 57 78 H 6 68 N 9 90 $C_{20}H_{27}Cl_2N_3O_2$ requiere C 58 13 H 6,61 N 10 17%

EJEMPLO 50

3-{[4-(3,5-Diclorofenoxi)-3,5-dietil-1*H*-pirazol-1-il]metil}morfolina



Se añadió hidruro sódico (dispersión en aceite al 60%, 37 mg, 0,925 mmol) a una solución agitada del mesilato de la Preparación 11 (273 mg, 0,925 mmol) y el pirazol del Ejemplo 3 (220 mg, 0,772 mmol) en N,N-dimetilformamida seca (4 ml) a 0°C en una atmósfera de nitrógeno. La mezcla se calentó a 50°C durante 3 horas, tiempo durante el cual la solución amarilla se volvió parda oscura. La mezcla de reacción se inactivó por la adición de agua (5 ml) y la mezcla se concentró a presión reducida. Una solución del residuo en acetato de etilo (20 ml) se lavó con agua (10 ml) y salmuera (10 ml), se secó sobre sulfato de magnesio, se filtró y concentró a presión reducida, dando un aceite pardo. El aceite se disolvió en diclorometano (3 ml), se añadió ácido trifluoroacético (1 ml) y la reacción se agitó a temperatura

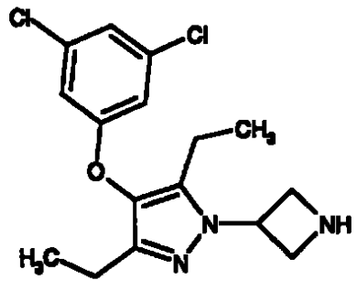
ambiente durante 12 horas. La mezcla se concentró a presión reducida y el residuo se disolvió en acetato de etilo (10 ml) y se lavó con ácido clorhídrico acuoso 1 M (2x5 ml). Las fases acuosas reunidas se neutralizaron con carbonato sódico sólido y se extrajeron con acetato de etilo (3x20 ml). Las capas de acetato de etilo reunidas se secaron sobre sulfato de magnesio, se filtraron y se concentraron a presión reducida. El producto bruto se purificó por cromatografía en columna ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco (95:4:1, en volumen), proporcionando el compuesto del título (3 mg) en forma de un aceite incoloro.

^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,15 (m, 6H), 2,41 (q, 2H), 2,51 (q, 2H), 2,89 (m, 2H), 3,30 (m, 2H), 3,58 (m, 1H), 3,78 (m, 2H), 3,87 (d, 2H), 6,88 (s, 2H), 7,00 (1H, s).

LRMS (termonebulización): m/z [MH^+] 384.

EJEMPLO 51

1-(3-Azetidinil)-4-(3,5-diclorofenoxi)-3,5-dietil-1*H*-pirazol



Se añadió hidruro sódico (dispersión en aceite al 60%,

30 mg, 0,750 mmol) a una solución agitada del pirazol del Ejemplo 3 (200 mg, 0,702 mmol) y metanosulfonato de 1-benzhidril-3-azetidinilo (222 mg, 0,702 mmol) (véase J. Org. Chem., 1972, 37, 3953) en *N,N*-dimetilformamida (5 ml) a 0°C en una atmósfera de nitrógeno. La mezcla se calentó a 50°C durante 4 horas y después se enfrió a temperatura ambiente. La mezcla de reacción se inactivó por la adición de agua (30 ml) y la mezcla acuosa se extrajo con éter (2x50 ml). Las fases orgánicas reunidas se lavaron con agua (10 ml) y salmuera (10 ml), se secaron sobre sulfato de magnesio, se filtraron y se concentraron a presión reducida, dando un aceite pardo. El aceite se purificó por cromatografía en columna ultrarrápida sobre gel de sílice eluyendo con diclorometano, proporcionando el intermedio (60 mg) en forma de un aceite amarillo. El aceite se disolvió en diclorometano (5 ml) y se añadió cloroformiato de 1-cloroetilo (20 µl, 0,182 mmol) a temperatura ambiente en una atmósfera de nitrógeno. La mezcla se calentó a reflujo durante 4 horas, se enfrió a temperatura ambiente y se concentró a presión reducida, dando un aceite amarillo. El aceite se disolvió en metanol (5 ml) y la solución resultante se calentó a reflujo durante 1 hora, se enfrió a temperatura ambiente y se concentró a presión reducida. El producto bruto se purificó por cromatografía en columna ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco (95:4:1, en

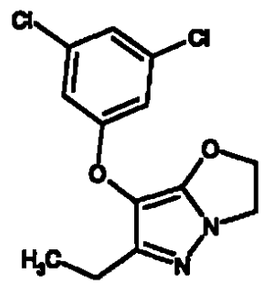
volumen), proporcionando el compuesto del título (17 mg) en forma de un aceite incoloro.

^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,08 (t, 3H), 1,16 (t, 3H), 2,48 (m, 4H), 3,87 (t, 2H), 4,40 (t, 2H), 5,07 (q, 1H), 6,79 (s, 2H), 7,01 (m, 1H).

LRMS (termonebulización): m/z [MH^+] 340.

EJEMPLO 52

7-(3,5-Diclorofenoxi)-6-etil-2,3-dihidropirazolo[5,1-*b*][1,3]oxazol



El triflato de la Preparación 15 (282 mg, 0,500 mmol), tributilvinilestaño (175 µl, 0,600 mmol), dibencilideno acetona de paladio (23 mg, 0,025 mmol), trifenilarsina (12 mg, 0,040 mmol) y cloruro de litio (64 mg, 1,50 mmol) se calentaron en *N*,*N*-dimetilformamida (3 ml) a 80°C en una atmósfera de nitrógeno durante 12 horas. La reacción se enfrió a temperatura ambiente y se repartió entre agua (20 ml) y acetato de etilo (20 ml). La capa orgánica se lavó con salmuera (10 ml), se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida. El producto bruto

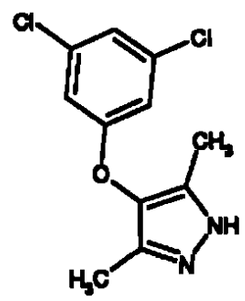
se purificó por cromatografía en columna ultrarrápida sobre gel de sílice eluyendo con pentano:acetato de etilo (90:10, en volumen), proporcionando el compuesto del título (34 mg) en forma de un aceite incoloro.

^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,16 (t, 3H), 2,45 (q, 2H), 4,29 (t, 2H), 5,03 (t, 2H), 6,89 (s, 2H), 7,02 (s, 1H).

LRMS (termonebulización): m/z [MH^+] 299.

EJEMPLO 53

4-(3,5-Diclorofenoxi)-3,5-dimetil-1*H*-pirazol



Una mezcla de 3-cloro-2,4-pentanodiona (5,00 g, 37,0 mmol), 3,5-diclorofenol (6,03 g, 37,0 mmol), carbonato de cesio (12,0 g, 37,0 mmol) y acetona (40 ml) se calentó a reflujo durante 18 horas. Después de la refrigeración, el sólido se retiró por filtración y el filtrado se concentró a presión reducida. El intermedio se disolvió en etanol (30 ml) y se añadió hidrato de hidrazina (1,85 g, 37,0 mmol) y la mezcla se calentó a 60°C durante 30 minutos. Después de la refrigeración, la mezcla se concentró a presión reducida y el residuo se purificó por cromatografía en columna

ultrarrápida sobre gel de sílice eluyendo con acetato de etilo:pentano (30:70, en volumen), proporcionando el compuesto del título (3,00 g) en forma de un aceite amarillo que solidificó tras reposo, dando un sólido amarillo, p.f. 85-87°C.

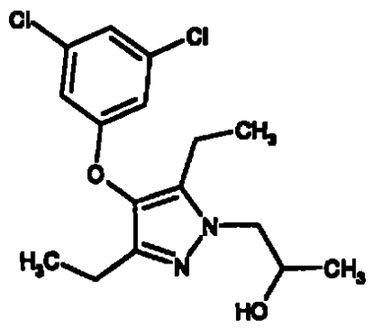
^{1}H-RMN (300 MHz, $CDCl_3$): δ = 2,14 (s, 6H), 5,24 (s a, 1H), 6,81 (s, 2H), 7,02 (s, 1H).

LRMS (termonebulización): m/z [MH^+] 257.

Microanálisis: Encontrado: C, 49,58; H, 4,06; N, 11,05. $C_{11}H_{10}Cl_2N_2O.0,4H_2O$ requiere C, 49,98; H, 4,12; N, 10,60%.

EJEMPLO 54

1-[4-(3,5-Diclorofenoxi)-3,5-dietil-1*H*-pirazol-1-il]-2-propanol



Se añadió gota a gota tetróxido de osmio (1,00 ml de una solución al 2,5% p/v en *terc*-butanol) a una solución agitada del pirazol del Ejemplo 64 (3,00 g, 9,23 mmol) y peryodato sódico (4,93 g, 23,1 mmol) en acetona (90 ml) y agua (30 ml) a temperatura ambiente.Después de 5 minutos, se formó un

precipitado blanco y la suspensión se agitó durante 3 horas más. El sólido se retiró por filtración y el filtrado se concentró a presión reducida. El residuo se repartió entre acetato de etilo (300 ml) y agua (100 ml) y la fase orgánica se separó, se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida, produciendo el aldehído intermedio. Una alícuota del aldehído (250 mg, 0,765 mmol) se disolvió en tetrahidrofurano (5 ml) y se almacenó en una atmósfera de nitrógeno. En un matraz separado, se añadió tricloruro de cerio anhidro (377 mg, 1,53 mmol) a una solución agitada de bromuro de metil magnesio (0,51 ml de una solución 3 M en éter, 1,53 mmol) en tetrahidrofurano (5 ml) a temperatura ambiente en una atmósfera de nitrógeno. La mezcla se agitó a temperatura ambiente durante 1,5 horas y se añadió gota a gota el aldehído en tetrahidrofurano. La mezcla se agitó durante 12 horas y la reacción después se inactivó con ácido acético acuoso 1 M a temperatura ambiente. La mezcla se diluyó con diclorometano (20 ml), se lavó con agua (5 ml) y salmuera (5 ml), se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida. El producto bruto se purificó por cromatografía en columna ultrarrápida sobre gel de sílice eluyendo con pentano:acetato de etilo (70:30, en volumen), proporcionando el compuesto del título (30 mg) en forma de un aceite incoloro.

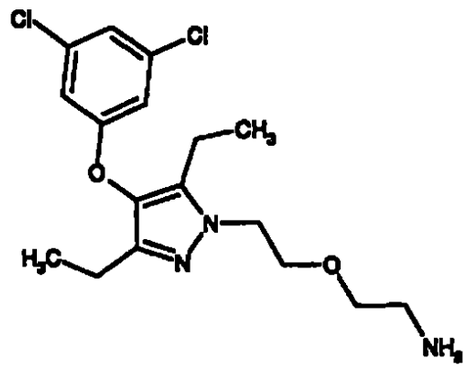
^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,05 (t, 3H), 1,10 (t, 3H), 1,21

(d, 2H), 2,40 (q, 2H), 2,47 (q, 2H), 3,79 (dd, 1H), 3,97 (dd, 1H), 4,24 (s, 1H), 6,76 (s, 2H), 6,98 (s, 1H).

LRMS (termonebulización): m/z [MH^+] 343.

EJEMPLO 55

2-{2-[4-(3,5-Diclorofenoxi)-3,5-dietil-1*H*-pirazol-1-il)etoxi}etanamina



Se añadió hidruro sódico (dispersión en aceite al 60%, 24 mg, 0,600 mmol) a una solución agitada del pirazol del Ejemplo 2 (100 mg, 0,303 mmol) en *N,N*-dimetilformamida seca (4 ml) a 0°C en una atmósfera de nitrógeno. La mezcla se agitó a 0°C durante 30 minutos y se añadió clorhidrato de 2-cloroetilamina (53 mg, 0,455 mmol). La mezcla de reacción se agitó a 0°C durante 30 minutos y después se agitó a temperatura ambiente durante 30 minutos. La reacción se enfrió a 0°C, se añadieron más hidruro sódico (dispersión en aceite al 60%, 24 mg, 0,600 mmol) y clorhidrato de 2-cloroetilamina (53 mg, 0,455 mmol) y la reacción se agitó

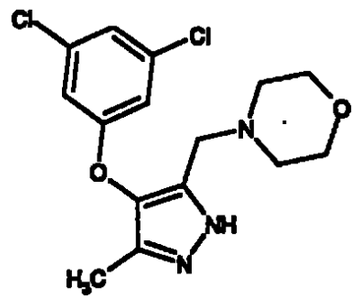
durante 1 hora. La reacción se interrumpió por la adición de agua (5 ml) y se extrajo con éter (10 ml). La capa orgánica se lavó con ácido clorhídrico acuoso 2 M (30 ml). El ácido se neutralizó con carbonato sódico sólido y se extrajo con éter (3x20 ml). Las capas de éter reunidas se secaron sobre sulfato de magnesio, se filtraron y se concentraron a presión reducida. El producto bruto se purificó por cromatografía en columna ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco (95:4:1, en volumen), proporcionando el compuesto del título (21 mg) en forma de un aceite incoloro.

^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,19 (m, 6H), 2,42 (q, 2H), 2,58 (q, 2H), 2,80 (t, 2H), 3,38 (t, 2H), 3,81 (t, 2H), 4,18 (t, 2H), 6,78 (s, 2H), 7,02 (s, 1H).

LRMS (termonebulización): m/z [MH^+] 372.

EJEMPLO 56

<u>4-{[4-(3,5-Diclorofenoxi)-3-metil-1*H*-pirazol-5-il]metil}morfolina</u>



Se añadió en una porción morfolina (140 µl, 1,59 mmol)

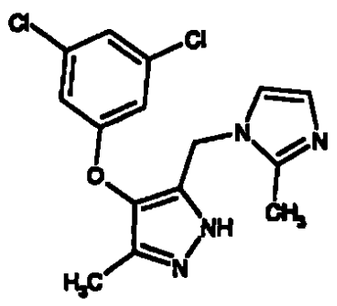
a una solución agitada del bromuro de la Preparación 8 (200 mg, 0,531 mmol) en isopropanol (4 ml) a temperatura ambiente. La mezcla se calentó a 50°C durante 1 hora, se enfrió a temperatura ambiente y se concentró a presión reducida, dando un aceite amarillo. El producto bruto se purificó por cromatografía en columna ultrarrápida sobre gel de sílice eluyendo con acetato de etilo, proporcionando el compuesto del título (60 mg) en forma de un aceite incoloro.

^{1}H-RMN (400 MHz, $CDCl_3$): δ = 2,13 (s, 3H), 2,42 (m, 4H), 3,38 (s, 2H), 3,64 (m, 4H), 6,79 (s, 2H), 7,02 (s, 1H).

LRMS (termonebulización): m/z [MH^+] 342.

EJEMPLO 57

4-[3,5-Diclorofenoxi)-3-metil-5-[(2-metil-1*H*-imidazol-1-il)metil]-1*H*-pirazol



Se añadió hidruro sódico (dispersión en aceite al 60%, 32 mg, 0,800 mmol) a una solución agitada de 2-metilimidazol (65 mg, 0,800 mmol) en *N*,*N*-dimetilformamida (5 ml) a 0°C en una atmósfera de nitrógeno. La mezcla se agitó durante 10 minutos y después se añadió el bromuro de la Preparación 8

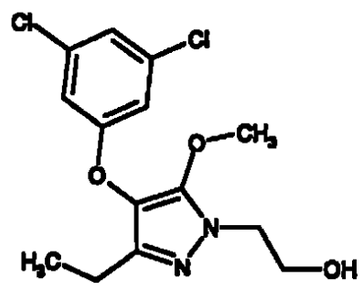
(100 mg, 0,261 mmol) y la reacción se agitó a temperatura ambiente durante 1 hora. La mezcla de reacción se inactivó por la adición de una solución acuosa 1 M de hidróxido sódico (5 ml) y la mezcla se concentró a presión reducida. Una solución del residuo en acetato de etilo (20 ml) se lavó con agua (10 ml) y salmuera (10 ml), se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida, dando un aceite pardo. El producto bruto se purificó por cromatografía en columna ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco (95:4,5:0,5, en volumen), proporcionando el compuesto del título (10 mg) en forma de un aceite incoloro.

^{1}H-RMN (300 MHz, $CDCl_3$): δ = 2,14 (s, 3H), 2,35 (s, 3H), 4,89 (s, 2H), 6,68 (s, 2H), 6,78 (s, 1H), 6,82 (s, 1H), 7,03 (s, 1H).

LRMS (termonebulización): m/z [MH^+] 337.

EJEMPLO 58

2-[4-(3,5-Diclorofenoxi)-3-etil-5-metoxi-1*H*-pirazol-1-il]etanol



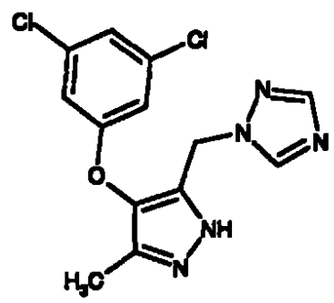
Se disolvió el triflato de la Preparación 15 (282 mg, 0,500 mmol) en metanol (3 ml) y se añadió en una porción cloruro de 1,1'-bis(difenilfosfino)ferrocenopalladio(II) (18 mg, 0,025 mmol) a temperatura ambiente. La mezcla se calentó a 50°C en una atmósfera de monóxido de carbono (345 kPa) durante 10 horas. La reacción se enfrió a temperatura ambiente y se concentró a presión reducida, dando un aceite pardo. El aceite se disolvió en una mezcla de tetrahidrofurano (0,5 ml), ácido acético glacial (1,0 ml) y agua (0,5 ml) y se agitó a temperatura ambiente durante 12 horas. El disolvente se retiró en una corriente de nitrógeno, dando un sólido amarillo y el producto bruto se purificó por cromatografía en columna ultrarrápida sobre gel de sílice eluyendo con diclorometano:acetonitrilo (95:5, en volumen) y después diclorometano:acetonitrilo (90:10, en volumen), proporcionando el compuesto del título (6 mg) en forma de un aceite incoloro.

^{1}H-RMN (300 MHz, $CDCl_3$): δ = 1,13 (t, 3H), 2,41 (q, 2H), 3,44 (s a, 1H), 3,94 (s, 3H), 4,23 (m, 4H), 6,87 (s, 2H), 7,09 (s, 1H).

LRMS (termonebulización): m/z [MH^+] 331.

EJEMPLO 59

1-{[4-(3,5-Diclorofenoxi)-3-metil-1*H*-pirazol-5-il]metil}-1*H*-1,2,4-triazol



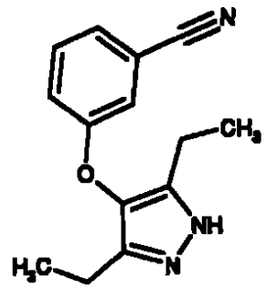
Se calentó una suspensión del bromuro de la Preparación 8 (100 mg, 0,264 mmol), 1,2,4-triazol (92 mg, 1,32 mmol) y carbonato sódico (140 mg, 1,32 mmol) en tolueno (5 ml) a 100°C durante 12 horas. La suspensión se enfrió a temperatura ambiente y se añadió una solución acuosa 1 M de hidróxido sódico (5 ml). La mezcla se extrajo con acetato de etilo (3x20 ml) y las fases orgánicas reunidas se secaron sobre sulfato de magnesio, se filtraron y se concentraron a presión reducida, dando un aceite transparente. El producto bruto se purificó por cromatografía en columna ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco (95:4,5:0,5, en volumen), proporcionando el compuesto del título (62 mg) en forma de un aceite incoloro.

^{1}H-RMN (300 MHz, $CDCl_3$): δ = 2,16 (s, 3H), 5,25 (s, 2H), 6,70 (s, 2H), 7,04 (s, 1H), 7,89 (s, 1H), 8,04 (s, 1H).

LRMS (termonebulización): m/z [MH^+] 324.

EJEMPLO 60

3-[(3,5-Dietil-1*H*-pirazol-4-il)oxi]benzonitrilo



Se añadió hidrato de hidrazina (153 µl, 3,14 mmol) a una solución agitada de la ß-dicetona de la Preparación 9 (771 mg, 3,14 mmol) en etanol (16 ml) y la solución resultante se calentó a reflujo durante 12 horas. Después de la refrigeración, la mezcla se concentró a presión reducida y el residuo se purificó por cromatografía en columna ultrarrápida sobre gel de sílice eluyendo con pentano:acetato de etilo (75:25, en volumen), proporcionando el compuesto del título (712 mg) en forma de un sólido amarillo, p.f. 81-84°C.

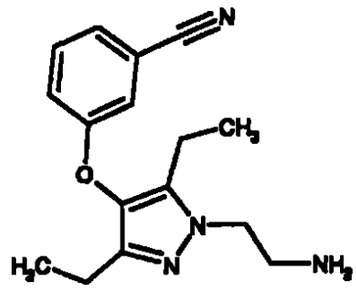
^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,15 (t, 6H), 2,47 (q, 4H), 7,11 (m, 2H), 7,24 (d, 1H), 7,35 (t, 1H).

LRMS (termonebulización): m/z [MH^+] 242.

Microanálisis: Encontrado: C, 69,03; H, 6,43; N, 17,20. $C_{14}H_{15}N_3O_3.0,13H_2O$ requiere C, 69,02; H, 6,31; N, 17,25%.

EJEMPLO 61

3-{[1-(2-Aminoetil)-3,5-dietil-1*H*-pirazol-4-il]oxi}benzonitrilo



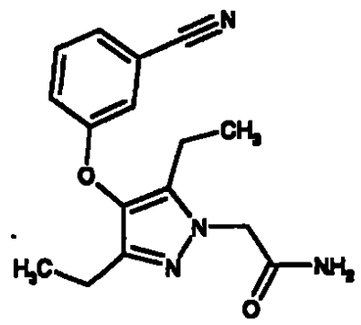
Se calentaron el pirazol del Ejemplo 60 (200 mg, 0,829 mmol) y clorhidrato de 2-cloroetilamina (144 mg, 1,24 mmol) en forma de un fundido a 150°C durante 17 horas. Después de la refrigeración, el sólido se disolvió en carbonato sódico ácido acuoso saturado (15 ml) y se extrajo con diclorometano (2x10 ml). Las fases orgánicas reunidas se lavaron con ácido clorhídrico acuoso 2 M (20 ml) y la capa acuosa se neutralizó con carbonato sódico sólido y se extrajo con diclorometano (3x10 ml). Las fase orgánicas reunidas se secaron sobre sulfato de magnesio, se filtraron y se concentraron a presión reducida, dando una goma naranja. El producto bruto se purificó por cromatografía en columna ultrarrápida sobre gel de sílice, eluyendo con diclorometano:metanol (90:10) y después con diclorometano:metanol:amoniaco (90:9:1, en volumen), proporcionando el compuesto del título (124 mg) en forma de un aceite amarillo pálido.

^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,11 (m, 6H), 2,41 (q, 2H), 2,52 (q, 2H), 3,18 (t, 2H), 4,04 (t, 2H), 7,15 (m, 2H), 7,29 (d, 1H), 7,38 (t, 1H).

LRMS (termonebulización): m/z [MH^+] 285.

EJEMPLO 62

2-[4-(3-Cianofenoxi)-3,5-dietil-1*H*-pirazol-1-il]acetamida



Se añadió una solución saturada de amoniaco en metanol (2,3 ml) al éster del Ejemplo 63 (75 mg, 0,229 mmol) en un vial a temperatura ambiente, después el vial se cerró herméticamente y se calentó a 75°C durante 17 horas. Después de la refrigeración a temperatura ambiente, la mezcla se concentró a presión reducida, dando un sólido de color crema. El producto bruto se purificó por cromatografía en columna ultrarrápida sobre gel de sílice eluyendo con diclorometano después diclorometano:metanol (99:1, en volumen), proporcionando el compuesto del título (49 mg) en forma de un sólido blanco, p.f. 159-160°C.

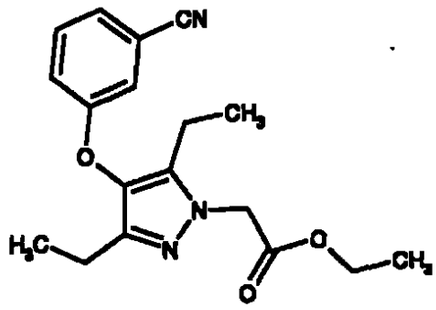
^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,10 (t, 3H), 1,17 (t, 3H), 2,44 (q, 2H), 2,53 (q, 2H), 4,69 (s, 2H), 5,44 (s a, 1H), 6,22 (s a, 1H), 7,14 (m, 2H), 7,31 (d, 1H), 7,40 (t, 1H).

LRMS (termonebulización): m/z [MH^+] 299.

Microanálisis: Encontrado: C, 64,20; H, 6,12; N, 18,79. $C_{16}H_{18}N_4O_2$ requiere C, 64,41; H, 6,08; N, 18,78%.

EJEMPLO 63

[4-(3-Cianofenoxi)-3,5-dietil-1*H*-pirazol-1-il]acetato de etilo



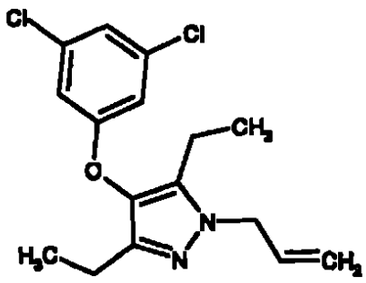
Se añadió una solución de hidrazinoacetato de etilo (88 mg, 0,571 mmol) en etanol (2,0 ml) a una solución agitada de la β-dicetona de la Preparación 9 (140 mg, 0,571 mmol) y trietilamina (88 µl, 0,628 ml) en etanol (1,0 ml) y la solución resultante se calentó a reflujo durante 18 horas. Después de la refrigeración, la mezcla se concentró a presión reducida y el residuo se repartió entre diclorometano (20 ml) y agua (10 ml). La capa orgánica se separó, se lavó con salmuera (10 ml), se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida. El producto bruto se purificó por cromatografía en columna ultrarrápida sobre gel de sílice eluyendo con pentano:acetato de etilo (75:25, en volumen) y después acetato de etilo, proporcionando el

compuesto del título (131 mg) en forma de un aceite amarillo. ^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,08 (m, 6H), 1,25 (t, 3H), 2,40 (m, 4H), 4,20 (q, 2H), 4,77 (s, 2H), 7,12 (m, 2H), 7,23 (d, 1H), 7,34 (t, 1H).

LRMS (termonebulización): m/z [MH^+] 328.

EJEMPLO 64

1-Alil-4-(3,5-diclorofenoxi)-3,5-dietil-1*H*-pirazol



Se añadió hidruro sódico (dispersión en aceite al 60%, 770 mg, 19,2 mmol) a una solución agitada de bromuro de alilo (1,70 ml, 19,2 mmol) y el pirazol del Ejemplo 3 (5,00 g, 17,5 mmol) en *N,N*-dimetilformamida (20 ml) a 0°C en una atmósfera de nitrógeno. La reacción se calentó a temperatura ambiente y se agitó durante 1 hora. La mezcla de reacción se inactivó por la adición de agua (100 ml) y la fase acuosa se extrajo con éter (2x50 ml). Las fases orgánicas reunidas se lavaron con agua (30 ml) y salmuera (30 ml), se secaron sobre sulfato de magnesio, se filtraron y se concentraron a presión reducida, dando un aceite pardo. El producto bruto se purificó por cromatografía en columna ultrarrápida sobre gel

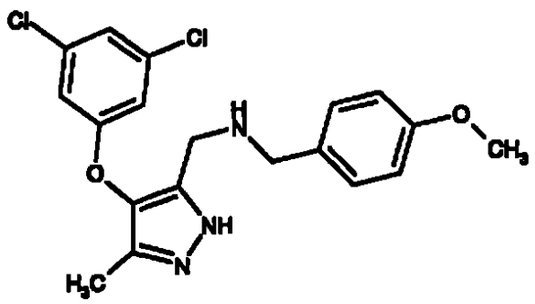
de sílice eluyendo con pentano:acetato de etilo (80:20, en volumen), proporcionando el compuesto del título (5,00 g) en forma de un aceite amarillo.

^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,11 (m, 6H), 2,46 (m, 4H), 4,65 (d, 2H), 5,04 (d, 1H), 5,22 (d, 1H), 5,99 (m, 1H), 6,79 (s, 2H), 6,99 (s, 1H).

LRMS (termonebulización): m/z [MH^+] 325.

EJEMPLO 65

N-{[4-(3,5-Diclorofenoxi)-3-metil-1*H*-pirazol-5-il]metil}-*N*-(4-metoxibencil)amina



Se añadió en una porción 4-metoxibencilamina (0,104 ml, 0,800 mmol) a una solución agitada del bromuro de la Preparación 8 (100 mg, 0,265 mmol) en isopropanol (2 ml) a temperatura ambiente. La mezcla se calentó a 50°C durante 1 hora, se enfrió a temperatura ambiente y se concentró a presión reducida, dando un aceite amarillo. El aceite se diluyó con dietil éter (20 ml), se lavó con carbonato sódico ácido acuoso saturado (5 ml) y agua (5 ml), se secó sobre sulfato de magnesio, se filtró y se concentró a presión

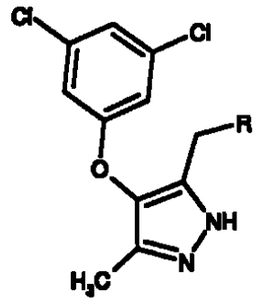
reducida. El producto bruto se purificó por cromatografía en columna ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco (95:4:1, en volumen), proporcionando el compuesto del título (50 mg) en forma de un aceite incoloro.

^{1}H-RMN (300 MHz, $CDCl_3$): δ = 2,13 (s, 3H), 3,68 (s, 2H), 3,71 (s, 2H), 3,80 (s, 3H), 6,83 (m, 4H), 7,03 (s, 1H), 7,17 (m, 2H).

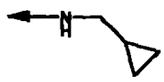
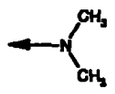
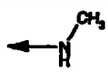
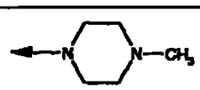
LRMS (termonebulización): m/z [MH^+] 392.

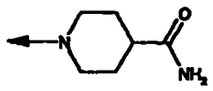
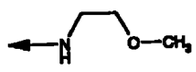
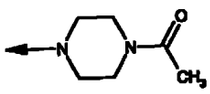
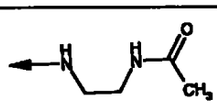
EJEMPLOS 66 A 75

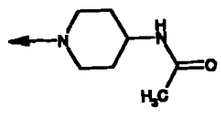
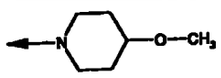
Los compuestos de los siguientes Ejemplos indicados en la tabla, de formula general:



se prepararon por un procedimiento similar al del Ejemplo 65 usando el apropiado material de partida de amina y el bromuro de la Preparación 8.

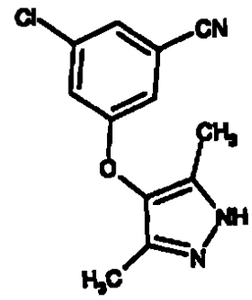
Ejemplo No.	R	LRMS (termonebulización)	Datos Analíticos
66		m/z [MH] 326	^{1}H RMN (300 MHz, $CDCl_3$) δ = 0,09 (m, 2H), 0,49 (q 2H) 0 90 (m, 1H), 2,34 (s 3H) 2,47 (d 2H) 3 73 (s 2H), 6,82 (s 2H) 7,03 (s 1H)
67		m/z [MH] 300.	^{1}H RMN (400 MHz, $CDCl_3$) δ 2,08 (s 3H), 2,20 (s 6H) 3,31 (s 2H) 6 76 (s 2H) 6,97 (s 1H)
68		m/z [MH] 286.	^{1}H RMN (400 MHz, $CDCl_3$) δ = 2,12 (s 3H) 2,42 (s 3H) 3,65 (s 2H) 6,80 (s 2H) 7,02 (s 1H)
69		m/z [MH] 355	^{1}H RMN (400 MHz, $CDCl_3$) δ = 2,08 (s 3H) 2,22 (s 3H) 2,31 (m, 8H) 3,36 (s 2H) 6,76 (s 2H) 6,97 (s 1H)

70		m/z [MH] 385	^{1}H RMN (400 MHz, $CDCl_3$) δ = 1,50 (m, 2H) 1,60 (m, 2H) 1 90 (m, 4H), 2,41 (m, 2H) 3,25 (s 2H) 3 75 (m, 2H) 5,52 (s, 1H) 5 80 (s 1H) 6,67 (s 2H) 6,86 (s, 1H)
71		m/z [MH] 330	^{1}H-RMN (400 MHz, $CDCl_3$) δ = 2,08 (s, 3H), 2 74 (m, 2H) 3,30 (s 3H) 3,44 (m, 2H) 3,68 (s 2H) 6 76 (s, 2H) 6,98 (s, 1H)
72		m/z [MH$^+$] 383	^{1}H RMN (400 MHz, $CDCl_3$) δ = 2,02 (s 3H) 2 10 (s 3H), 2,38 (m, 4H) 3,34 (m, 2H), 3,38 (s 2H) 3,51 (m, 2H) 6 76 (s 2H) 6,98 (s, 1H)
73		m/z [MH] 357	^{1}H RMN (400 MHz, $CDCl_3$) δ = 1 92 (s 3H) 2,09 (s 3H) 2,70 (m, 2H) 3,29 (m, 2H) 3,65 (s 2H) 6,01 (s 1H) 6 76 (s 2H) 6 99 (s 1H)

74		m/z [MH] 397	^{1}H-RMN (400 MHz, $CDCl_3$) δ = 1,30 (m, 2H), 1,80 (m, 2H) 1 92 (s, 3H), 2,09 (m, 5H) 2,70 (m, 2H), 3,34 (s 2H), 3 71 (m, 1H), 6,76 (s 2H), 6 98 (s 1H)
75		m/z [MH] 370.	^{1}H RMN (300 MHz, $CDCl_3$) δ = 1,60 (m, 2H), 1,80 (m, 2H) 2 13 (s 3H) 2,20 (m, 2H), 2 71 (m, 2H) 3,22 (m, 1H), 3,33 (s 3H) 3,39 (s, 2H), 6,81 (s 2H) 7,03 (s 1H)

EJEMPLO 76

3-Cloro-5-[(3,5-dimetil-1*H*-pirazol-4-il)oxi]benzonitrilo



Se añadió hidrato de hidrazina (1,10 ml, 21,9 mol) a una solución agitada de la β-dicetona de la Preparación 16 (5,50 g, 21,9 mmol) en ácido acético glacial (22 ml) y la solución resultante se agitó a temperatura ambiente durante 14 horas. La mezcla se concentró a presión reducida y el residuo se purificó por cromatografía en columna ultrarrápida sobre gel de sílice eluyendo con diclorometano y después con diclorometano:acetato de etilo (85:15, en volumen), proporcionando el compuesto del título (4,80 g) en forma de un sólido amarillo, p.f. 136-140°C.

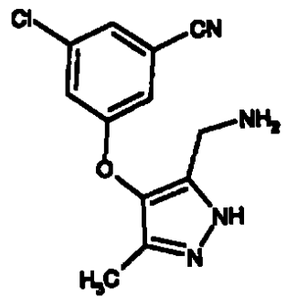
^{1}H-RMN (400 MHz, $CDCl_3$): δ = 2,09 (s, 6H), 7,02 (m, 1H), 7,10 (m, 1H), 7,25 (m, 1H).

LRMS (electronebulización): m/z [MH^+] 248.

Microanálisis: Encontrado: C, 57,91; H, 4,03; N, 16,79. $C_{12}H_{10}N_3OCl$ requiere C, 58,19; H, 4,07; N, 16,97%.

EJEMPLO 77

3-{[5-(Aminometil)-3-metil-1*H*-pirazol-4-iloxi}-5-clorobenzonitrilo



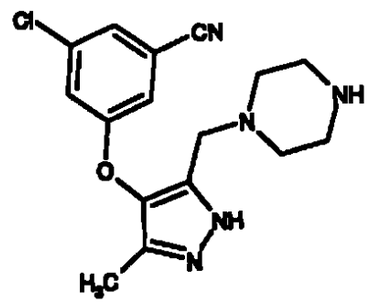
Se añadió el bromuro de la Preparación 18 (300 mg, 0,800 mmol) a una solución saturada de amoniaco en isopropanol (50 ml) a 0°C. La reacción se agitó durante 2 horas y se dejó calentar lentamente a temperatura ambiente. La mezcla se concentró a presión reducida y el aceite amarillo resultante se disolvió en diclorometano (50 ml). La solución de diclorometano se lavó con una solución acuosa 1 M de carbonato sódico (20 ml), se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida, proporcionando el compuesto del título (220 mg) en forma de una espuma blanca.

^{1}H-RMN (300 MHz, $CDCl_3$): δ = 2,14 (s, 3H), 3,79 (s, 2H), 7,08 (s, 1H), 7,16 (s, 1H), 7,31 (s, 1H).

LRMS (termonebulización): m/z [MH^+] 263.

EJEMPLO 78

3-Cloro-5-{[3-metil-5-(1-piperazinilmetil)-1*H*-pirazol-4-iloxi}benzonitrilo



Se añadió en una porción carboxilato de t-butil-1-piperazina (1,17 g, 6,30 mmol) a una solución agitada del bromuro de la Preparación 18 (500 mg, 1,40 mmol) en isopropanol (20 ml) a temperatura ambiente. La mezcla se calentó a 60°C durante 1 hora, se enfrió a temperatura ambiente y se concentró a presión reducida, dando un aceite amarillo. El aceite se disolvió en diclorometano (100 ml) y la solución resultante se lavó con carbonato sódico acuoso 1 M (20 ml) y salmuera (20 ml), se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida. El producto bruto se purificó por cromatografía en columna ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco (95:4:1, en volumen), proporcionando una espuma amarilla. La espuma se disolvió en diclorometano (10 ml), la solución resultante se enfrió a 0°C y se añadió ácido trifluoroacético (2 ml). La reacción se dejó calentar a temperatura ambiente y se agitó durante 24 horas. La mezcla se diluyó con diclorometano (50 ml), se lavó con carbonato sódico acuoso 1 M (20 ml) y salmuera (20 ml),

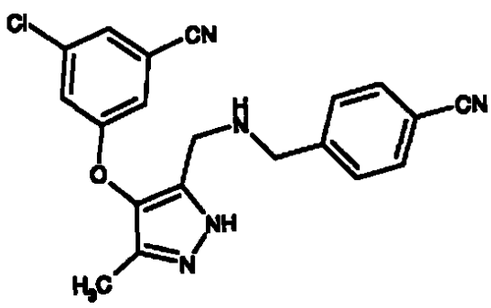
se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida. El producto bruto se purificó por cromatografía en columna ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco (90:9:1, en volumen), proporcionando el compuesto del título (400 mg) en forma de una espuma blanca.

^{1}H-RMN (300 MHz, $CDCl_3$): δ = 2,14 (s, 3H), 2,40 (m, 4H), 2,83 (m, 4H), 3,38 (s, 2H), 7,09 (s, 1H), 7,16 (s, 1H), 7,30 (s, 1H).

LRMS (termonebulización): m/z [MH^+] 332.

EJEMPLO 79

3-Cloro-5-[(5-{[4-cianobencil)amino]metil}-3-metil-1*H*-pirazol-4-il)oxi]benzonitrilo



Una mezcla de 4-cianobenzaldehído (60 mg, 0,460 mmol), la amina del Ejemplo 77 (120 mg, 0,460 mmol), sulfato de magnesio (500 mg) y diclorometano (5 ml) se agitó en una atmósfera de nitrógeno a temperatura ambiente durante 3 días. La mezcla se concentró a presión reducida y el producto bruto

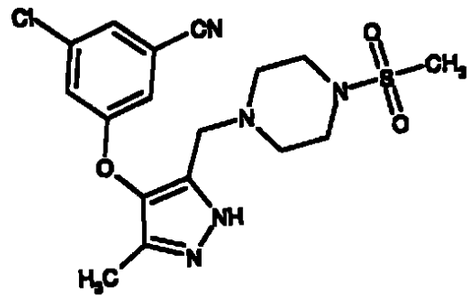
se purificó por cromatografía en columna ultrarrápida sobre gel de sílice eluyendo con metanol:acetato de etilo (5:95, en volumen), proporcionando una espuma. La espuma se disolvió en metanol (5 ml), se añadió en una porción borohidruro sódico (50 mg, 1,31 mmol) a temperatura ambiente y la reacción se agitó durante 30 minutos. La mezcla se concentró a presión reducida y el residuo se disolvió en diclorometano (20 ml). La solución resultante se lavó con una solución acuosa 1 M de carbonato sódico (10 ml) y salmuera (10 ml), se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida. El producto bruto se purificó por cromatografía en columna ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco (95:4:1, en volumen), proporcionando el compuesto del título (35 mg) en forma de una espuma blanca.

^{1}H-RMN (300 MHz, $CDCl_3$): δ = 2,15 (s, 3H), 3,69 (s, 2H), 3,84 (s, 2H), 7,06 (s, 1H), 7,15 (s, 1H), 7,31 (s, 1H), 7,38 (d, 2H), 7,60 (d, 2H).

LRMS (termonebulización): m/z [MH^+] 378.

EJEMPLO 80

3-Cloro-5-[(3-metil-5-{[4-(metilsulfonil)-1-piperazinil]metil}-1*H*-pirazol-4-il)oxi-benzonitrilo



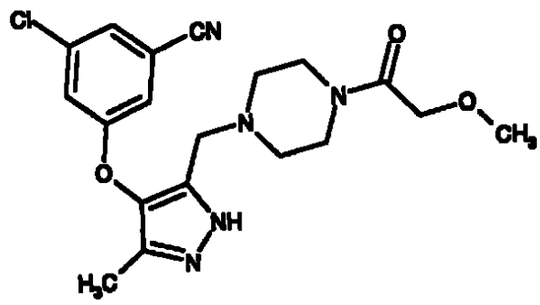
Se añadió gota a gota cloruro de metanosulfonilo (19 µl, 0,240 mmol) a una solución agitada de la amina del Ejemplo 78 (80 mg, 0,240 mmol) y trietilamina (45 µl, 0,288 mmol) en diclorometano (3 ml) a temperatura ambiente en una atmósfera de nitrógeno. La reacción se agitó durante 30 minutos y después se concentró a presión reducida, dando un aceite amarillo. El producto bruto se purificó por cromatografía en columna ultrarrápida sobre gel de sílice eluyendo con diclorometano y después con diclorometano:metanol:amoniaco (95:4:1, en volumen), proporcionando el compuesto del título (65 mg) en forma de una espuma blanca.

^{1}H-RMN (400 MHz, $CDCl_3$): δ = 2,14 (s, 3H), 2,51 (m, 4H), 2,72 (s, 3H), 3,12 (m, 4H), 3,39 (s, 2H), 7,08 (m, 1H), 7,13 (m, 1H), 7,26 (s, 1H).

LRMS (termonebulización): m/z [MH^+] 410.

EJEMPLO 81

3-Cloro-5-[(5-{[4-(metoxiacetil)-1-piperazinil]metil}-3-metil-1*H*-pirazol-4-il)oxi]benzonitrilo



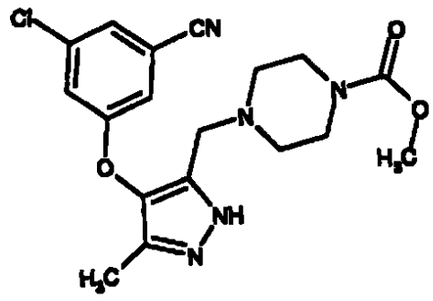
Se añadió en una porción polímero de *N*-bencil-*N'*-ciclohexilcarbodiimida unido (624 mg de 1,3 mmol/g, 0,480 mmol) a una solución agitada de ácido metoxiacético (37 µl, 0,480 mmol) y la amina del Ejemplo 78 (80 mg, 0,240 mmol) en diclorometano (5 ml) a temperatura ambiente en una atmósfera de nitrógeno. La reacción se agitó durante 1 hora y el reactivo de polímero unido se retiró por filtración. El filtrado se concentró a presión reducida y el producto bruto se purificó por cromatografía en columna ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco (95:4:1, en volumen), proporcionando el compuesto del título (45 mg) en forma de una espuma blanca.

^{1}H-RMN (400 MHz, $CDCl_3$): δ = 2,11 (s, 3H), 2,38 (m, 4H), 3,37 (m, 7H), 3,51 (m, 2H), 4,04 (s, 2H), 7,04 (m, 1H), 7,10 (m, 1H), 7,26 (m, 1H).

LRMS (termonebulización): m/z [MH^+] 404.

EJEMPLO 82

4-{[4-(3-cloro-5-cianofenoxi)-3-metil-1*H*-pirazol-5-il]metil}-1-piperazinocarboxilato de metilo



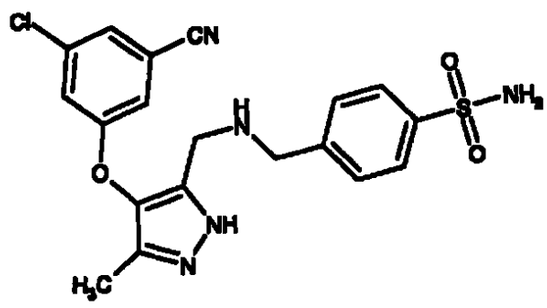
Se añadió gota a gota cloroformiato de metilo (19 µl, 0,240 mmol) a una solución agitada de la amina del Ejemplo 78 (80 mg, 0,240 mmol) y trietilamina (45 µl, 0,288 mmol) en diclorometano (5 ml) a temperatura ambiente en una atmósfera de nitrógeno. La reacción se agitó durante 90 minutos y después se concentró a presión reducida, dando un aceite amarillo. El producto bruto se purificó por cromatografía en columna ultrarrápida sobre gel de sílice eluyendo con diclorometano y después con diclorometano:metanol:amoniaco (95:4:1, en volumen), proporcionando el compuesto del título (55 mg) en forma de una espuma blanca.

^{1}H-RMN (400 MHz, $CDCl_3$): δ = 2,09 (s, 3H), 2,34 (m, 4H), 3,36 (m, 6H), 3,64 (s, 3H), 7,02 (m, 1H), 7,10 (m, 1H), 7,25 (m, 1H).

LRMS (termonebulización): m/z [MH^+] 390.

EJEMPLO 83

4-[({[4-(3-Cloro-5-cianofenoxi)-3-metil-1*H*-pirazol-5-il]metil}amino)metil]bencenosulfonamida



Se añadió en una porción trietilamina (125 µl, 0,860 mmol) a una suspensión agitada de clorhidrato de 4-aminometilbencenosulfonamida (144 mg, 0,590 mmol) y el bromuro de la Preparación 18 (100 mg, 0,270 mmol) en isopropanol (5 ml) a temperatura ambiente en una atmósfera de nitrógeno. La reacción se calentó a 70°C durante 1 hora y después se enfrió a temperatura ambiente. La mezcla se concentró a presión reducida y el producto bruto se purificó por cromatografía en columna ultrarrápida sobre gel de sílice eluyendo con diclorometano y después con diclorometano:metanol:amoniaco (90:9:1, en volumen), proporcionando una espuma. La espuma se purificó adicionalmente usando una columna Phenomenex Luna C18 eluyendo con dietilamina:metanol (0,1 :99,1, en volumen), proporcionando el compuesto del título (8 mg) en forma de una espuma blanca.

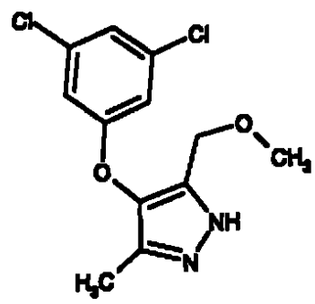
^{1}H-RMN (400 MHz, $CDCl_3$): δ = 2,06 (s, 3H), 3,27 (s, 2H), 3,62 (s, 2H), 3,79 (s, 2H), 7,17 (s, 1H), 7,21 (s, 1H), 7,40 (m,

3H), 7,77 (d, 2H).

LRMS (termonebulización): m/z [MH^+] 432.

EJEMPLO 84

4-(3,5-Diclorofenoxi)-5-(metoximetil)-3-metil-1*H*-pirazol



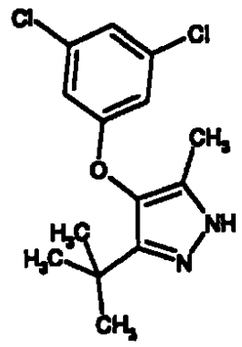
Se añadió en una porción tetraquis(trifenilfosfina)paladio (60 mg) a una solución agitada del bromuro de la Preparación 8 (590 mg, 1,56 mmol) en metanol (20 ml) y tetrahidrofurano (20 ml) a temperatura ambiente. La mezcla se calentó a 80°C en una atmósfera de monóxido de carbono (690 kPa) durante 18 horas. La reacción se enfrió a temperatura ambiente y se concentró a presión reducida, dando a aceite pardo. El aceite se disolvió en diclorometano (100 ml) y la solución resultante se lavó con agua (50 ml), se secó sobre sulfato de magnesio, se filtró y se evaporó a presión reducida. El producto bruto se purificó por cromatografía en columna ultrarrápida sobre gel de sílice eluyendo con éter, proporcionando el compuesto del título (110 mg) en forma de un aceite incoloro.

^{1}H-RMN (400 MHz, $CDCl_3$): δ = 2,15 (s, 3H), 3,34 (s, 3H), 4,35 (s, 2H), 6,83 (s, 2H), 7,03(s,1H).

LRMS (termonebulización): m/z [MH^+] 287.

EJEMPLO 85

3-*terc*-Butil-4-(3,5-diclorofenoxi)-5-metil-1*H*-pirazol



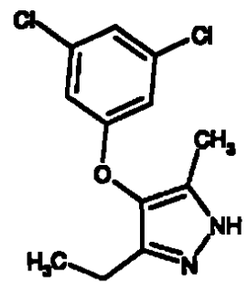
Una mezcla de la diona de la Preparación 19 (1,00 g, 5,68 mmol), 3,5-diclorofenol (930 mg, 5,68 mmol), carbonato de cesio (1,85 g, 5,68 mmol) y acetona (20 ml) se calentó a reflujo durante 18 horas. Después de la refrigeración, el sólido se retiró por filtración y el filtrado se concentró a presión reducida. El intermedio se disolvió en etanol (20 ml), se añadió hidrato de hidrazina (284 mg, 5,68 mmol) y la mezcla se calentó a 60°C durante 1 hora. Después de la refrigeración, la mezcla se concentró a presión reducida y el residuo se purificó por cromatografía en columna ultrarrápida sobre gel de sílice eluyendo con acetato de etilo:pentano (25:75, en volumen), proporcionando el compuesto del título (200 mg) en forma de un aceite amarillo.

^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,30 (s, 9H), 2,06 (s, 3H), 6,81 (s, 2H), 7,02 (s, 1H).

LRMS (termonebulización): m/z [MH^+] 299.

EJEMPLO 86

4-(3,5-Diclorofenoxi)-3-etil-5-metil-1*H*-pirazol



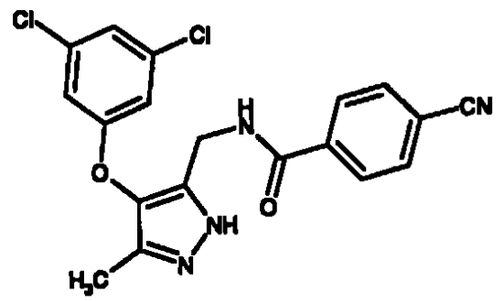
Una mezcla de la diona de la Preparación 50 (4,50 g, 30,8 mmol), 3,5-diclorofenol (5,00 g, 30,8 mmol), carbonato sódico (10,0 g, 30,8 mmol) y acetona (40 ml) se calentó a reflujo durante 18 horas. Después de la refrigeración, el sólido se retiró por filtración y el filtrado se concentró a presión reducida. El intermedio se disolvió en etanol (40 ml), se añadió hidrato de hidrazina (1,00 ml, 30,8 mmol) y la mezcla se calentó a 60°C durante 1 hora. Después de la refrigeración, la mezcla se concentró a presión reducida y el residuo se purificó por cromatografía en columna ultrarrápida sobre gel de sílice eluyendo con acetato de etilo:pentano (20:80, en volumen), proporcionando el compuesto del título (1,50 g) en forma de un aceite naranja.

^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,18 (t, 3H), 2,11 (s, 3H), 2,53 (q, 2H), 6,79 (s, 2H), 7,01 (s, 1H).

LRMS (termonebulización): m/z [MH^+] 271.

EJEMPLO 87

4-Ciano-*N*-{[4-(3,5-diclorofenoxi)-3-metil-1*H*-pirazol-5-il]metil}benzamida



Se añadió en una porción 1-(3-(dimetilamino)propil)-3-etilcarbodiimida (93 mg, 0,490 mmol) a una solución agitada de la amina del Ejemplo 109 (120 mg, 0,440 mmol) y ácido 4-cianobenzoico (71 mg, 0,490 mmol) en diclorometano (5 ml) a temperatura ambiente en una atmósfera de nitrógeno. La reacción se agitó durante 20 minutos y después se lavó con una solución acuosa 1 M de hidróxido sódico (10 ml), ácido clorhídrico acuoso 1 M (10 ml) y agua (10 ml). La capa orgánica se secó sobre sulfato de magnesio, se filtró y se evaporó a presión reducida, dando una espuma amarilla. El producto bruto se purificó por cromatografía en columna ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco (95:4:1, en volumen),

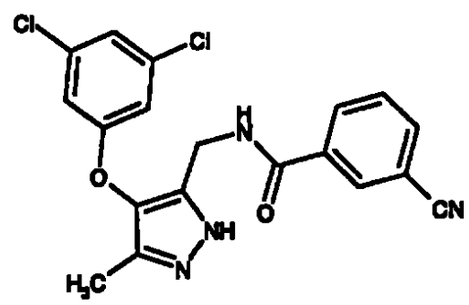
produciendo el compuesto del título (110 mg) en forma de una espuma blanca.

^{1}H-RMN (400 MHz, $CDCl_3$): δ = 2,09 (s, 3H), 4,91 (d, 2H), 6,74 (s, 2H), 6,95 (s, 1H), 6,98 (d, 1H), 7,65 (d, 2H), 7,77 (d, 2H).

LRMS (termonebulización): m/z [MNH_4^+] 418.

EJEMPLO 88

3-Ciano-*N*-{[4-(3,5-diclorofenoxi)-3-metil-1*H*-pirazol-5-il]metil}benzamida



Se añadió en una porción 1-(3-(dimetilamino)propil)-3-etilcarbodiimida (93 mg, 0,490 mmol) a una solución agitada de la amina del Ejemplo 109 (120 mg, 0,440 mmol) y ácido 3-cianobenzoico (71 mg, 0,490 mmol) en diclorometano (5 ml) a temperatura ambiente en una atmósfera de nitrógeno. La reacción se agitó durante 10 minutos y después se lavó con una solución acuosa 1 M de hidróxido sódico (10 ml), ácido clorhídrico acuoso 1 M (10 ml) y salmuera (10 ml). La capa orgánica se secó sobre sulfato de magnesio, se filtró y se evaporó a presión reducida, dando una espuma de color crema.

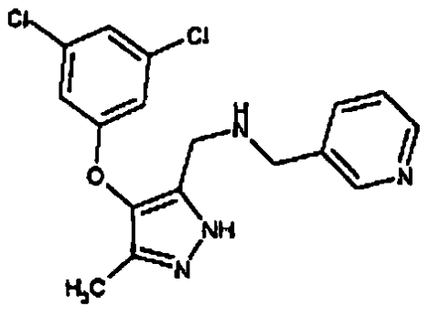
El producto bruto se purificó por cromatografía en columna ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco (95:4:1, en volumen), produciendo el compuesto del título (100 mg) en forma de una espuma blanca.

^{1}H-RMN (400 MHz, $CDCl_3$): δ = 2,14 (s, 3H), 4,53 (d, 2H), 6,78 (s, 2H), 6,98 (m, 2H), 7,54 (dd, 1H), 7,76 (d, 1H), 7,95 (d, 1H), 7,99 (s, 1H).

LRMS (termonebulización): m/z [MH^+] 401.

EJEMPLO 89

N-{[4-(3,5-Diclorofenoxi)-3-metil-1*H*-pirazol-5-il]metil}-*N*-(3-piridinilmetil)amina



Una mezcla de 3-piridinocarboxaldehído (55 mg, 0,514 mmol), la amina del Ejemplo 109 (140 mg, 0,514 mmol), sulfato de magnesio (500 mg) y diclorometano (5 ml) se agitó en una atmósfera de nitrógeno a temperatura ambiente durante 18 horas. Se añadió en una porción triacetoxiborohidruro sódico (163 mg, 0,771 mmol) y después se añadió ácido acético (3

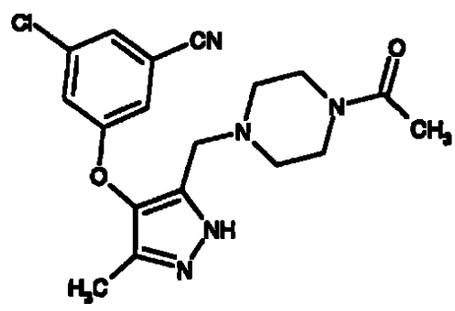
gotas). Después de 5 minutos, la mezcla se filtró. El filtrado se lavó con una solución acuosa 1 M de carbonato sódico (10 ml), agua (10 ml) y salmuera (10 ml), se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida, dando un aceite transparente. El producto bruto se purificó por cromatografía en columna ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco (95:4:1, en volumen), proporcionando el compuesto del título (60 mg) en forma de un aceite incoloro.

^{1}H-RMN (400 MHz, $CDCl_3$): δ = 2,09 (s, 3H), 3,66 (s, 2H), 3,74 (s, 2H), 6,75 (s, 2H), 6,97 (s, 1H), 7,17 (m, 1H), 7,55 (d, 1H), 8,49 (m, 2H).

LRMS (electronebulización): m/z [MH^+] 363.

EJEMPLO 90

3-({5-[(4-Acetil-1-piperazinil)metil]-3-metil-1*H*-pirazol-4-il}oxi)-5-clorobenzonitrilo



Se añadió en una porción N-acetilpiperazina (104 mg, 0,810 mmol) a una solución agitada del bromuro de la

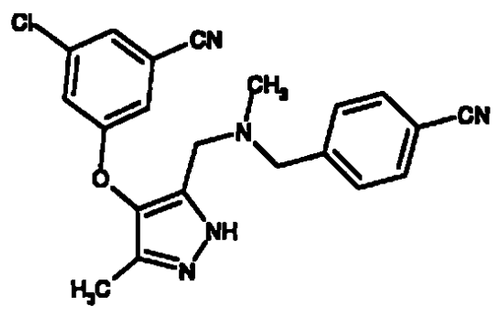
Preparación 18 (100 mg, 0,271 mmol) en isopropanol (5 ml) a temperatura ambiente. La mezcla se calentó a 50°C durante 1 hora, se enfrió a temperatura ambiente y se concentró a presión reducida, dando un aceite amarillo. El producto bruto se purificó por cromatografía en columna ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco (95:4:1, en volumen), proporcionando el compuesto del título (90 mg) en forma de un aceite incoloro.

^{1}H-RMN (300 MHz, $CDCl_3$): δ = 2,08 (s, 3H), 2,16 (s, 3H), 2,43 (m, 4H), 3,42 (m, 4H), 3,55 (m, 2H), 7,08 (s, 1H), 7,16 (s, 1H), 7,31 (s, 1H).

LRMS (termonebulización): m/z [MH^+] 374.

EJEMPLO 91

3-Cloro-5-[(5-{[(4-cianobencil)(metil)amino]metil}-3-metil-1*H*-pirazol-4-il)oxi]benzonitrilo



Se añadió en una porción la amina de la Preparación 20 (127 mg, 0,870 mmol) a una solución agitada del bromuro de la Preparación 18 (100 mg, 0,271 mmol) en isopropanol (5 ml)

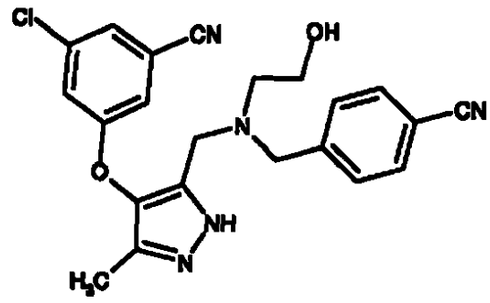
a temperatura ambiente. La mezcla se calentó a 50°C durante 12 horas, se enfrió a temperatura ambiente y se concentró a presión reducida, dando un aceite amarillo. El aceite se disolvió en ácido clorhídrico 1 M y la solución acuosa se lavó con acetato de etilo (10 ml) . Se añadió carbonato sódico sólido hasta que cesó la efervescencia y la mezcla se extrajo con acetato de etilo (3x20 ml). Las fases orgánicas reunidas se secaron sobre sulfato de magnesio, se filtraron y se concentraron a presión reducida. El residuo se purificó por cromatografía en columna ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco (95:4:1, en volumen), proporcionando el compuesto del título (45 mg) en forma de un aceite incoloro.

^{1}H-RMN (300 MHz, $CDCl_3$): δ = 2,14 (s, 3H), 2,17 (s, 3H), 3,45 (s, 2H), 3,55 (s, 2H), 7,05 (s, 1H), 7,14 (s, 1H), 7,31 (m, 3H), 7,59 (d, 2H).

LRMS (termonebulización): m/z [MH^+] 392.

EJEMPLO 92

3-Cloro-5-[(5-{[(4-cianobencil)(2-hidroxietil)amino]metil}-3-metil-1*H*-pirazol-4-il)oxi]benzonitrilo



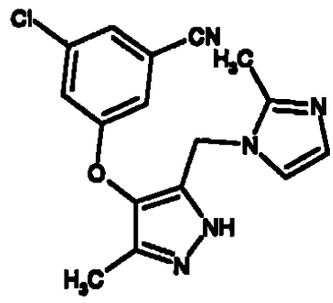
Se añadió en una porción la amina de la Preparación 21 (153 mg, 0,870 mmol) a una solución agitada del bromuro de la Preparación 18 (100 mg, 0,271 mmol) en isopropanol (5 ml) a temperatura ambiente. La mezcla se calentó a 50°C durante 12 horas, se enfrió a temperatura ambiente y se concentró a presión reducida, dando un aceite amarillo. El aceite se disolvió en una solución acuosa 1 M de hidróxido sódico y La solución resultante se agitó a temperatura ambiente durante 1 hora. El extracto acuoso se extrajo con acetato de etilo (3x20 ml) y las fases orgánicas reunidas se secaron sobre sulfato de magnesio, se filtraron y se concentraron a presión reducida. El residuo se purificó por cromatografía en columna ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco (95:4:1, en volumen), proporcionando el compuesto del título (20 mg) en forma de un aceite incoloro.

^{1}H-RMN (300 MHz, $CDCl_3$): δ = 2,14 (s, 3H), 2,71 (m, 2H), 3,50 (s, 1H), 3,58 (s, 2H), 3,67 (m, 2H), 3,72 (s, 2H), 6,99 (s, 1H), 7,09 (s, 1H), 7,31 (s, 1H), 7,41 (d, 2H), 7,58 (d,2H).

LRMS (termonebulización): m/z [MH^+] 422.

EJEMPLO 93

3-Cloro-5-({3-metil-5-[(2-metil-1*H*-imidazol-1-il)metil]-1*H*-pirazol-4-il}oxi)benzonitrilo



Una suspensión del bromuro de la Preparación 18 (100 mg, 0,264 mmol), 2-metilimidazol (111 mg, 1,35 mmol) y carbonato sódico (143 mg, 1,35 mmol) en tolueno (5 ml) se calentó a 100°C durante 12 horas. La suspensión se enfrió a temperatura ambiente, se añadió una solución acuosa 1 M de hidróxido sódico (5 ml) y la mezcla se agitó durante 1 hora. La mezcla se extrajo con acetato de etilo (3x20 ml) y las fases orgánicas reunidas se secaron sobre sulfato de magnesio, se filtraron y se concentraron a presión reducida, dando un sólido blanco. El producto bruto se purificó por cromatografía en columna ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco (95:4,5:0,5, en volumen), proporcionando el compuesto del título (77 mg) en forma de un sólido blanco, p.f. 212-214°C.

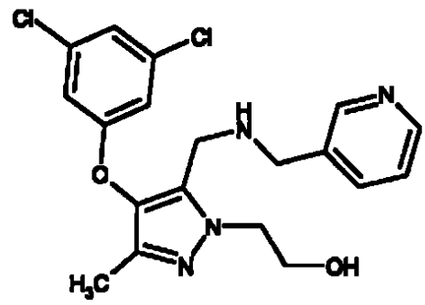
^{1}H-RMN (300 MHz, $CDCl_3$): δ = 2,14 (s, 3H), 2,33 (s, 3H), 4,92

(s, 2H), 6,76 (s, 1H), 6,79 (s, 1H), 6,86 (s, 1H), 7,27 (s, 2H).

LRMS (termonebulización): m/z [MH^+] 328.

EJEMPLO 94

2-(4-(3,5-Diclorofenoxi)-3-metil-5-{[(3-piridinilmetil)amino]metil}-1*H*-pirazol-1-il)etanol



Se añadió en una porción fluoruro de tetrabutilamonio (0,58 ml de una solución 1,0 M en tetrahidrofurano, 0,580 mmol) a una solución agitada de la amina de la Preparación 22 (150 mg, 0,290 mmol) en diclorometano (5 ml) a temperatura ambiente. La reacción se agitó durante 12 horas y se concentró a presión reducida, dando un aceite incoloro. El producto bruto se purificó por cromatografía en columna ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco (95:4:1, en volumen), proporcionando el compuesto del título (100 mg) en forma de un aceite incoloro.

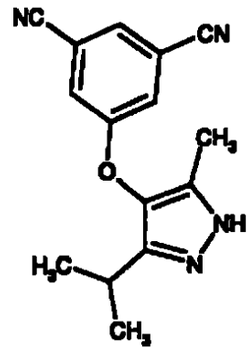
^{1}H-RMN (400 MHz, $CDCl_3$): δ = 2,07 (s, 3H), 3,65 (s, 2H), 3,76

(s, 2H), 3,96 (m, 2H), 4,24 (m, 2H), 6,76 (s, 2H), 7,02 (s, 1H), 7,26 (m, 1H), 7,59 (d, 1H), 8,50 (m, 2H).

LRMS (termonebulización): m/z [MH^+] 407.

EJEMPLO 95

5-[(3-Isopropil-5-metil-1*H*-pirazol-4-il)oxi]isoftalonitrilo



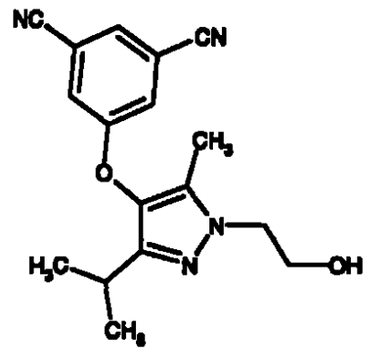
Se añadió hidrato de hidrazina (110 µl, 2,24 mmol) a una solución agitada de la β-dicetona de la Preparación 24 (550 mg, 2,04 mmol) en ácido acético glacial (5 ml) y la solución resultante se agitó a temperatura ambiente durante 1 hora. La mezcla se concentró a presión reducida y el residuo se purificó por cromatografía en columna ultrarrápida sobre gel de sílice eluyendo con pentano:acetato de etilo (60:40, en volumen), proporcionando el compuesto del título (350 mg) as un sólido amarillo, p.f. 142-144°C.

^{1}H-RMN (300 MHz, $CDCl_3$): δ = 1,21 (d, 6H), 2,09 (s, 3H), 2,90 (sept, 1H), 7,40 (s, 2H), 7,60 (s, 1H).

LRMS (termonebulización): m/z [MH^+] 267.

EJEMPLO 96

5-{[1-(2-Hidroxietil)-3-isopropil-5-metil-1*H*-pirazol-4-il]oxi}isoftalonitrilo



Se añadió en una porción fluoruro de tetrabutilamonio (0,28 ml de una solución 1,0 M en tetrahidrofurano, 0,280 mmol) a una solución agitada del pirazol de la Preparación 25 (60 mg, 0,140 mmol) en diclorometano (5 ml) a temperatura ambiente. La reacción se agitó durante 12 horas y se concentró a presión reducida, dando un aceite incoloro. El producto bruto se purificó por cromatografía en columna ultrarrápida sobre gel de sílice eluyendo con pentano:acetato de etilo (20:80, en volumen), proporcionando el compuesto del título (30 mg) en forma de un sólido blanco.

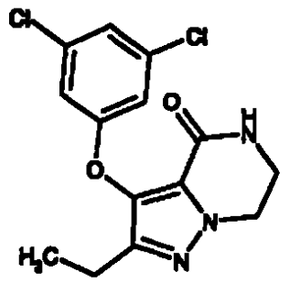
^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,17 (d, 6H), 2,08 (s, 3H), 2,76 (sept, 1H), 3,52 (m, 2H), 4,10 (m, 2H), 7,40 (s, 2H), 7,59 (s, 1H).

LRMS (electronebulización): m/z [MH^+] 311.

Microanálisis: Encontrado: C, 65,44; H, 5,87; N, 17,91. $C_{17}H_{18}N_4O_2$ requiere C, 65,79; H, 5,85; N, 18,05%.

EJEMPLO 97

3-(3,5-Diclorofenoxi)-2-etil-6,7-dihidropirazolo[1,5-a]pirazin-4(5*H*)-ona



Se añadió gota a gota diisopropilamida de litio (18,0 ml de una solución 1,5 M en ciclohexano, 27,0 mmol) a una solución agitada del pirazol de la Preparación 26 (12,3 g, 24,6 mmol) en tetrahidrofurano (120 ml) a -78°C en una atmósfera de nitrógeno. La reacción se agitó durante 14 horas, se calentó lentamente a temperatura ambiente y se inactivo cuidadosamente con una solución acuosa saturada de cloruro amónico (20 ml). La mezcla se concentró a presión reducida y el residuo se disolvió en diclorometano (200 ml). La solución resultante se lavó con una solución acuosa saturada de cloruro amónico (100 ml), se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida, dando un sólido blanco. El sólido se trituró con una mezcla de diclorometano y pentano (100 ml y 100 ml), dando el compuesto del título (2,63 g) en forma de un sólido blanco, p.f. 220-223°C.

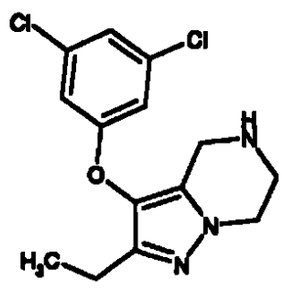
^{1}H-RMN (400 MHz, D_6DMSO): δ = 1,08 (t, 3H), 2,44 (q, 2H), 3,60 (m, 2H), 4,24 (t, 2H), 7,00 (s, 2H), 7,26 (s, 1H), 8,15 (s, 1H).

LRMS (termonebulización): m/z [MNH_4^+] 343.

Microanálisis: Encontrado: C, 51,52; H, 3,98; N, 12,74. $C_{14}H_{31}Cl_2N_3O_2$ requiere C, 51,55; H, 4,02; N, 12,88%.

EJEMPLO 98

3-(3,5-Diclorofenoxi)-2-etil-4,5,6,7-tetrahidropirazolo[1,5-a]pirazina



Se añadió borano (2,00 ml de una solución 1,0 M en tetrahidrofurano, 2,00 mmol) a una solución agitada del pirazol del Ejemplo 97 (326 mg, 1,00 mmol) en tetrahidrofurano (10 ml) a temperatura ambiente en una atmósfera de nitrógeno. La reacción se calentó a reflujo durante 5 horas y se añadió más borano (3,00 ml de una solución 1,0 M en tetrahidrofurano, 3,00 mmol). La reacción se calentó a reflujo durante 14 horas y se añadió más borano (2,00 ml de una solución 1,0 M en tetrahidrofurano, 2,00 mmol). La reacción se calentó a reflujo durante 3 horas y se

añadió más borano (2,00 ml de una solución 1,0 M en tetrahidrofurano, 2,00 mmol). La mezcla se enfrió a temperatura ambiente, se añadió ácido clorhídrico 2 M (10 ml) y la mezcla se calentó a reflujo durante 1 hora. La mezcla se enfrió a temperatura ambiente y se concentró a presión reducida. El residuo se disolvió en diclorometano (40 ml), se lavó con una solución acuosa 1 M de carbonato potásico (30 ml), se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida. El producto bruto se purificó por cromatografía en columna ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol (98:2, en volumen), después con diclorometano:metanol (95:5, en volumen) y después con diclorometano:metanol:amoniaco (90:9:1, en volumen), proporcionando el compuesto del título (219 mg) en forma de un sólido blanco, p.f. 76-77°C.

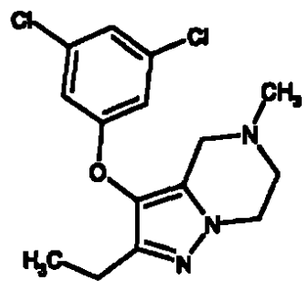
^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,10 (t, 3H), 2,42 (q, 2H), 3,24 (t, 2H), 3,80 (s, 2H), 4,05 (t, 2H), 6,76 (s, 2H), 6,95 (s, 1H).

LRMS (termonebulización): m/z [MH^+] 312.

Microanálisis: Encontrado: C, 53,79; H, 4,88; N, 13,14. $C_{14}H_{15}Cl_2N_3O$ requiere C, 53,86; H, 4,84; N, 13,46%.

EJEMPLO 99

<u>3-(3,5-Diclorofenoxi)-2-etil-5-metil-4,5,6,7-tetrahidropirazolo[1,5-a]pirazina</u>



Se añadió yoduro de metilo (11 µl, 0,176 mmol) a una solución agitada de carbonato potásico (24 mg, 0,176 mmol) y la amina del Ejemplo 98 (50 mg, 0,160 mmol) en *N,N*-dimetilformamida (2 ml) a temperatura ambiente en una atmósfera de nitrógeno. La reacción se agitó durante 3 horas y después se concentró a presión reducida. El residuo se disolvió en acetato de etilo (20 ml), se lavó con una solución acuosa 1 M de carbonato potásico (20 ml), se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida. El producto bruto se purificó por cromatografía en columna ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol (98:2, en volumen), proporcionando el compuesto del título (18 mg) en forma de un aceite incoloro.

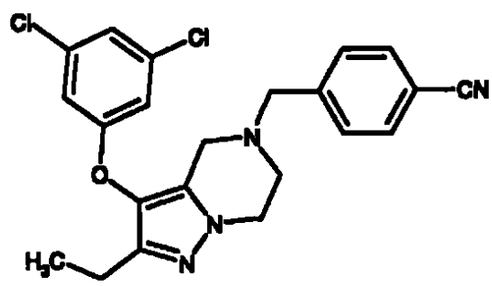
^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,11 (t, 3H), 2,42 (m, 5H), 2,84 (t, 2H), 3,37 (s, 2H), 4,11 (t, 2H), 6,77 (s, 2H), 6,98 (s, 1H).

LRMS (termonebulización): m/z [MH^+] 326.

EJEMPLO 100

4-[(3-(3,5-Diclorofenoxi)-2-etil-6,7-dihidropirazolo[1,5-

alpirazin-5(4*H*)-il)metil]benzonitrilo



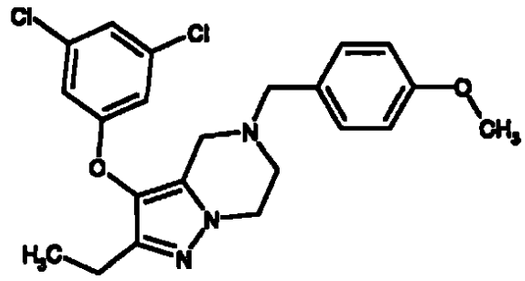
Se añadió bromuro de 4-cianobencilo (35 mg, 0,176 mmol) a una solución agitada de carbonato potásico (24 mg, 0,176 mmol) y la amina del Ejemplo 98 (50 mg, 0,160 mmol) en *N*,*N*-dimetilformamida (2 ml) a temperatura ambiente en una atmósfera de nitrógeno. La reacción se agitó durante 14 horas y después se concentró a presión reducida. El residuo se disolvió en acetato de etilo (20 ml) y la solución resultante se lavó con una solución acuosa 1 M de carbonato potásico (15 ml), se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida. El producto bruto se purificó por cromatografía en columna ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol (98:2, en volumen), proporcionando el compuesto del título (66 mg) en forma de un sólido blanco, p.f. 149-150°C.

^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,13 (t, 3H), 2,44 (q, 2H), 2,92 (t, 2H), 3,42 (s, 2H), 3,71 (s, 2H), 4,13 (t, 2H), 6,74 (s, 2H), 6,97 (s, 1H), 7,42 (d, 2H), 7,60 (d, 2H).

LRMS (termonebulización): m/z [MH^+] 427.

EJEMPLO 101

3-(3,5-Diclorofenoxi)-2-etil-5-(4-metoxibencil)-4,5,6,7-tetrahidropirazolo[1,5-a]pirazina



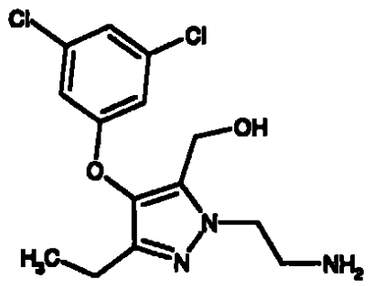
Se añadió cloruro de 4-metoxibencilo (24 µl, 0,176 mmol) a una solución agitada de carbonato potásico (24 mg, 0,176 mmol) y la amina del Ejemplo 98 (50 mg, 0,160 mmol) en *N,N*-dimetilformamida (6 ml) a temperatura ambiente en una atmósfera de nitrógeno. La reacción se agitó durante 14 horas y se añadieron carbonato potásico (12 mg, 0,088 mmol) y cloruro de 4-metoxibencilo (12 µl, 0,088 mmol). La reacción se agitó durante 3 horas y después se concentró a presión reducida. El residuo se disolvió en acetato de etilo (20 ml) y la solución resultante se lavó con una solución acuosa 1 M de carbonato potásico (20 ml), se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida. El producto bruto se purificó por cromatografía en columna ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol (99:1, en volumen), proporcionando el compuesto del título (50 mg) en forma de un aceite incoloro.

^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,13 (t, 3H), 2,45 (q, 2H), 2,92 (t, 2H), 3,44 (s, 2H), 3,60 (s, 2H), 3,80 (s, 3H), 4,10 (t, 2H), 6,77 (s, 2H), 6,85 (d, 2H), 7,00 (s, 1H), 7,23 (d,2H).

LRMS (termonebulización): m/z [MH^+] 432.

EJEMPLO 102

[1-(2-Aminoetil)-4-(3,5-diclorofenoxi)-3-etil-1*H*-pirazol-5-il]metanol



Se añadió cloruro de hidrógeno (0,50 ml de una solución 4,0 M en dioxano, 2,00 mmol) a una solución agitada del pirazol del Ejemplo 135 (86 mg, 0,200 mmol) en dioxano (0,5 ml) a temperatura ambiente en una atmósfera de nitrógeno. La reacción se agitó durante 24 horas y se concentró a presión reducida. El residuo se disolvió en diclorometano (20 ml) y la solución resultante se lavó con una solución acuosa 1 M de carbonato potásico (10 ml), se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida. El producto bruto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol (99:1, en volumen), proporcionando el compuesto del título (40 mg)

en forma de un sólido blanco, p.f. 105-107°C.

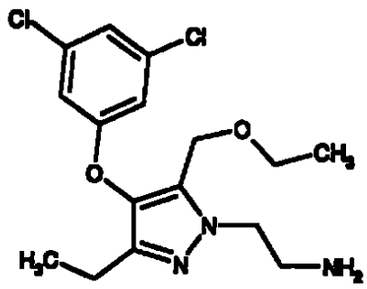
^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,10 (t, 3H), 2,42 (q, 2H), 2,55 (s, 2H), 3,13 (t, 2H), 4,13 (t, 2H), 4,37 (s, 2H), 6,79 (s, 2H), 6,98 (s, 1H).

LRMS (termonebulización): m/z [MH^+] 330.

Microanálisis: Encontrado: C, 50,61; H, 5,23; N, 12,31. $C_{14}H_{17}Cl_2N_3O_2$ requiere C, 50,92; H, 5,19; N, 12,73%.

EJEMPLO 103

2-[4-(3,5-Diclorofenoxi)-5-(etoximetil)-3-etil-1*H*-pirazol-1-il]etilamina



Se añadió cloruro de hidrógeno (0,50 ml de una solución 4,0 M en dioxano, 2,00 mmol) a una solución agitada del pirazol del Ejemplo 136 (60 mg, 0,130 mmol) en dioxano (0,5 ml) a temperatura ambiente en una atmósfera de nitrógeno. La reacción se agitó durante 2 días y se concentró a presión reducida. El residuo se disolvió en diclorometano (20 ml) y la solución resultante se lavó con una solución acuosa 1 M de carbonato potásico (10 ml), se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida. El

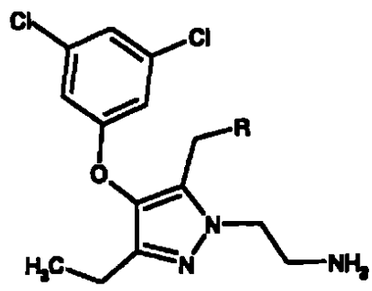
producto bruto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco (99:9:1, en volumen), proporcionando el compuesto del título (32 mg) en forma de un aceite incoloro.

^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,10 (m, 6H), 2,42 (q, 2H), 3,15 (t, 2H), 3,40 (q, 2H), 4,11 (t, 2H), 4,29 (s, 2H), 6,79 (s, 2H), 6,98 (s, 1H).

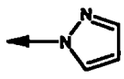
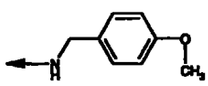
LRMS (termonebulización): m/z [MH^+] 358.

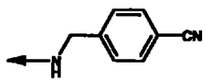
EJEMPLOS 104 A 106

Los compuestos de los siguientes Ejemplos indicados en la tabla, de formula general:



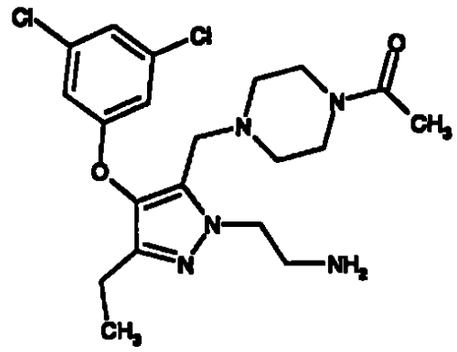
se prepararon por un procedimiento similar al del Ejemplo 103 usando el apropiado material de partida.

Ejemplo No (Material de partida)	R	LRMS (termonebulización)	Datos Analíticos
104 (Ejemplo 140)		m/z [MH] 380.	^{1}H RMN (400 MHz, $CDCl_3$) δ = 1 10 (t, 3H) 2,40 (q 2H) 2 97 (t, 2H) 4 15 (t 2H), 5 20 (s 2H), 6 16 (s 1H) 6,71 (d 2H) 6 97 (s 1H) 7 15 (s 1H), 7,42 (s 1H) Microanálisis Encontrado C 52 78, H 5,09 N 17 86 $C_{17}H_{17}Cl_2O.0.12CH_2Cl_2$ requiere C 52,66 H 4 97 N 17 94%
105 (Ejemplo 142)		m/z [MH] 449	^{1}H RMN (400 MHz, $CDCl_3$) δ = 1 10 (t 3H) 2,42 (q 2H), 3 11 (t, 2H) 3,55 (s, 2H) 3,60 (s 2H) 3 75 (s 3H) 4,07 (t 2H) 6,73 (s 2H) 6 79 (d 2H) 6 97 (s 1H) 7 10 (d 2H) Microanálisis Encontrado: C 56,88 H 5,67 N 11,88. $C_{20}H_{24}Cl_2N_2O_2.0.23CH_2Cl_2$ requiere C 56 94 H 5,69 N 11 95%

106 (Ejemplo 143)		m/z [MH] 444	^{1}H RMN (400 MHz, $CDCl_3$) δ = 1 10 (t, 3H) 2,41 (q 2H) 3 15 (t, 2H) 3,60 (s 2H) 3 74 (s 2H) 4 10 (d 2H) 6,73 (s 2H) 6,97 (s 1H) 7,29 (d 2H) 7,53 (d 2H) Microanálisis Encontrado. C 57,53 H 5,09 N 15,05 $C_{28}H_{26}Cl_4N_4O.0,22CH_2Cl_2$ requiere C 57,64 H 5 10, N 15 12%

EJEMPLO 107

2-[5-[(4-Acetil-1-piperazinil)metil]-4-(3,5-diclorofenoxi)-3-etil-1*H*-pirazol-1-il]etilamina



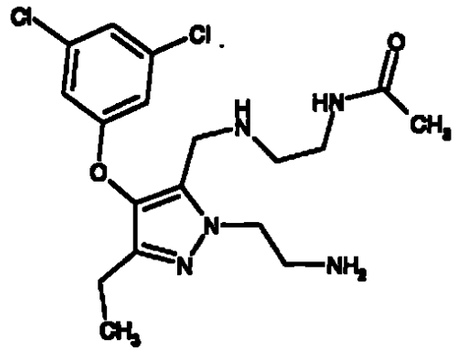
Se añadió ácido trifluoroacético (1 ml) a una solución agitada del pirazol del Ejemplo 139 (150 mg, 0,28 mmol) en diclorometano (2 ml) a temperatura ambiente en una atmósfera de nitrógeno. La reacción se agitó durante 3 horas y la mezcla se concentró a presión reducida. El residuo se disolvió en diclorometano (20 ml) y la solución resultante se lavó con una solución acuosa 1 M de carbonato potásico (30 ml), se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida. El producto bruto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco (90:9:1, en volumen), proporcionando el compuesto del título (103 mg) en forma de un aceite incoloro.

^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,11 (t, 3H), 2,05 (s, 3H), 2,32 (m, 4H), 2,42 (q, 2H), 3,13 (m, 2H), 3,33 (s, 2H), 3,34 (m,

2H), 3,52 (m, 2H), 4,15 (t, 2H), 6,73 (s, 2H), 6,97 (s, 1H). LRMS (termonebulización): m/z [MH^+] 440.

EJEMPLO 108

N-[2-({[(1-(2-Aminoetil)-4-(3,5-diclorofenoxi)-3-etil-1*H*-pirazol-5-il]metil}amino)etil]acetamida



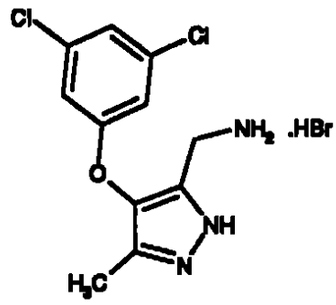
Se añadió ácido trifluoroacético (1 ml) a una solución agitada del pirazol del Ejemplo 141 (122 mg, 0,24 mmol) en diclorometano (2 ml) a temperatura ambiente en una atmósfera de nitrógeno. La reacción se agitó durante 3 horas y la mezcla se concentró a presión reducida. El residuo se disolvió en diclorometano (50 ml) y la solución resultante se lavó con una solución acuosa 1 M de carbonato potásico (30 ml), se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida. El producto bruto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco (90:9:1, en volumen), proporcionando el compuesto del título (64 mg) en forma de un aceite incoloro.

^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,15 (t, 3H), 1,95 (s, 3H), 2,45 (q, 2H), 2,69 (t, 2H), 3,20 (t, 2H), 3,27 (m, 2H), 3,65 (s, 2H), 4,15 (t, 2H), 6,31 (s, 1H), 6,81 (s, 2H), 7,02 (s, 1H).

LRMS (termonebulización): m/z [MH^+] 414.

EJEMPLO 109

Bromhidrato de [4-(3,5-diclorofenoxi)-3-metil-1*H*-pirazol-5-il]metanamida



Se añadió en porciones el bromuro de la Preparación 8 (500 mg, 1,30 mmol) a una solución saturada de amoniaco en isopropanol (50 ml) a 0°C. La reacción se agitó durante 2 horas y se dejó calentar lentamente a temperatura ambiente. La mezcla se concentró a presión reducida y el sólido resultante se trituró con dietil éter, proporcionando el compuesto del título (340 mg) en forma de un sólido blanco.

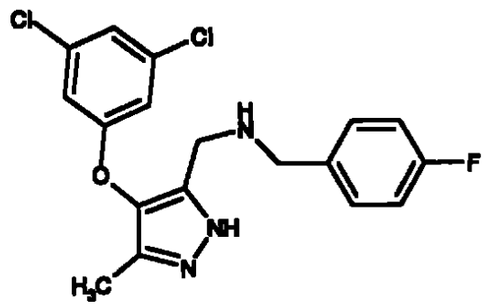
^{1}H-RMN (400 MHz, $CDCl_3$): δ = 2,38 (s, 3H), 4,78 (s, 2H), 6,88 (s, 2H), 7,19 (s, 1H).

LRMS (termonebulización): m/z [MH^+] 272.

EJEMPLO 110

N-{[4-(3,5-Diclorofenoxi)-3-metil-1*H*-pirazol-5-il]metil}-*N*-

(4-fluorobencil)amina



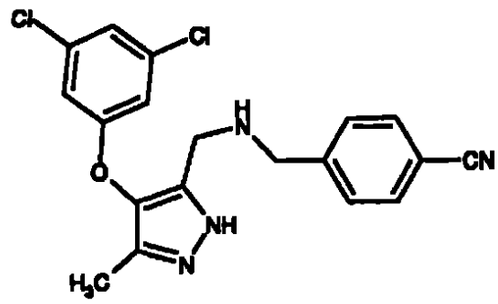
Se añadió en una porción triacetoxiborohidruro sódico (36 mg, 0,160 mmol) a una solución agitada del pirazol del Ejemplo 109 (150 mg, 0,400 mmol), 4-fluorobenzaldehído (11 mg, 0,080 mmol) y ácido acético (3 gotas) en diclorometano (15 ml) a temperatura ambiente en una atmósfera de nitrógeno. La reacción se agitó durante 3 horas y después se concentró a presión reducida. El producto bruto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco (90:9:1, en volumen), proporcionando el compuesto del título (6 mg) en forma de un aceite incoloro.

^{1}H-RMN (300 MHz, $CDCl_3$): δ = 2,17 (s, 3H), 3,67 (s, 2H), 3,73 (s, 2H), 6,81 (s, 2H), 6,99 (s, 2H), 7,02 (s, 1H), 7,22 (s, 2H).

LRMS (electronebulización): m/z [M-H$^+$] 378.

EJEMPLO 111

4-[({[4-(3,5-Diclorofenoxi)-3-metil-1*H*-pirazol-5-il]metil}amino)metil]benzonitrilo



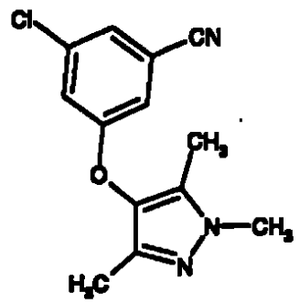
Se añadió en una porción triacetoxiborohidruro sódico (216 mg, 1,09 mmol) a una solución agitada del pirazol del Ejemplo 109 (300 mg, 0,850 mmol), 4-cianobenzaldehído (111 mg, 0,850 mmol) y ácido acético (3 gotas) en diclorometano (25 ml) a temperatura ambiente en una atmósfera de nitrógeno. La reacción se agitó durante 14 horas y después se lavó con una solución acuosa 1 M de carbonato sódico (2x10 ml) y salmuera (10 ml), se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida. El producto bruto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco (95:4:1, en volumen), proporcionando el compuesto del título (10 mg) en forma de un aceite incoloro.

^{1}H-RMN (300 MHz, $CDCl_3$): δ = 2,16 (s, 3H), 3,70 (s, 2H), 3,85 (s, 2H), 6,78 (s, 2H), 7,01 (s, 2H), 7,35 (d, 2H), 7,58 (d, 2H).

LRMS (electronebulización): m/z [MH^+] 387.

EJEMPLO 112

3-Cloro-5-[(1,3,5-trimetil-1*H*-pirazol-4-il)oxi]benzonitrilo



Se añadió metil hidrazina (250 mg, 5,17 mol) a una solución agitada de la β-dicetona de la Preparación 16 (1,00 g, 3,97 mmol) en ácido acético glacial (10 ml) y la solución resultante se agitó a temperatura ambiente durante 2 días. La mezcla se concentró a presión reducida y el aceite naranja resultante se purificó por cromatografía en columna ultrarrápida sobre gel de sílice eluyendo con pentano:acetato de etilo (50:50, en volumen), proporcionando el compuesto del título (500 mg) en forma de un sólido blanco, p.f. 114-116°C.

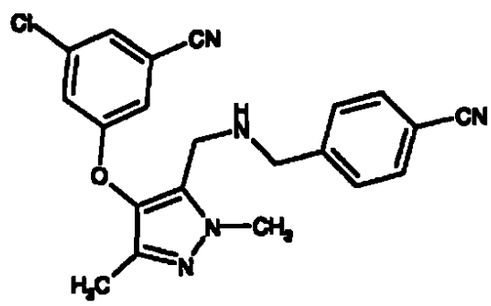
^{1}H-RMN (300 MHz, $CDCl_3$): δ = 1,85 (s, 3H), 1,87 (s, 3H), 3,61 (s, 3H), 6,88 (s, 1H), 6,98 (s, 1H), 7,11 (s, 1H).

LRMS (termonebulización): m/z [MH^+] 262.

Microanálisis: Encontrado: C, 59,48; H, 4,60; N, 15,88. $C_{13}H_{12}N_3OCl$ requiere C, 59,66; H, 4,62; N, 16,06%.

EJEMPLO 113

3-Cloro-5-[(5-{[(4-cianobencil)amino]metil}-1,3-dimetil-1*H*-pirazol-4-il)oxi]benzonitrilo



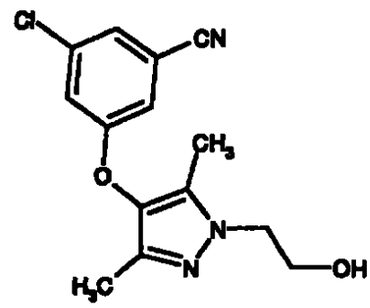
Se añadió en una porción 4-cianobencilamina (155 mg, 1,17 mmol) a una solución agitada del bromuro del Ejemplo 144 (100 mg, 0,300 mmol) en isopropanol (10 ml) a temperatura ambiente. La mezcla se calentó a 50°C durante 1 hora, se enfrió a temperatura ambiente y se concentró a presión reducida, dando un aceite amarillo. El producto bruto se purificó por cromatografía en columna ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco (95:4:1, en volumen), proporcionando el compuesto del título (97 mg) en forma de un aceite incoloro.

^{1}H-RMN (300 MHz, $CDCl_3$): δ = 2,03 (s, 3H), 3,66 (s, 2H), 3,79 (s, 2H), 3,84 (s, 3H), 7,02 (s, 1H), 7,13 (s, 1H), 7,31 (s, 1H), 7,37 (d, 2H), 7,58 (d, 2H).

LRMS (termonebulización): m/z [MH^+] 392.

EJEMPLO 114

3-Cloro-5-{[1-(2-hidroxietil)-3,5-dimetil-1*H*-pirazol-4-il]oxi}benzonitrilo



Se añadió 2-hidroxietil hidrazina (1,80 g, 24,0 mol) a una solución agitada de la β-dicetona de la Preparación 16 (5,80 g, 23,0 mmol) en ácido acético glacial (30 ml) y la solución resultante se agitó a temperatura ambiente durante 2 días. La mezcla se concentró a presión reducida y el aceite pardo resultante se purificó por cromatografía en columna ultrarrápida sobre gel de sílice eluyendo con pentano:acetato de etilo (50:50, en volumen), proporcionando el compuesto del título (4,80 g) en forma de un sólido amarillo, p.f. 114-116°C.

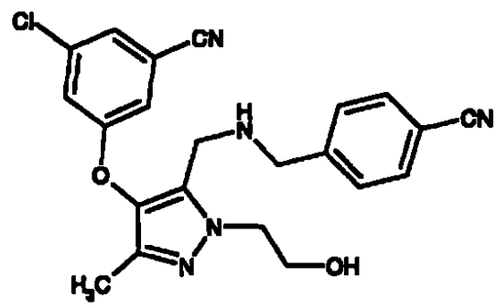
^{1}H-RMN (300 MHz, $CDCl_3$): δ = 2,04 (s, 3H), 2,12 (s, 3H), 3,24 (s, 1H), 4,08 (m, 4H), 7,03 (s, 1H), 7,15 (s, 1H), 7,28 (s, 1H).

LRMS (termonebulización): m/z [MH^+] 292.

Microanálisis: Encontrado: C, 57,40; H, 4,86; N, 14,14. $C_{14}H_{14}N_3O_2Cl$ requiere C, 57,69; H, 4,84; N, 14,40%.

EJEMPLO 115

3-Cloro-5-{[5-{[(4-cianobencil)amino]metil}-1-(2-hidroxietil)-3-metil-1*H*-pirazol-4-il]-oxi}benzonitrilo



Se añadió 4-cianobencilamina (131 mg, 0,910 mmol) a una solución agitada del pirazol de la Preparación 30 (120 mg, 0,240 mmol) en *N*-metilpirrolidina (10 ml) y la solución resultante se calentó a 60°C durante 3 horas. La mezcla se concentró a presión reducida y el aceite pardo resultante se disolvió en ácido acético (10 ml) y se calentó a 40°C durante 6 horas. La mezcla se concentró a presión reducida y el producto bruto se purificó por cromatografía en columna ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco (95:4:1, en volumen), proporcionando el compuesto del título (5 mg) en forma de un sólido blanco.

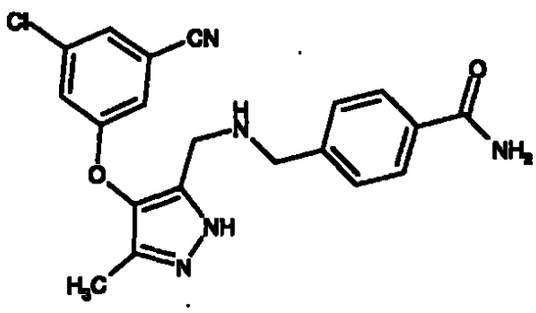
^{1}H-RMN (300 MHz, $CDCl_3$): δ = 2,05 (s, 3H), 3,04 (s, 2H), 3,91 (s, 2H), 3,99 (t, 2H), 4,32 (m, 2H), 7,06 (s, 1H), 7,11 (s, 1H), 7,33 (s, 1H), 7,46 (d, 2H), 7,62 (d, 2H).

LRMS (termonebulización): m/z [MNa^+] 444.

EJEMPLO 116

4-[({[4-(3-Cloro-5-cianofenoxi)-3-metil-1*H*-pirazol-5-

il]metil}amino)metil]benzamida

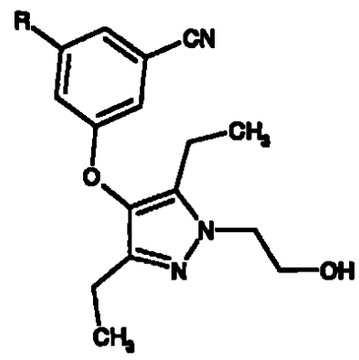


Se añadió la amina de la Preparación 55 (150 mg, 0,800 mmol) a una solución agitada del pirazol de la Preparación 18 (100 mg, 0,270 mmol) y trietilamina (81 mg, 0,800 mmol) en isopropanol (10 ml) y *N,N*-dimetilformamida (5 ml) y la solución resultante se calentó a 60°C durante 3 horas. La mezcla se concentró a presión reducida y el aceite pardo resultante se disolvió en acetato de etilo (20 ml). La solución se lavó con una solución acuosa 1 M de carbonato sódico (2x10 ml) y salmuera (10 ml), se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida. El producto bruto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:-metanol:amoniaco (90:9:1, en volumen), proporcionando el compuesto del título (5 mg) en forma de un aceite incoloro. ^{1}H-RMN (300 MHz, $CDCl_3$): δ = 2,16 (s, 3H), 3,68 (s, 2H), 3,82 (s, 2H), 7,05 (s, 1H), 7,13 (s, 1H), 7,28 (s, 1H), 7,32 (d, 2H), 7,76 (d, 2H).

LRMS (electronebulización): m/z [MH^+] 396.

EJEMPLOS 117 A 120

Los compuestos de los siguientes Ejemplos indicados en la tabla, de formula general:

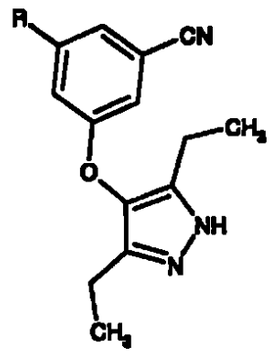


se prepararon por un procedimiento similar al del Ejemplo 114 usando el apropiado material de partida de dicetona y 2-hidroxietilhidrazina.

Ejemplo No. (Decisona No)	R	LRMS	Datos Analíticos
117 (Preparación 43)	F	m/z [MH] 303 (termonebulización)	^{1}H RMN (300 MHz, $CDCl_3$). δ = 1 10 (m, 6H) 2,39 (q 2H), 2,49 (q 2H) 4,04 (m, 4H) 6,85 (dd 1H), 6 99 (s 1H), 7,00 (dd 1H). Microanálisis Encontrado: C 62 96, H 5 94 N 13 75 $C_{16}H_{19}N_2O_2F$ requiere C 63,35 H 5 98 N 13,85%
118 (Preparación 44)	Me	m/z [MH] 300 (electronebulización)	^{1}H RMN (400 MHz, $CDCl_3$) δ 1,09 (t 3H) 1 12 (t, 3H) 2,34 (s 3H) 2,39 (q 2H), 2,50 (q 2H) 3 70 (s 1H) 4,60 (m, 4H) 6,91 (s 1H) 6 97 (s 1H) 7 10 (s 1H)
119 (Preparación 45)	CN	m/z [MH] 311 (electronebulización)	^{1}H RMN (400 MHz $CDCl_3$) δ = 1 13 (m 6H) 2 40 (q 2H), 2,53 (q 2H) 3,53 (m, 1H) 4 11 (m, 4H) 7,40 (s 2H), 7,58 (s 1H) Microanálisis Encontrado: C 65,64 H 5 84 N 18,05 $C_{17}H_{18}N_4O_2$ requiere C 65 79· H 5 85 N 18,05% p f 120-121°C
120 (Preparación 46)	Cl	m/z [MH] 320 (termonebulización)	^{1}H RMN (400 MHz, $CDCl_3$) δ = 1.08 (m, 6H) 2,39 (q 2H) 2,50 (q 2H) 4,01 (m, 2H) 4,08 (m, 2H) 7,03 (s 1H) 7 13 (s 1H) 7,24 (s 1H) Microanálisis Encontrado: C 59,67 H 5 71 N 12 99 $C_{16}H_{18}N_2O_2Cl$ requiere C 60,09 H 5,67 N 13 14%

EJEMPLOS 121 A 124

Los compuestos de los siguientes Ejemplos indicados en la tabla, de formula general:

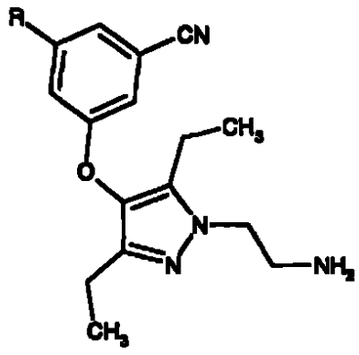


se prepararon por un procedimiento similar al del Ejemplo 76 usando el apropiado material de partida de dicetona e hidrazina.

Ejemplo No. (Dicetona No.)	R	LRMS	Datos Analíticos
121 (Preparación 43)	F	m/z [MH] 260. (termonebulización)	^{1}H RMN (400 MHz, $CDCl_3$) δ = 1 18 (t, 6H) 2,47 (q 4H) 6,85 (dd 1H), 6,98 (s 1H), 7,01 (dd 1H)
122 (Preparación 45)	CN	m/z [MH] 267 (termonebulización)	^{1}H RMN (400 MHz, $CDCl_3$) δ = 1,20 (6H m), 2,47 (q 4H) 7,39 (s 2H) 7,59 (s 1H)
123 (Preparación 44)	Me	m/z [MH] 256 (electronebulización)	^{1}H RMN (400 MHz, $CDCl_3$) δ = 1 17 (t 6H) 2,34 (s 3H) 2,48 (q 4H), 6 92 (s 1H) 6 96 (s 1H), 7 10 (s 1H)
124 (Preparación 46)	Cl	m/z [MH] 276. (termonebulización)	^{1}H RMN (400 MHz, $CDCl_3$) δ = 1 18 (t, 6H), 2,49 (q 4H), 7,07 (s 1H) 7 13 (s 1H) 7,27 (s 1H)

EJEMPLOS 125 A 128

Los compuestos de los siguientes Ejemplos indicados en la tabla, de formula general:

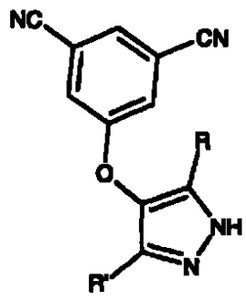


se prepararon por un procedimiento similar al del Ejemplo 13 usando el apropiado material de partida de pirazol y clorhidrato de cloroetilamina.

Ejemplo No. (Pirazol de partida No)	R	LRMS	Datos Analíticos
125 (Ejemplo 123)	Me	m/z [MH] 299 (termonebulización)	^{1}H RMN (400 MHz, $CDCl_3$) δ = 1 10 (m, 6H) 2,34 (s, 3H), 2,39 (q 2H) 2,43 (q 2H) 3 17 (t 2H) 4,04 (t, 2H) 6 91 (s 1H) 6 96 (s 1H) 7,09 (s 1H)
126 (Ejemplo 124)	Cl	m/z [MH] 319 (termonebulización)	^{1}H RMN (400 MHz, $CDCl_3$) δ = 1,09 (m, 6H) 2,40 (q 2H) 2,51 (q 2H) 3 15 (m, 2H) 4,02 (m, 2H) 7,04 (s, 1H) 7 12 (s 1H) 7 28 (s, 1H)
127 (Ejemplo 122)	CN	m/z [MH] 310 (termonebulización)	^{1}H RMN (400 MHz, $CDCl_3$) δ = 1,09 (m, 6H) 2,38 (q 2H), 2,50 (q 2H) 3 15 (m, 2H) 4,03 (m, 2H) 7,39 (s 2H) 7,57 (s 1H)
128 (Ejemplo 121)	F	m/z [MH] 303 (termonebulización)	^{1}H RMN (400 MHz, $CDCl_3$) δ = 1,06 (m, 6H) 2,37 (q 2H) 2,48 (q 2H) 3 13 (t, 2H) 4,03 (t, 2H), 6,84 (d 1H) 6,94 (s 1H), 6,97 (d 1H)

EJEMPLOS 129 A 131

Los compuestos de los siguientes Ejemplos indicados en la tabla, de formula general:

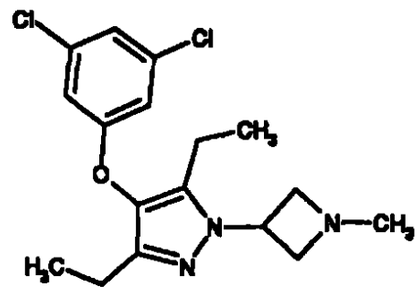


se prepararon por un procedimiento similar al del Ejemplo 76 usando el apropiado material de partida de dicetona e hidrazina.

Ejemplo No (Dicetona No.)	R	R	LRMS	Datos Analíticos
129 (Preparación 52)	ciclopPr	Et	m/z [MH] 279 (electronebulización)	^{1}H RMN (400 MHz, $CDCl_3$) δ = 0 73 (m, 2H) 0,81 (m, 2H) 1 16 (t, 3H) 1,58 (m, 1H) 2,46 (q 2H), 7,42 (s 2H) 7,58 (s, 1H) P f 136-141°C
130 (Preparación 53)	tBu	Me	m/z [MH] 281 (electronebulización)	^{1}H RMN (300 MHz, $CDCl_3$). δ = 1 21 (s 9H) 1 94 (s 3H) 7 34 (s 2H), 7,56 (s 1H) Microanálisis Encontrado· C 68 18 H 5 74 N 19 72 $C_{16}H_{16}N_4O$ requiere C 68,55 H 5 75 N 19 99% P f 61-63°C
131 (Ejemplo 54)	iPr	Et	m/z [MH] 281 (electronebulización)	^{1}H-RMN (400 MHz, $CDCl_3$) δ = 1 15 (m, 9H) 2,41 (q 2H) 2,82 (m 1H) 7 36 (s 2H) 7,58 (s 1H) P f 136-141°C

EJEMPLO 132

4-(3,5-Diclorofenoxi)-3,5-dietil-1-(1-metil-3-azetidinil)-1*H*-pirazol



Se añadió en una porción paraformaldehído (30 mg, 0,330 mmol) a una solución agitada del pirazol del Ejemplo 51 (120 mg, 0,330 mmol) en ácido fórmico (2 ml) a temperatura ambiente. La mezcla se calentó a 100°C durante 5 horas, se enfrió a temperatura ambiente y se concentró a presión reducida, dando un aceite incoloro. El aceite se disolvió en acetato de etilo (50 ml) y la solución resultante se lavó con carbonato sódico ácido acuoso saturado (20 ml), agua (20 ml) y salmuera (20 ml), se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida. El producto bruto se purificó por cromatografía en columna ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco (95:4:1, en volumen), proporcionando el compuesto del título (85 mg) en forma de un aceite incoloro.

^{1}H-RMN (300 MHz, $CDCl_3$): δ = 1,08 (t, 3H), 1,16 (t, 3H), 2,49 (m, 7H), 3,63 (m, 2H), 3,81 (m, 2H), 4,79 (m, 1H), 6,79 (s,

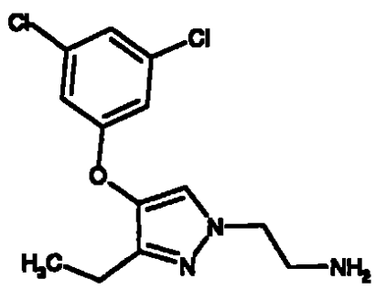
2H), 7,00 (s, 1H).

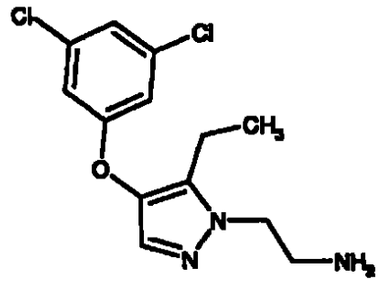
LRMS (termonebulización): m/z [MH^+] 354.

EJEMPLOS 133-134

2-[4-(3,5-Diclorofenoxi)-3-etil-1*H*-pirazol-1-il]etilamina (Ejemplo 133) y

2-[4-(3,5-Diclorofenoxi)-5-etil-1*H*-pirazol-1-il]etilamina (Ejemplo 134)





Una mezcla del pirazol (1,03 g, 4,00 mmol) del Ejemplo 42 y clorhidrato de cloroetilamina (510 mg, 4,40 mmol) se agitó y se calentó a 150°C durante 24 horas. Después de la refrigeración la mezcla se repartió entre una solución acuosa 1 M de carbonato potásico (30 ml) y diclorometano (30 ml).La capa orgánica se lavó con salmuera (30 ml), se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida. El aceite pardo resultante se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco (93:6:1, en volumen), produciendo los compuestos del título (768 mg) en una

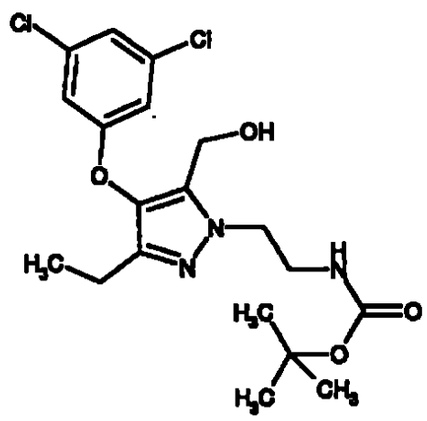
relación 85:15 de regioisómeros en forma de un aceite incoloro.

^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,16 (principal, t, 3H), 1,16 (minoritario, t, 3H), 2,48 (principal, q, 2H), 2,60 (minoritario, q, 2H), 3,13 (principal, t, 2H), 3,19 (minoritario, t, 2H), 4,10 (principal, t, 2H), 4,10 (minoritario, t, 2H), 6,85 (principal, s, 2H), 6,85 (minoritario, s, 2H), 7,02 (principal, s, 1H), 7,02 (minoritario, s, 1H), 7,27 (principal, s, 1H), 7,31 (minoritario, s, 1H).

LRMS (termonebulización): m/z [MH^+] 300.

EJEMPLO 135

2-[4-(3,5-Diclorofenoxi)-3-etil-5-(hidroximetil)-1*H*-pirazol-1-il]etilcarbamato de *terc*-butilo



Una solución del pirazol del Ejemplo 97 (1,96 g, 6,00 mmol) en ácido clorhídrico concentrado (50 ml) se calentó a reflujo durante 20 horas. La reacción se enfrió a temperatura

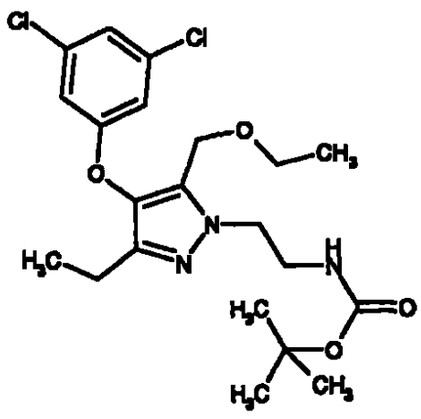
ambiente y se concentró a presión reducida. El residuo se disolvió en dioxano (80 ml) y agua (60 ml), se añadieron dicarbonato de di-t-butilo (1,44 g, 6,60 mmol) y carbonato sódico ácido (1,26 g, 15,0 mmol) y la reacción se agitó a temperatura ambiente durante 3 días. La reacción se concentró a presión reducida. Una solución del residuo en diclorometano (300 ml) se lavó con ácido clorhídrico acuoso 2 M (100 ml), se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida. Una solución del producto bruto en tetrahidrofurano (50 ml) se enfrió a -40°C en una atmósfera de nitrógeno y se añadieron gota a gota trietilamina (0,79 ml, 5,68 mmol) y cloroformiato de isopropilo (5,68 ml de una solución 1,0 M en tolueno, 5,68 mmol). La reacción se agitó a - 40°C durante 40 minutos y después se calentó a 0°C. Se añadió en una porción borohidruro sódico (537 mg, 14,2 mmol) y después se añadió agua (3 gotas) y la reacción se agitó a 0°C durante 1 hora y a temperatura ambiente durante 14 horas. La mezcla se concentró a presión reducida y se lavó una solución del residuo en diclorometano (100 ml) con agua (100 ml), se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida. El producto bruto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol (97:3, en volumen), proporcionando el compuesto del título (1,37 g) en forma de una espuma blanca.

^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,10 (t, 3H), 1,37 (s, 9H), 2,40 (q, 2H), 3,00 (s, 1H) 3,56 (m, 2H), 4,20 (t, 2H), 4,48 (d, 2H), 5,00 (m, 1H), 6,80 (s, 2H), 6,97 (s, 1H).

LRMS (termonebulización): m/z [MH^+] 430.

EJEMPLO 136

2-[4-(3,5-diclorofenoxi)-5-(etoximetil)-3-etil-1*H*-pirazol-1-il]etilcarbamato de terc-butilo



Se añadió en una porción óxido de plata (I) (210 mg, 0,900 mmol) a una solución agitada del alcohol del Ejemplo 135 (129 mg, 0,300 mmol) en yoduro de etilo (1,75 ml) a temperatura ambiente en una atmósfera de nitrógeno. La reacción se calentó a 40°C durante 1 día y después se enfrió a temperatura ambiente. La mezcla se filtró y el sólido residual se lavó con diclorometano (10 ml). El filtrado se concentró a presión reducida. El producto bruto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol (99:1, en volumen), proporcionando

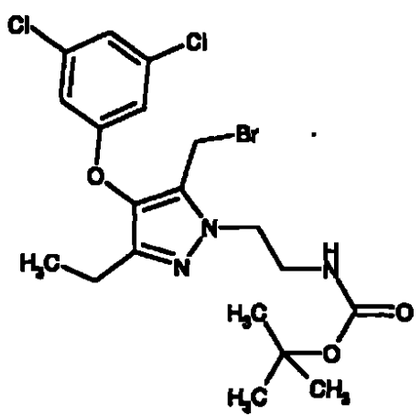
el compuesto del título (60 mg) en forma de un aceite incoloro.

^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,15 (m, 6H), 1,44 (s, 9H), 2,45 (q, 2H), 3,45 (q, 2H), 3,58 (m, 2H), 4,18 (m, 2H), 4,29 (s, 2H), 5,26 (m, 1H), 6,92 (s, 2H), 7,00 (s, 1H).

LRMS (electronebulización): m/z [MNa^+] 480.

EJEMPLO 137

2-[5-(bromometil)-4-(3,5-diclorofenoxi)-3-etil-1*H*-pirazol-1-il]etilcarbamato de *terc*-butilo



Se añadió gota a gota bromo (160 µl, 3,12 mmol) a una solución agitada de trifenilfosfina (820 mg, 3,12 mmol) e imidazol (213 mg, 3,12 mmol) en diclorometano (15 ml) a temperatura ambiente en una atmósfera de nitrógeno. Después se añadió una solución del alcohol del Ejemplo 135 (1,12 g, 2,60 mmol) en diclorometano (5 ml) a la reacción. La reacción se agitó a temperatura ambiente durante 2 horas, se diluyó con diclorometano (50 ml), se lavó con salmuera (20 ml), se

secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida. El producto bruto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol (98:2, en volumen), proporcionando el compuesto del título (969 mg) en forma de una espuma blanca.

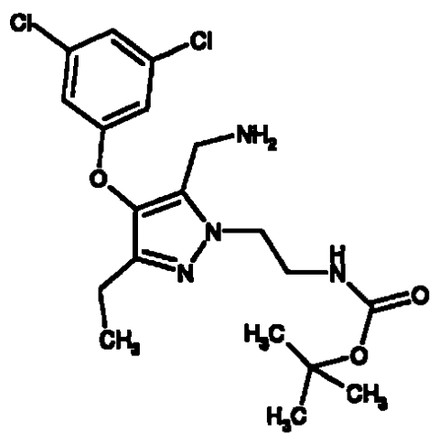
^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,10 (t, 3H), 1,40 (s, 9H), 2,40 (q, 2H), 3,60 (m, 2H), 4,18 (t, 2H), 4,27 (s, 2H), 4,95 (s, 1H), 6,82 (s, 2H), 7,00 (s, 1H).

LRMS (electronebulización): m/z [MH^+] 494.

Microanálisis: Encontrado: C, 46,22; H, 4,89; N, 8,44. $C_{19}H_{24}BrCl_2N_3O_3$ requiere C, 46,27; H, 4,90; N, 8,52%.

EJEMPLO 138

2-[5-(aminometil)-4-(3,5-diclorofenoxi)-3-etil-1*H*-pirazol-1-il]etilcarbamato de *terc*-butilo



Se añadió el bromuro del Ejemplo 137 (444 mg, 0,900 mmol) a una solución saturada de amoniaco en isopropanol (25 ml) y diisopropiletilamina (173 µl, 1,00 mmol) a temperatura

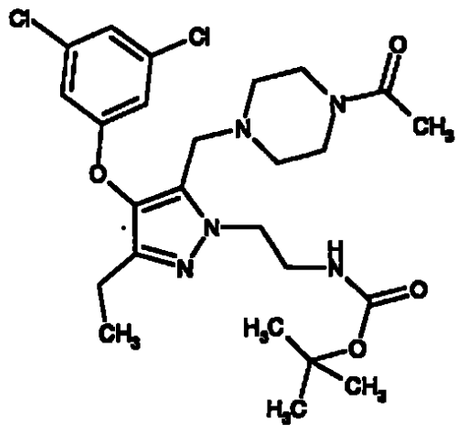
ambiente. La reacción se agitó durante 5 horas y después se concentró a presión reducida. El producto bruto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol (95:5, en volumen), proporcionando el compuesto del título (359 mg) en forma de un sólido blanco, p.f. 112-114°C.

^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,11 (t, 3H), 1,40 (s, 9H), 2,40 (q, 2H), 3,55 (m, 2H) 3,73 (s, 2H), 4,18 (t, 2H), 5,60 (s, 1H), 6,77 (s, 2H), 6,98 (s, 1H).

LRMS (termonebulización): m/z [MH^+] 429.

EJEMPLO 139

2-[5-[(4-Acetil-1-piperazinil)metil]-4-(3,5-diclorofenoxi)-3-etil-1*H*-pirazol-1-il]etilcarbamato de *terc*-butilo



Se añadió *N*-acetilpiperazina (42 mg, 0,330 mmol) en *N*,*N*-dimetilformamida (1 ml) a una solución agitada del bromuro del Ejemplo 137 (148 mg, 0,300 mmol) y diisopropiletilamina (57 µl, 0,330 mmol) en *N*,*N*-dimetilformamida (2 ml) a

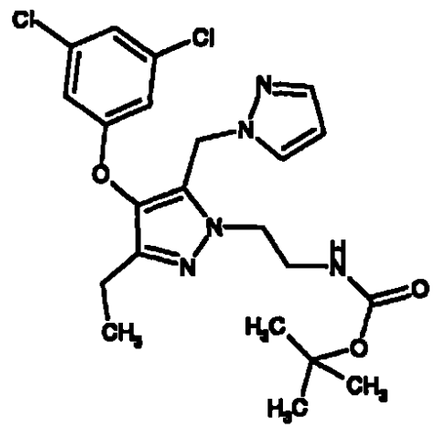
temperatura ambiente. La reacción se agitó durante 5 horas y la mezcla se concentró a presión reducida. Una solución del residuo en diclorometano (30 ml) se lavó con una solución acuosa 1 M de carbonato potásico (10 ml), se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida. El producto bruto se purificó por cromatografía ultrarrápida sobre gel de sílice, eluyendo con diclorometano:metanol (98:2, en volumen), produciendo el compuesto del título (150 mg) en forma de un aceite incoloro.

^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,15 (t, 3H), 1,42 (s, 9H), 2,06 (s, 3H), 2,44 (m, 6H), 3,32 (s, 2H), 3,47 (m, 2H), 3,60 (m, 2H), 3,65 (m, 2H), 4,23 (m, 2H), 5,89 (s, 1H), 6,76 (s, 2H), 7,02 (s, 1H).

LRMS (termonebulización): m/z [MH^+] 540.

EJEMPLO 140

2-[4-(3,5-diclorofenoxi)-3-etil-5-(1*H*-pirazol-1-ilmetil)-1*H*-pirazol-1-il]etilcarbamato de *terc*-butilo



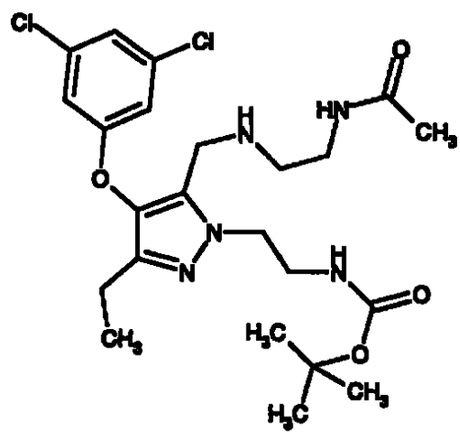
Se añadió en una porción pirazol (23 mg, 0,330 mmol) a una solución agitada del bromuro del Ejemplo 137 (148 mg, 0,300 mmol) e hidruro sódico (dispersión en aceite al 60%, 13,2 mg, 0,330 mmol) en *N,N*-dimetilformamida (2 ml) a temperatura ambiente en una atmósfera de nitrógeno. La reacción se agitó durante 5 horas, se inactivó con agua (1,00 ml) y se concentró a presión reducida. El residuo se disolvió en diclorometano (30 ml) y la solución resultante se lavó con una solución acuosa 1 M de carbonato potásico (10 ml), se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida. El producto bruto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol (98:2, en volumen), proporcionando el compuesto del título (125 mg) en forma de un aceite incoloro. ^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,13 (t, 3H), 1,44 (s, 9H), 2,42 (q, 2H), 3,52 (m, 2H), 4,26 (t, 2H), 5,18 (s, 2H), 5,48 (s,

1H), 6,16 (s, 1H), 6,73 (s, 2H), 7,00 (s, 1H), 7,18 (s, 1H), 7,45 (s, 1H).

LRMS (termonebulización): m/z [MH^+] 480.

EJEMPLO 141

2-[5-({[2-(acetilamino)etil]amino}metil)-4-(3,5-diclorofenoxi)-3-etil-1*H*-pirazol-1-il]etilcarbamato de *terc*-butilo



Se añadió N-acetiletilenodiamina (153 mg, 1,50 mmol) en isopropanol (1 ml) a una solución agitada del bromuro del Ejemplo 137 (148 mg, 0,300 mmol) y diisopropiletilamina (57 µl, 0,330 mmol) en isopropanol (2 ml) a temperatura ambiente. La reacción se agitó durante 5 horas y la mezcla se concentró a presión reducida. Una solución del residuo en diclorometano (50 ml) se lavó con una solución acuosa 1 M de carbonato potásico (20 ml), se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida. El producto bruto se purificó por cromatografía ultrarrápida sobre gel de

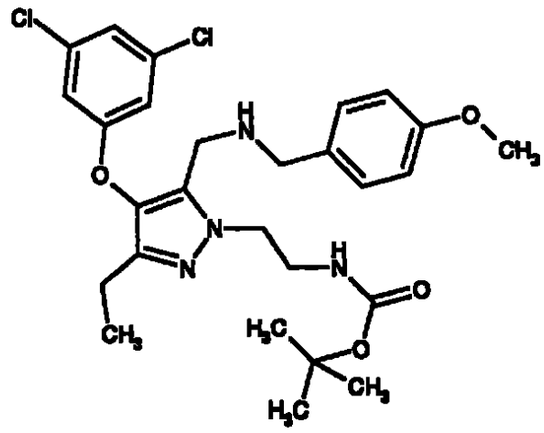
sílice eluyendo con diclorometano:metanol (90:10, en volumen) y después con diclorometano:metanol:amoniaco (90:9:1, en volumen), proporcionando el compuesto del título (122 mg) en forma de un aceite incoloro.

^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,13 (t, 3H), 1,42 (s, 9H), 1,94 (d, 3H), 2,44 (q, 2H), 2,74 (m, 2H), 3,35 (m, 2H), 3,58 (m, 4H), 4,19 (m, 2H), 5,68 (s, 1H), 6,77 (s, 2H), 7,00 (s, 1H), 7,65 (s, 1H).

LRMS (termonebulización): m/z [MH^+] 514.

EJEMPLO 142

2-(4-(3,5-Diclorofenoxi)-3-etil-5-{[(4-metoxibencil)-aminolmetil}-1*H*-pirazol-1-il)etilcarbamato de *terc*-butilo



Se agitaron 4-metoxibenzaldehído (46 µl, 0,380 mmol), la amina del Ejemplo 138 (172 mg, 0,400 mmol) y sulfato de magnesio (200 mg) en diclorometano (4 ml) a temperatura ambiente durante 4 días. La mezcla se filtró y el filtrado se concentró a presión reducida, dando un aceite amarillo.

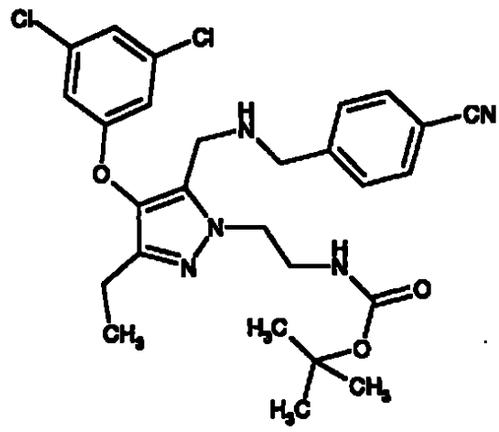
El aceite se disolvió en metanol (4 ml) y se añadió borohidruro sódico (18 mg, 0,480 mmol) con agitación vigorosa. Una vez completada la adición, la reacción se agitó durante 4 horas y después se añadió agua (2 ml). La mezcla se concentró a presión reducida y el residuo se disolvió en diclorometano (50 ml). La solución resultante se lavó con una solución acuosa 1 M de carbonato potásico (20 ml), se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida. El producto bruto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol (99:1, en volumen) y después con diclorometano:metanol (95:5, en volumen), proporcionando el compuesto del título (142 mg) en forma de un aceite incoloro.

^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,10 (t, 3H), 1,40 (s, 9H), 2,42 (m, 2H), 3,55 (m, 5H), 3,66 (s, 2H), 3,77 (s, 2H), 4,15 (m, 2H), 6,11 (s, 1H), 6,74 (s, 2H), 6,80 (d, 2H), 7,00 (s, 1H), 7,11 (d, 2H).

LRMS (termonebulización): m/z [MH^+] 549.

EJEMPLO 143

2-[5-{[(4-Cianobencil)amino]metil}-4-(3,5-diclorofenoxi)-3-etil-1*H*-pirazol-1-il]etilcarbamato de *terc*-butilo



Una mezcla de 4-cianobenzaldehído (50 mg, 0,380 mmol), la amina del Ejemplo 138 (172 mg, 0,400 mmol), sulfato de magnesio (200 mg) y diclorometano (4 ml) se agitó a temperatura ambiente durante 4 días. La mezcla se filtró y el filtrado se concentró a presión reducida, dando un aceite amarillo. El aceite se disolvió en metanol (4 ml) y se añadió borohidruro sódico (18 mg, 0,480 mmol) con agitación vigorosa. Una vez completada la adición, la reacción se agitó durante 4 horas y después se añadió agua (2 ml). La mezcla se concentró a presión reducida y el residuo se disolvió en diclorometano (50 ml). La solución resultante se lavó con una solución acuosa 1 M de carbonato potásico (20 ml), se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida. El producto bruto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol (99:1, en volumen) y después con diclorometano:metanol (95:5, en volumen), proporcionando el

compuesto del título (120 mg) en forma de un aceite incoloro. ^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,10 (t, 3H), 1,35 (s, 9H), 2,40 (q, 2H), 3,55 (m, 2H), 3,58 (s, 2H), 3,76 (s, 2H), 4,16 (m, 2H), 5,45 (s, 1H), 6,73 (s, 2H), 6,98 (s, 1H), 7,32 (d, 2H), 7,55 (d, 2H).

LRMS (termonebulización): m/z [MH^+] 544.

EJEMPLO 144

3-{[5-(Bromometil)-1,3-dimetil-1*H*-pirazol-4-il]oxi}-5-clorobenzonitrilo



Se añadió *N*-bromosuccinimida (340 mg, 1,90 mmol) a una solución agitada del pirazol del Ejemplo 112 (500 mg, 1,90 mmol) en tetracloruro de carbono (10 ml) y azobisisobutironitrilo (20 mg) a temperatura ambiente en una atmósfera de nitrógeno. La reacción se calentó a reflujo durante 1 hora, se enfrió a temperatura ambiente y se concentró a presión reducida. El producto bruto se purificó por cromatografía en columna ultrarrápida sobre gel de sílice eluyendo con pentano:acetato de etilo (80:20, en volumen), proporcionando el compuesto del título (340 mg) en forma de

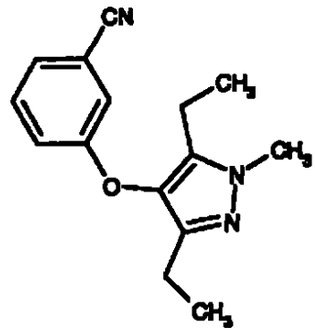
un sólido blanco, p.f. 76-78°C.

^{1}H-RMN (300 MHz, $CDCl_3$): δ = 2,03 (s, 3H), 3,45 (s, 3H), 4,32 (s, 2H), 7,12 (s, 1H), 7,19 (s, 1H), 7,34 (s, 1H).

LRMS (termonebulización): m/z [MH^+] 342.

EJEMPLO 145

3-[(3,5-Dietil-1-metil-1*H*-pirazol-4-il)oxi]benzonitrilo



Se añadió hidruro sódico (dispersión en aceite al 60%, 22 mg, 0,53 mmol) a una solución del pirazol del Ejemplo 60 (100 mg, 0,41 mmol) y yoduro de metilo (34 μl, 0,53 mmol) en dimetilformamida (1,5 ml) a 0°C en una atmósfera de nitrógeno. La reacción se dejó calentar a temperatura ambiente y se agitó durante 4 horas. La reacción se inactivó con agua y el disolvente se retiró a presión reducida. El residuo se repartió entre acetato de etilo (20 ml) y agua (10 ml) y la fase orgánica se lavó con agua (2x10 ml), se secó sobre sulfato de magnesio y se concentró a presión reducida. El aceite residual se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con un gradiente de disolvente

de pentano al 100% cambiando a acetato de etilo al 100% y finalmente acetato de etilo:metanol (10:1, en volumen), proporcionando el compuesto del título (65 mg) en forma de un aceite incoloro.

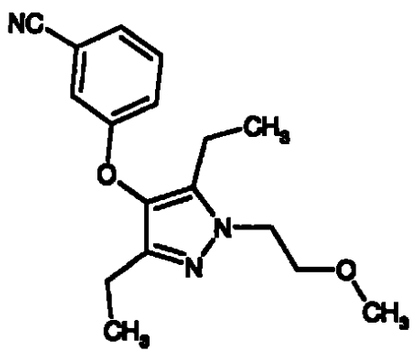
^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,09 (t, 3H), 1,12 (t, 3H), 2,41 (q, 2H), 2,50 (q, 2H), 3,77 (s, 3H), 7,12-7,38 (m, 4H).

LRMS (electronebulización) : m/z [MH^+] 256, [MNa^+] 278.

Microanálisis: Encontrado C, 70,15; H, 6,78; N, 16,42. $C_{15}H_{15}N_3O.0,08H_2O$ requiere C, 70,17; H, 6,74; N, 16,37%.

EJEMPLO 146

3-{[3,5-Dietil-1-(2-metoxietil)-1*H*-pirazol-4-il]oxi}benzonitrilo



Se añadió hidruro sódico (dispersión en aceite al 60%, 22 mg, 0,54 mmol) a una solución del pirazol del Ejemplo 60 (100 mg, 0,41 mmol) y 1-bromo-2-metoxi-etano (51 µl, 0,54 mmol) en dimetilformamida (1,5 ml) a 0°C en una atmósfera de nitrógeno. La reacción se dejó calentar a temperatura ambiente y se agitó durante 4 horas. La reacción se inactivó

con agua y el disolvente se retiró a presión reducida. El residuo se repartió entre acetato de etilo (20 ml) y agua (10 ml) y la fase orgánica se lavó con agua (2x10 ml), se secó sobre sulfato de magnesio y se concentró a presión reducida. El aceite residual se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con un gradiente de disolvente de pentano al 100% cambiando a acetato de etilo al 100% y finalmente acetato de etilo:metanol (90:10, en volumen), proporcionando el compuesto del título (66 mg) en forma de un aceite incoloro.

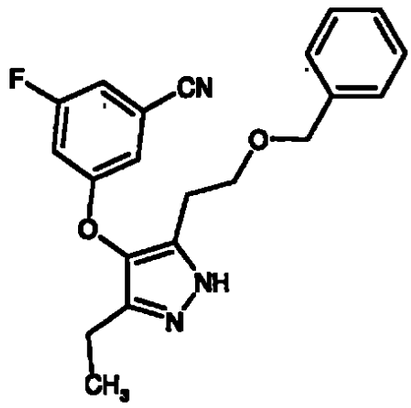
^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,09 (t, 3H), 1,12 (t, 3H), 2,42 (q, 2H), 2,54 (q, 2H), 3,34 (s, 3H), 3,75 (t, 2H), 4,16 (t, 2H), 7,11-7,38 (m, 4H).

LRMS (electronebulización) : m/z [MH^+] 300, [MNa^+] 322.

Microanálisis: Encontrado C, 68,21; H, 7,07; N, 14,04. $C_{17}H_{21}N_3O_2$ requiere C, 67,85; H, 7,12; N, 14,09%.

EJEMPLO 147

3-({5-[2-(Benciloxi)etil]-3-etil-1*H*-pirazol-4-il}oxi)-5-fluorobenzonitrilo



Se añadió hidrato de hidrazina (390 µl, 8,00 mmol) a una solución del enol de la Preparación 60 (2,47 g, 6,69 mmol) en ácido acético (5 ml) en una atmósfera de nitrógeno a temperatura ambiente. Después de agitar durante 18 horas, la mezcla se concentró a presión reducida y se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con pentano:acetato de etilo (70:30 cambiando a 50:50, en volumen), proporcionando el compuesto del título (5,8 g) en forma de un aceite amarillo.

^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,13 (t, 3H), 2,41 (q, 2H), 2,67 (t, 2H), 3,62 (t, 2H), 4,48 (s, 2H), 6,79 (m, 1H), 6,98 (m, 2H), 7,24 (m, 5H).

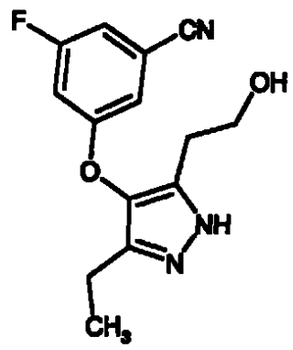
LRMS (electronebulización) : m/z [M-H$^+$] 364.

Microanálisis: Encontrado C, 66,96; H, 5,62; N, 11,25. $C_{21}H_{20}N_3O_2F.0,60H_2O$ requiere C, 67,04; H, 5,68; N, 11,17%.

EJEMPLO 148

3-{[3-Etil-5-(2-hidroxietil)-1*H*-pirazol-4-il]oxi}-5-

fluorobenzonitrilo



Se añadió cloruro de hierro(III) (9,30 g, 57,5 mmol) a una solución del pirazol del Ejemplo 147 (2,10 g, 5,75 mmol) en diclorometano (90 ml) en una atmósfera de nitrógeno a temperatura ambiente. Después de agitar durante 20 minutos, la mezcla se diluyó con diclorometano (50 ml), se lavó con agua (100 ml) y después con una solución acuosa saturada de etilendiaminotetraacetato (70 ml), se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol (98:2 cambiando a 95:5, en volumen), proporcionando el compuesto del título (1,2 g) en forma de un aceite pardo que solidificó tras reposo.

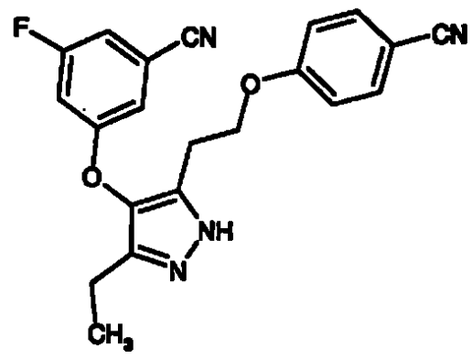
^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,16 (t, 3H), 2,44 (q, 2H), 2,63 (t, 2H), 3,82 (t, 2H), 6,82 (m, 1H), 6,98 (m, 2H).

LRMS (electronebulización) : m/z [MH^+] 276.

Microanálisis: Encontrado C, 60,69; H, 5,12; N, 15,08. $C_{14}H_{14}N_3O_2F$ requiere C, 61,08; H, 5,13; N, 15,26%.

EJEMPLO 149

3-({5-[2-(4-Cianofenoxi)etil]-3-etil-1*H*-pirazol-4-il}oxi)-5-fluorobenzonitrilo



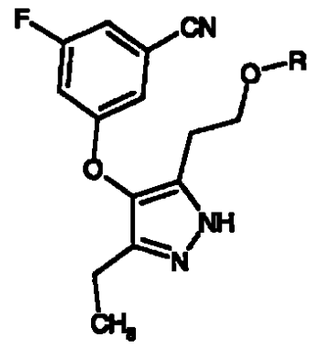
Se añadieron secuencialmente 4-hidroxi-benzonitrilo (49 mg, 0,41 mmol), trifenilfosfina (106 mg, 0,41 mmol) y azodicarboxilato de dietilo (65 µl, 0,41 mmol) a una solución del alcohol del Ejemplo 148 (74 mg, 0,27 mmol) en tetrahidrofurano (2 ml) en una atmósfera de nitrógeno a 0°C. La reacción se dejó calentar a temperatura ambiente y se agitó durante 18 horas. La mezcla se concentró a presión reducida y se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con tolueno:acetato de etilo (75:25, en volumen), proporcionando el compuesto del título (50 mg) en forma de un aceite amarillo.

^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,18 (t, 3H), 2,49 (q, 2H), 2,98 (t, 2H), 4,21 (t,2H), 6,82 (m, 3H), 6,99 (m, 2H), 7,56 (m, 2H).

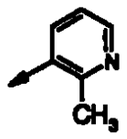
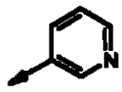
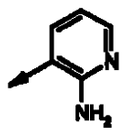
LRMS (electronebulización) : m/z [MH^+] 377.

EJEMPLOS 150-152

Los compuestos de los siguientes Ejemplos indicados en la tabla, de formula general:



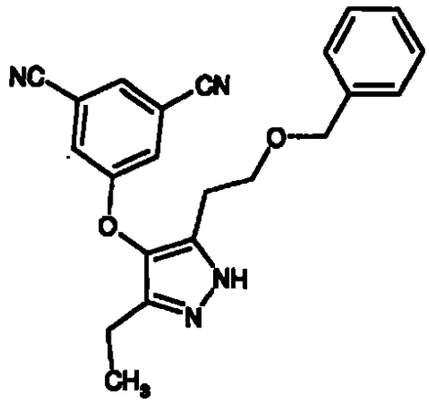
se prepararon por un procedimiento similar al del Ejemplo 149 usando el apropiado alcohol arílico como el material de partida.

Ejemplo No.	No de Ejemplo del Material de Partida	R	datos analíticos
150[1]	148		^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,18 (t, 3H), 2,42 (s, 3H), 2,52 (q, 2H), 2,99 (t, 2H), 4,18 (t, 2H), 6,83 (m, 1H), 6,99 (m, 4H), 8,04 (m, 1H). LRMS (termonebulización): m/z [MH$^+$] 367.
151[1]	148		^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,19 (t, 3H), 2,50 (q, 2H), 2,98 (t, 2H), 4,22 (t, 2H), 6,85 (m, 1H), 6,99 (m, 2H), 7,12 (m, 1H), 7,18 (m, 1H), 8,22 (m, 2H). LRMS (termonebulización: m/z [MH$^+$] 353.
152[1]	148		^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,20 (t, 3H), 2,53 (q, 2H), 2,98 (t, 2H), 4,19 (t, 2H), 4,85 (a a, 2H), 6,58 (m, 1H), 6,83 (m, 2H), 6,99 (m, 2H), 7,63 (d, 1H). LRMS (termonebulización): m/z [MH$^+$] 368.

[1] Estos compuestos se purificaron sobre gel de sílice eluyendo con un gradiente de disolvente de ciclohexano:acetato de etilo (75:25, después 66:34 y después 50:50, en volumen), cambiando a acetato de etilo y finalmente acetato de etilo:metanol (90:10, en volumen).

EJEMPLO 153

5-({5-[2-(benciloxi)etil]-3-etil-1*H*-pirazol-4-il}oxi)isoftalonitrilo



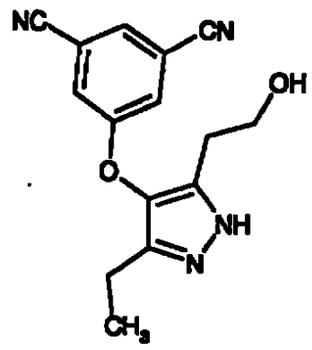
Se añadió hidrato de hidrazina (177 µl, 3,66 mmol) a una solución del enol bruto de la Preparación 61 (917 mg, 2,40 mmol) en ácido acético (10 ml) en una atmósfera de nitrógeno a temperatura ambiente. Después de agitar durante 18 horas, la mezcla se concentró a presión reducida y se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con pentano:ciclohexano (75:25, en volumen) cambiando a tolueno:acetato de etilo (50:50, en volumen), dando el producto, que se purificó adicionalmente por HPLC preparativa usando una columna de 3 µm Develosil combi-rp C30 de 50x4,6 mm, eluyendo con un gradiente de disolvente de 5:95 de ácido trifluoroacético acuoso al 0,1% en agua:acetonitrilo, proporcionando el compuesto del título (5 mg) en forma de un aceite incoloro.

^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,18 (t, 3H), 2,44 (q, 2H), 2,77 (t, 2H), 3,63 (t, 2H), 4,52 (s, 2H), 7,30 (m, 7H), 7,55 (s, 1H).

LRMS (electronebulización) : m/z [MH^+] 231, [MNa^+] 253.

EJEMPLO 154

5-{[3-etil-5-(2-hidroxietil)-1*H*-pirazol-4-iloxi}isoftalonitrilo



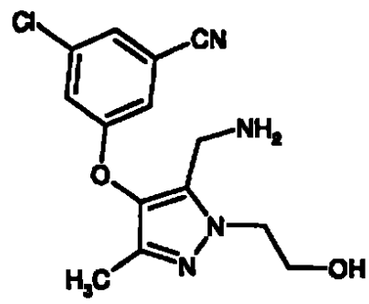
Se añadió cloruro de hierro(III) (217 mg, 1,30 mmol) a una solución del pirazol del Ejemplo 153 (50 mg, 0,13 mmol) en diclorometano (5 ml) en una atmósfera de nitrógeno a temperatura ambiente. Después de agitar durante 30 minutos, la mezcla se diluyó con diclorometano (20 ml), se lavó con agua (100 ml) y después con una solución acuosa saturada de etilendiamintetraacetato de sodio (20 ml), se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol (98:2 cambiando a 95:5, en volumen), proporcionando el compuesto del título (20 mg) en forma de un sólido blanco.

^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,19 (t, 3H), 2,51 (q, 2H), 2,69 (t, 2H), 3,88 (t, 2H), 7,40 (s, 2H), 7,59 (s, 1H).

LRMS (electronebulización) : m/z [MH^+] 283.

EJEMPLO 155

3-{[5-(Aminometil)-1-(2-hidroxietil)-3-metil-1*H*-pirazol-4-il]oxi}-5-clorobenzonitrilo



El alcohol protegido de la Preparación 31 (100 mg, 0,23 mmol) y fluoruro de terc-butil-amonio (360 µl de una solución 1 M en tetrahidrofurano, 0,36 mmol) se agitaron en diclorometano (5 ml) a temperatura ambiente en una atmósfera de nitrógeno durante 3 horas. La mezcla de reacción se concentró a presión reducida y el residuo se disolvió en metanol (2 ml) y se purificó en una columna de ácido sulfónico soportada en polímero BondElut® SCX lavando con metanol (2x3 ml) para eliminar las impurezas y con amoniaco acuoso 2 N para retirar el producto. Este procedimiento se repitió dos veces, proporcionando el compuesto del título (40 mg) en forma de un aceite incoloro.

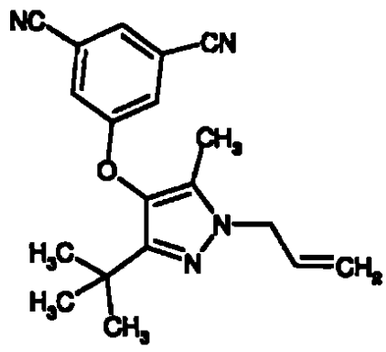
^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,99 (s, 3H), 3,85 (t, 2H), 4,02 (s, 2H), 4,32 (t, 2H), 7,22 (s, 1H), 7,28 (s, 1H), 7,47 (s, 1H).

LRMS (termonebulización) : m/z [MH^+] 309.

Microanálisis: Encontrado C, 53,32; H, 5,17; N, 16,38. $C_{14}H_{15}ClN_4O_2.0,85CH_3OH$ requiere C, 53,40; H, 5,55; N, 16,77%.

EJEMPLO 156

5-[(1-Alil-3-terc-butil-5-metil-1*H*-pirazol-4-il)oxi]isoftalonitrilo



Se añadió hidruro sódico (dispersión en aceite al 60%, 120 mg, 3,15 mmol) a una solución del pirazol del Ejemplo 130 (800 mg, 2,80 mmol) y bromuro de alilo (345 mg, 2,80 mmol) en dimetilformamida (30 ml) a temperatura ambiente en una atmósfera de nitrógeno y la reacción se agitó durante 3 horas. La reacción se diluyó con acetato de etilo (50 ml), se lavó con agua (2x50 ml) y después con salmuera (50 ml) y la fase orgánica se concentró a presión reducida. El aceite residual se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con gradiente de disolvente de pentano cambiando a acetato de etilo:pentano (20:80, en volumen), proporcionando el compuesto del título (600 mg) en forma de

un aceite incoloro.

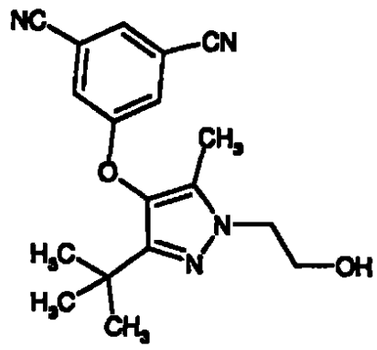
^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,21 (s, 9H), 1,96 (s, 3H), 4,66 (s, 2H), 5,04 (d, 1H), 5,24 (d, 1H), 5,98 (m, 1H), 7,37 (s, 2H), 7,57 (s, 1H).

LRMS (termonebulización) : m/z [MH^+] 322.

Microanálisis: Encontrado: C, 70,79; H, 6,29; N, 17,11. $C_{19}H_{20}N_4O.0,05CH_2Cl_2$ requiere C, 70,48; H, 6,24; N, 17,26%.

EJEMPLO 157

5-{[3-terc-Butil-1-(2-hidroxietil)-5-metil-1*H*-pirazol-4-il]oxi}isoftalonitrilo



Se disolvieron peryodato sódico (1,00 g, 4,60 mmol), tetróxido de osmio (solución al 1,5% en terc-butanol, 190 mg, 0,02 mmol) y el pirazol del Ejemplo 156 (600 mg, 1,86 mmol) en acetona (9 ml) y agua (3 ml) en una atmósfera de nitrógeno a temperatura ambiente, y la reacción se agitó durante 5 horas. Se retiró la acetona a presión reducida y el residuo se extrajo con acetato de etilo (30 ml). la fase orgánica se lavó con agua (2x30 ml) y después con salmuera (30 ml), se

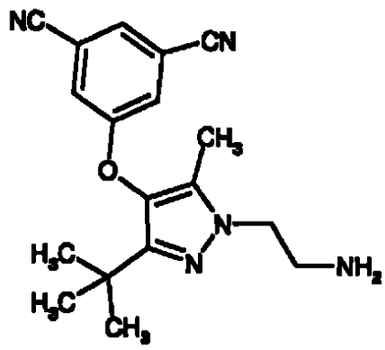
secó sobre sulfato de magnesio y se concentró a presión reducida. Después, el aldehído bruto se disolvió en metanol (15 ml) y se añadió en porciones borohidruro sódico (84 mg, 2,22 mmol) a temperatura ambiente en una atmósfera de nitrógeno. La reacción se agitó durante 3 horas y el disolvente se retiró a presión reducida. El residuo se repartió entre acetato de etilo (10 ml) y agua (10 ml) y la fase orgánica se lavó con agua (2x10 ml) y después con salmuera (10 ml), se secó sobre sulfato de magnesio y se concentró a presión reducida. El aceite residual se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con un gradiente de disolvente de pentano cambiando a acetato de etilo:pentano (50:50, en volumen), proporcionando el compuesto del título (250 mg) en forma de un aceite incoloro. ^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,17 (s, 9H), 1,98 (s, 3H), 3,67 (s, 1H), 4,04 (m, 4H), 7,35 (s, 2H), 7,54 (s, 1H).

LRMS (termonebulización) : m/z [MH^+] 325.

Microanálisis: Encontrado C, 64,30; H, 6,10; N, 16,35. $C_{18}H_{20}N_4O_2.0,20CH_2Cl_2$ requiere C, 64,04; H, 6,02; N, 16,41%.

EJEMPLO 158

5-{[1-(2-Aminoetil)-3-terc-butil-5-metil-1*H*-pirazol-4-il]oxi}isoftalonitrilo



Se disolvió difenilfosforilazida (305 mg, 1,10 mmol) en tetrahidrofurano (5 ml) y se añadió a una solución del pirazol del Ejemplo 157 (180 mg, 0,55 mmol), trifenilfosfina (291 mg, 1,10 mmol) y azodicarboxilato de dietilo (193 mg, 1,10 mmol) en tetrahidrofurano (20 ml) en una atmósfera de nitrógeno a temperatura ambiente. La reacción se agitó durante 18 horas, después se añadió trifenilfosfina (291 mg, 1,10 mmol) y la reacción se agitó durante 18 horas más. Después se añadió agua (180 µl, 10,0 mmol) y la reacción se agitó durante 64 horas. El disolvente se retiró a presión reducida y la pasta blanca residual se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco 0,88 (95:4,5:0,5, en volumen), proporcionando el compuesto del título (55 mg) en forma de un aceite incoloro.

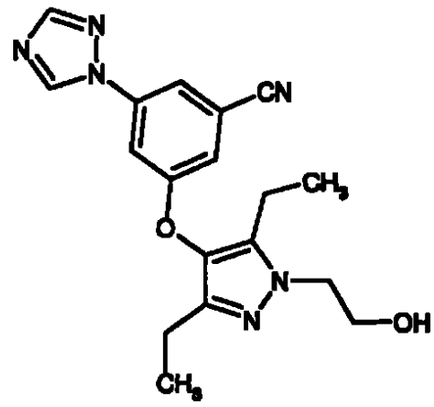
^{1}H-RMN (300 MHz, $CDCl_3$): δ = 1,22 (s, 9H), 1,78 (s, 2H), 2,03 (s, 3H), 3,18 (t, 2H), 4,05 (m, 2H), 7,38 (s, 2H), 7,58 (s, 1H).

LRMS (termonebulización) : m/z [MH^+] 324.

Microanálisis: Encontrado C, 64,46; H, 6,48; N, 20,47. $C_{18}H_{21}N_5O.0,20CH_2Cl_2$ requiere C, 64,22; H, 6,34; N, 20,57%.

EJEMPLO 159

3-{[3,5-Dietil-1-(2-hidroxietil)-1*H*-pirazol-4-il]oxi}-5-(1*H*-1,2,4-triazol-1-il)benzonitrilo



Se añadió carbonato de cesio (179 mg, 0,55 mmol) a una solución de 1H[1,2,4]triazol (38 mg, 0,55 mmol) en dimetilsulfóxido (1 ml) en una atmósfera de nitrógeno a temperatura ambiente y la reacción se agitó durante 10 minutos. Después se añadió el fluoruro de arilo de la Preparación 62 (210 mg, 0,5 mmol) disuelto en dimetilsulfóxido (1 ml) y la reacción se calentó a 100°C durante 18 horas. Después de enfriar a temperatura ambiente, la reacción se diluyó con agua (15 ml) y se extrajo con acetato de etilo (25 ml). La fase orgánica se lavó con salmuera (15 ml), se secó sobre sulfato de magnesio, se

concentró a presión reducida y el residuo se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con un gradiente de disolvente de diclorometano:metanol (98:2 cambiando a 90:10, en volumen), proporcionando el compuesto del título (67,5 mg) en forma de un sólido blanco, p.f. 122-124°C.

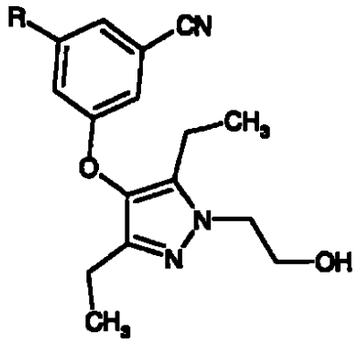
^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,10 (m, 6H), 2,39 (q, 2H), 2,51 (q, 2H), 3,61 (s a, 1H), 4,04 (m, 2H), 4,07 (m, 2H), 7,10 (s, 1H), 7,52 (s, 1H), 7,60 (s, 1H), 8,07 (s, 1H), 8,54 (s, 1H).

LRMS (termonebulización) : m/z [MH^+] 353.

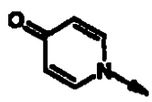
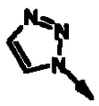
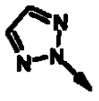
Microanálisis: Encontrado C, 60,69; H, 5,83; N, 22,98. $C_{18}H_{20}N_6O_2.0,08CH_2Cl_2$ requiere C, 60,46; H, 5,66; N, 23,40%.

EJEMPLOS 160-162

Los compuestos de los siguientes Ejemplos indicados en la tabla, de formula general:



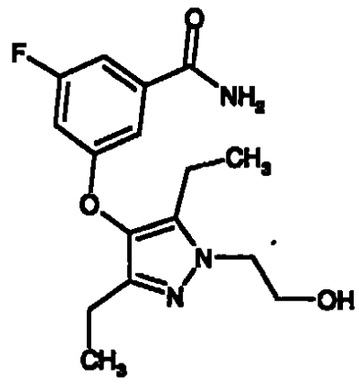
se prepararon por un procedimiento similar al del Ejemplo 159 usando el apropiado heterociclo como el material de partida.

Ejemplo No (No de la Preparación del Material de Partida)	R	Datos Analíticos
160 (62)		^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,10 (m, 6H), 2,39 (q, 2H), 2,53 (q, 2H), 3,62 (a a, 1H), 4,02 (t, 2H), 4,08 (t, 2H), 6,44 (d, 2H), 7,14 (s, 1H), 7,16 (s, 1H), 7,25 (s, 1H), 7,49 (d, 2H). P.f. 169-170°C. LRMS (termonebulización): m/z [MH$^+$] 379. Microanálisis: Encontrado: C, 65,68; H, 5,98; N, 14,31. $C_{21}H_{23}N_4O_2.0,09CH_2Cl_2$ requiere C, 65,61; H, 5,79; N, 14,51%.
161[1] (62)		^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,10 (m, 6H), 2,40 (q, 2H), 2,51 (q, 2H), 3,56 (t, 1H), 4,04 (m, 2H), 4,07 (m, 2H), 7,20 (s, 1H), 7,65 (s, 2H), 7,85 (s, 1H), 7,98 (s, 1H). LRMS (termonebulización: m/z [MH$^+$] 353. HRMS: [MH$^+$] 353,1722. $C_{18}H_{25}N_4O_3$ requiere 353,1720.
162[1] (62)		^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,10 (m, 6H), 2,41 (q, 2H), 2,51 (q, 2H), 3,62 (t, 1H), 4,04 (m, 2H), 4,07 (m, 2H), 7,08 (s, 1H), 7,80 (s, 2H), 7,87 (s, 1H), 8,02 (s, 1H). LRMS (termonebulización): m/z [MH$^+$] 353. HRMS: [MH$^+$] 353,1719. $C_{18}H_{25}N_4O_3$ requiere 353,1720.

[1] Los dos compuestos se aislaron a partir de una sola reacción partiendo de 1,2,3-triazol, siendo el más polar el Ejemplo 161.

EJEMPLO 163

3-{[3,5-Dietil-1-(2-hidroxietil)-1*H*-pirazol-4-il]oxi}-5-fluorobenzamida



El alcohol protegido de la Preparación 64 (432 mg, 1,07 mmol) y ácido p-tolueno-sulfónico (30,3 mg, 0,11 mmol) se disolvieron en metanol (4 ml) y se agitaron en una atmósfera de nitrógeno a temperatura ambiente durante 18 horas. El disolvente se retiró a presión reducida y el residuo se repartió entre una solución acuosa saturada de bicarbonato sódico (20 ml) y diclorometano (20 ml). La fase acuosa se extrajo con diclorometano (10 ml) y los extractos orgánicos reunidos se secaron sobre sulfato de magnesio, se concentraron a presión reducida y el residuo se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con un gradiente de disolventes de diclorometano:metanol (100:0 cambiando a 93:7, en volumen), proporcionando el compuesto del título (241 mg) en forma de una espuma blanca.

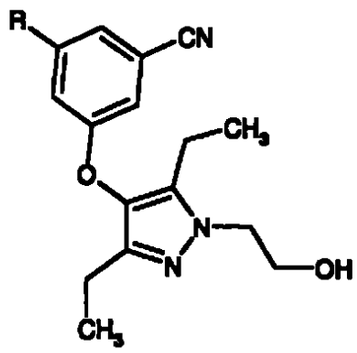
^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,10 (m, 6H), 2,39 (q, 2H), 2,49 (q, 2H), 3,68 (s a, 1H), 4,04 (m, 4H), 5,59 (s a, 1H), 5,88 (s a, 1H), 6,71 (d, 1H), 7,11 (m, 2H).

LRMS (termonebulización) : m/z [MH^+] 322.

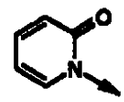
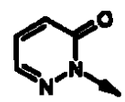
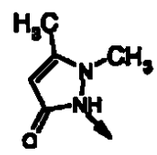
Microanálisis: Encontrado C, 57,91; H, 6,32; N, 12,56. $C_{16}H_{20}FN_3O_3.0,13CH_2Cl_2.0,12H_2O$ requiere C, 57,91; H, 6,18; N, 12,56%.

EJEMPLOS 164-167

Los compuestos de los siguientes Ejemplos indicados en la tabla, de formula general:



se prepararon por un procedimiento similar al del Ejemplo 163 usando el apropiado alcohol protegido como el material de partida.

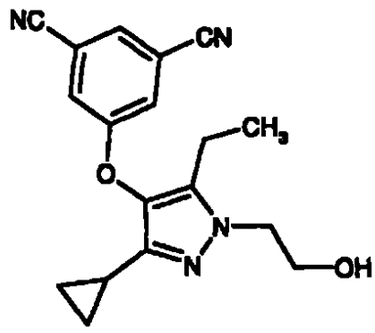
Ejemplo No (No de la Preparación del Material de Partida)	R	Datos Analíticos
161[a] (65)		^{1}H-RMN (400 MHz, $CDCl_3$): δ =1,13 (m, 6H), 2,44 (q, 2H), 2,54 (q, 2H), 3,65 (a a, 1H), 4,07 (t, 2H), 4,11 (t, 2H), 6,51 (s, 1H), 7,00 (s, 1H), 7,56 (s, 1H), 7,63 (s, 1H), 7,74 (s, 1H), 7,90 (s, 1H). LRMS (electronebulización): m/z [MH$^+$] 352, [MNa$^+$] 374. HRMS: [MH$^+$] Encontrado 352,1770. $C_{19}H_{22}N_5O_3$ requiere 352,1768.
165[i] (66)		^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,10 (m, 6H), 2,40 (q, 2H), 2,50 (q, 2H), 4,00 (t, 2H), 4,06 (t, 2H), 6,24 (t, 1H), 6,60 (d, 1H), 7,18 (d, 2H), 7,24 (d, 1H), 7,30 (s, 1H), 7,38 (t, 1H). LRMS (electronebulización: m/z [MH$^+$] 379, [MNa$^+$] 401. HRMS: [MH$^+$] Encontrado 379,1766. $C_{21}H_{23}N_4O_3$ requiere 379,1765 [HNa$^+$] Encontrado 401,1585. $C_{21}H_{22}N_4O_3$ requiere 401,1584.
166[j] (67)		^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,10 (m, 6H), 2,41 (q, 2H), 2,51 (q, 2H), 4,01 (t, 2H), 4,06 (t, 2H), 7,07 (d, 1H), 7,13 (s, 1H), 7,22 (m, 1H), 7,52 (s, 1H), 7,65 (s, 1H), 7,88 (s, 1H). LRMS (electronebulización): m/z [MH$^+$] 380, [MNa$^+$] 402. HRMS: [MH$^+$] Encontrado 380,1722. $C_{20}H_{25}N_5O_3$ requiere 380,1717.
167[k] (68)		^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,11 (m, 6H), 2,27 (s, 3H), 2,41 (q, 2H), 2,50 (q, 2H), 3,70 (s, 3H), 4,04 (t, 1H), 4,08 (t, 2H), 5,64 (s, 1H), 6,81 (s, 1H), 6,91 (s, 1H), 6,99 (s, 1H). LRMS (electronebulización): m/z [MH$^+$] 396, [MNa$^+$] 418. HRMS: [MH$^+$] Encontrado 396,2027. $C_{21}H_{25}N_5O_3$ requiere 396,2030.

[1] El eluyente usado para la purificación por cromatografía en columna ultrarrápida de estos compuestos fue diclorometano:metanol (99:1 cambiando a 80:20, en volumen).

[2] El eluyente usado para la purificación por cromatografía en columna ultrarrápida de estos compuestos fue diclorometano:metanol (99:1 cambiando a 98:2, en volumen).

EJEMPLO 168

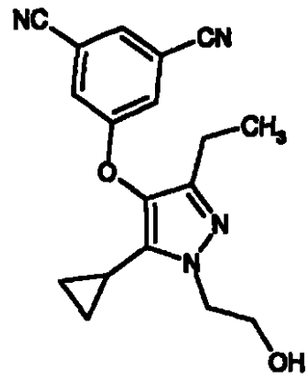
5-{[3-Ciclopropil-5-etil-1-(2-hidroxietil)-1*H*-pirazol-4-il]oxi}isoftalonitrilo



y

EJEMPLO 169

5-{[5-Ciclopropil-3-etil-1-(2-hidroxietil)-1*H*-pirazol-4-il]oxi}isoftalonitrilo



Se añadieron secuencialmente carbonato potásico (91 mg, 0,66 mmol) y 2-(2-bromoetoxi)-tetrahidropirano (91 µl, 0,61 mmol) a una solución del pirazol del Ejemplo 129 (152 mg, 0,55 mmol) disuelto en dimetilformamida (4 ml) y la reacción se calentó a 35°C en una atmósfera de nitrógeno durante 5 horas. Aún quedaba material de partida, por lo que se aumentó la temperatura hasta 80°C y la reacción se agitó durante 18 horas más. La reacción se enfrió a temperatura ambiente, se añadió hidruro sódico (dispersión en aceite al 60%, 24 mg, 0,60 mmol) y la reacción se agitó a temperatura ambiente durante 1 hora. La mezcla se diluyó con agua (50 ml) y se extrajo con acetato de etilo (2x50 ml). Los extractos orgánicos reunidos se lavaron con salmuera (30 ml), se secaron sobre sulfato de magnesio, se concentraron a presión reducida y el residuo se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con pentano:ciclohexano (75:25, en volumen), proporcionando una

mezcla de regioisómeros (239 mg). Los regioisómeros (239 mg, 0,55 mmol) y ácido p-toluenosulfónico (10 mg, 0,05 mmol) se disolvieron en metanol (5 ml) y se agitaron en una atmósfera de nitrógeno a temperatura ambiente durante 18 horas. El disolvente se retiró a presión reducida y el residuo se repartió entre una solución acuosa saturada de bicarbonato sódico (20 ml) y diclorometano (30 ml). La fase orgánica se secó sobre sulfato de magnesio, se concentró a presión reducida y el aceite residual se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con tolueno:acetato de etilo (50:50, en volumen), produciendo dos productos en forma de aceites incoloros.

Fracción menos polar (Ejemplo 168) - 34 mg

^{1}H-RMN (400 MHz, $CDCl_3$): δ = 0,76 (m, 4H), 1,05 (t, 3H), 1,45 (m, 1H), 2,48 (q, 2H), 3,39 (s a, 1H), 4,02 (m, 4H), 7,39 (s, 2H), 7,56 (s, 1H).

LRMS (electronebulización): m/z [M-H$^+$] 321.

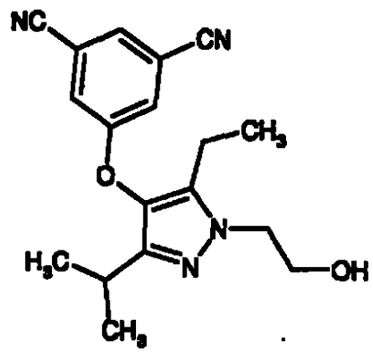
Fracción más polar (Ejemplo 169) - 9 mg

^{1}H-RMN (400 MHz, $CDCl_3$): δ = 0,62 (m, 2H), 0,78 (m, 2H), 1,18 (t, 3H), 1,46 (m, 1H), 2,38 (q, 2H), 3,42 (s a, 1H), 4,02 (m, 2H), 4,21 (t, 2H), 7,38 (s, 2H), 7,57 (s, 1H).

LRMS (electronebulización): m/z [MH$^+$] 323, [MH$^-$] 321.

EJEMPLO 170

5-{[5-Etil-1-(2-hidroxietil)-3-isopropil-1*H*-pirazol-4-il]oxi}isoftalonitrilo



Se añadió 2-(2-bromoetoxi)-tetrahidropirano (91 µl, 0,60 mmol) a una solución del pirazol del Ejemplo 131 (153 mg, 0,55 mmol) disuelto en dimetilformamida (4 ml) a temperatura ambiente en una atmósfera de nitrógeno, después se añadió hidruro sódico (dispersión en aceite al 60%, 24 mg, 0,60 mmol) y la reacción se agitó a temperatura ambiente durante 3 horas. La mezcla se diluyó con agua (50 ml) y se extrajo con acetato de etilo (2x50 ml). Los extractos orgánicos reunidos se lavaron con salmuera (30 ml), se secaron sobre sulfato de magnesio, se concentraron a presión reducida y el residuo se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con tolueno:acetato de etilo (85:15, en volumen), proporcionando los isómeros separados en forma de aceites incoloros (83 mg del Isómero 1, 55 mg del Isómero 2).

El isómero menos polar (isómero 1) (83 mg, 0,20 mmol) y ácido p-tolueno-sulfónico (4 mg, 0,02 mmol) se disolvieron en metanol (5 ml) y se agitaron en una atmósfera de nitrógeno a temperatura ambiente durante 18 horas. El disolvente se

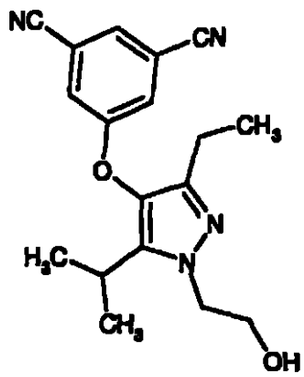
retiró a presión reducida y el residuo se repartió entre agua (30 ml) y diclorometano (30 ml). La fase acuosa se extrajo con diclorometano (20 ml) y los extractos orgánicos reunidos se secaron sobre sulfato de magnesio, se concentraron a presión reducida y el aceite residual se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con tolueno:acetato de etilo (66:34, en volumen), proporcionando el compuesto del título (39 mg) en forma de un aceite.

^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,05 (t, 3H), 1,14 (d, 6H), 2,44 (q, 2H), 2,68 (sept, 1H), 3,77 (s a, 1H), 4,06 (m, 4H), 7,38 (s, 2H), 7,58 (s, 1H).

LRMS (electronebulización) : m/z [MH^+] 325.

EJEMPLO 171

5-{[3-Etil-1-(2-hidroxietil)-5-isopropil-1*H*-pirazol-4-iloxi}isoftalonitrilo



El isómero más polar (isómero 2) del Ejemplo 170 (55 mg, 0,13 mmol) y ácido p-tolueno-sulfónico (3 mg, 0,01 mmol) se

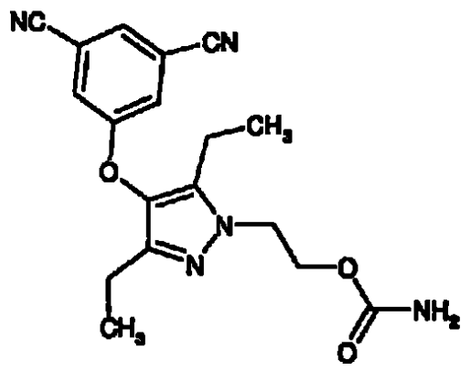
disolvieron en metanol (5 ml) y se agitaron en una atmósfera de nitrógeno a temperatura ambiente durante 18 horas. El disolvente se retiró a presión reducida y el residuo se repartió entre agua (30 ml) y diclorometano (30 ml). La fase acuosa se extrajo con diclorometano (20 ml) y los extractos orgánicos reunidos se secaron sobre sulfato de magnesio, se concentraron a presión reducida y el aceite residual se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con tolueno:acetato de etilo (66:33, en volumen), proporcionando el compuesto del título (39 mg) en forma de un sólido blanco.

^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,08 (t, 3H), 1,13 (d, 6H), 2,49 (q, 2H), 2,97 (sept, 1H), 3,59 (t, 1H), 4,06 (m, 4H), 7,37 (s, 2H), 7,57 (s, 1H).

LRMS (electronebulización) : m/z [MH^+] 325.

EJEMPLO 172

Carbamato de 2-[4-(3,5-dicianofenoxi)-3,5-dietil-1*H*-pirazol-1-il]etilo



Se añadió isocianato de tricloroacetilo (46 µl, 0,38 mmol) a una solución del alcohol del Ejemplo 119 (100 mg, 0,32 mmol) disuelto en diclorometano (3,2 ml) en una atmósfera de nitrógeno a 0°C. Después de agitar durante 2 horas, el diclorometano se retiró a presión reducida y se añadieron metanol (1,6 ml), agua (1,6 ml) y carbonato potásico (134 mg, 0,96 mmol) y la reacción se agitó durante 2 horas más. El metanol se retiró a presión reducida y el residuo se extrajo con diclorometano (3x10 ml). Los extractos orgánicos reunidos se secaron sobre sulfato de magnesio, se concentraron a presión reducida y el sólido residual se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol (98:2, en volumen), proporcionando el compuesto del título (60 mg) en forma de un sólido blanco.

^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,10 (m, 6H), 2,39 (q, 2H), 2,48 (q, 2H), 4,26 (m, 2H), 4,44 (m, 2H), 4,62 (s a, 2H), 7,41 (s,

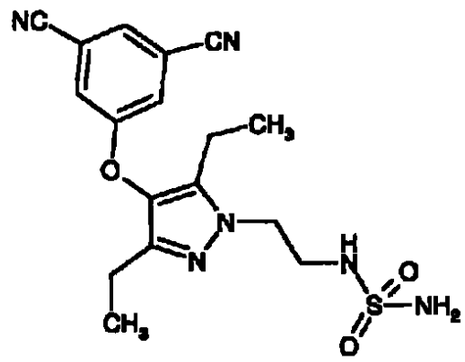
2H), 7,58 (s, 1H).

LRMS (termonebulización) : m/z [MH^+] 354.

Microanálisis: Encontrado C, 60,00; H, 5,55; N, 19,82. $C_{18}H_{19}N_5O_3$.0,23EtOAc requiere C, 60,30; H, 5,67; N, 18,58%.

EJEMPLO 173

N-{2-[4-(3,5-Dicianofenoxi)-3,5-dietil-1*H*-pirazol-1-il]etil}sulfamida



Se añadió sulfamida (31 mg, 0,32 mmol) a una solución de la amina del Ejemplo 127 (100 mg, 0,32 mmol) disuelta en dioxano (0,5 ml) en una atmósfera de nitrógeno a temperatura ambiente. La reacción se calentó a 100°C durante 18 horas, se enfrió a temperatura ambiente y se repartió entre acetato de etilo (15 ml) y agua (15 ml). La fase orgánica se secó sobre sulfato de magnesio, se concentró a presión reducida y el aceite pardo residual se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco 0,88 (95:5:0,5, en volumen), proporcionando el compuesto del título (25 mg) en forma de

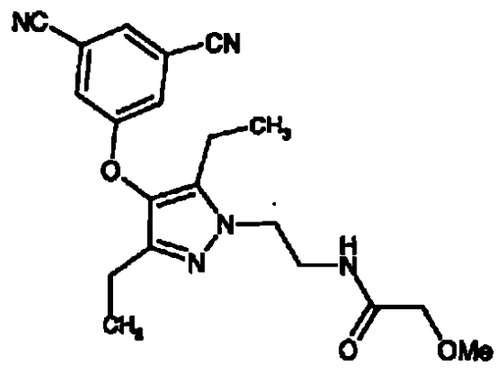
un sólido blanco.

^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,12 (m, 6H), 2,39 (q, 2H), 2,51 (q, 2H), 3,61 (m, 2H), 4,20 (m, 2H), 4,78 (s, 2H), 5,42 (s, 1H), 7,40 (s, 2H), 7,59 (s, 1H).

Microanálisis: Encontrado C, 50,33; H, 5,07; N, 20,60. $C_{17}H_{20}N_6O_3S.0,95H_2O$ requiere C, 50,35; H, 5,44; N, 20,72%.

EJEMPLO 174

N-{2-[4-(3,5-Dicianofenoxi)-3,5-dietil-1*H*-pirazol-1-il]etil}-2-metoxiacetamida



Se añadieron la amina del Ejemplo 127 (100 mg, 0,32 mmol), clorhidrato de 1-(3-dimetilaminopropil)-3-etilcarbodiimida (68 mg, 0,35 mmol) y *N*,*N*-dimetilaminopiridina (43 mg, 0,35 mmol) a una solución de ácido 1- metoxiacético (27 µl, 0,35 mmol) disuelto en diclorometano (10 ml) en una atmósfera de nitrógeno a temperatura ambiente. La reacción se agitó durante 18 horas, se concentró a presión reducida y el aceite amarillo residual

se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco 0,88 (95:5:0,5, en volumen), proporcionando el compuesto del título (32 mg) en forma de un aceite incoloro.

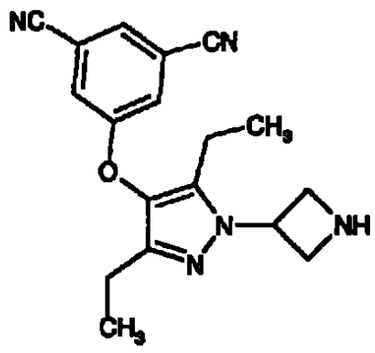
^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,11 (t, 3H), 1,16 (t, 3H), 2,38 (q, 2H), 2,47 (q, 2H), 3,41 (s, 3H), 3,77 (dd, 2H), 3,89 (s, 2H), 4,15 (m, 2H), 7,19 (s a, 1H), 7,40 (s, 2H), 7,59 (s, 1H).

LRMS (termonebulización) : m/z [MH^+] 382.

Microanálisis: Encontrado C, 61,26; H, 6,18; N, 17,59. $C_{20}H_{23}N_5O_3.0,60H_20$ requiere C, 61,24; H, 6,22; N, 17,85%.

EJEMPLO 175

5-{[1-(3-Azetidinil)-3,5-dietil-1*H*-pirazol-4-il]oxi}isoftalonitrilo



Se disolvió la amina protegida de la Preparación 69 (178 mg, 0,42 mmol) en una solución de ácido clorhídrico 4 M en dioxano (1 ml) y dioxano (1 ml) y la reacción se agitó a temperatura ambiente durante 18 horas. El disolvente se

retiró a presión reducida y el residuo se repartió entre diclorometano (20 ml) y una solución acuosa saturada de bicarbonato sódico (20 ml). La fase orgánica se secó sobre sulfato de magnesio, se concentró a presión reducida y se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con un gradiente de disolventes de diclorometano:metanol:amoniaco 0,88 (100:0:0, después 98:2:0, después 95:5:0, después 95:5:0,5, después 90:10:1 y después 80:20:1, en volumen), proporcionando el compuesto del título (33 mg) en forma de un sólido blanco.

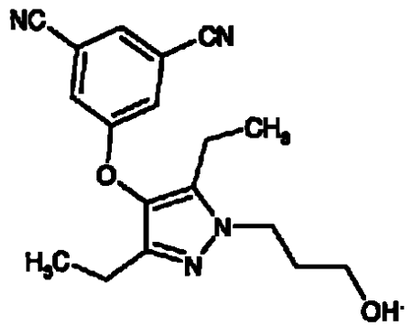
^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,05 (t, 3H), 1,11 (t, 3H), 2,44 (m, 4H), 3,85 (m, 2H), 4,38 (m, 2H), 5,05 (m, 1H), 7,37 (s, 2H), 7,56 (s, 1H).

LRMS (electronebulización) : m/z [MH^+] 322.

Microanálisis: Encontrado C, 65,87; H, 5,94; N, 20,98. $C_{18}H_{19}N_5O.0,38H_2$ requiere C, 65,87; H, 6,07; N, 21,04%.

EJEMPLO 176

5-{[3,5-Dietil-1-(3-hidroxipropil)-1*H*-pirazol-4-il]oxi}isoftalonitrilo



Se disolvieron el alcohol protegido de la Preparación 70 (215 mg, 0,53 mmol) y ácido p-tolueno-sulfónico (10 mg, 0,05 mmol) en metanol (2 ml) y se agitaron en una atmósfera de nitrógeno a temperatura ambiente durante 18 horas. El disolvente se retiró a presión reducida y el residuo se repartió entre agua (10 ml) y diclorometano (10 ml). La fase orgánica se secó sobre sulfato de magnesio y se concentró a presión reducida, proporcionando el compuesto del título (148 mg) en forma de un sólido amarillo pálido, p.f. 93-95°C.

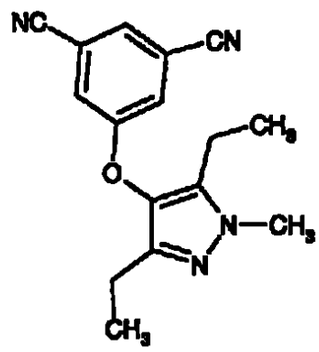
^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,11 (m, 6H), 2,04 (tt, 2H), 2,37 (q, 2H), 2,53 (q, 2H) 3,06 (t, 1H), 3,69 (dt, 2H), 4,18 (t, 2H), 7,38 (s, 2H), 7,58 (s, 1H).

LRMS (electronebulización) : m/z [MH^+] 325, [MNa^+] 347.

Microanálisis: Encontrado C, 66,27; H, 6,27; N, 17,00. $C_{18}H_{20}N_4O_2$ requiere C, 66,28; H 6,24; N, 17,18%.

EJEMPLO 177

5-[(3,5-Dietil-1-metil-1*H*-pirazol-4-il)oxi]isoftalonitrilo



Se añadió hidruro sódico (dispersión en aceite al 60%, 33 mg, 0,82 mmol) a una solución del pirazol del Ejemplo 122 (200 mg, 0,75 mmol) en dimetilformamida (3 ml) a 0°C en una atmósfera de nitrógeno y la reacción se agitó durante 10 minutos. Se añadió yoduro de metilo (117 mg, 0,82 mmol) y la reacción se agitó a temperatura ambiente durante 18 horas. La reacción se inactivó con agua (0,2 ml) y se concentró a presión reducida. El residuo se repartió entre diclorometano (5 ml) y agua (5 ml) y la fase orgánica se aisló usando un cartucho vitrificado 5 μM Whatman PTFE y después se concentró a presión reducida. El residuo se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con un gradiente de disolventes de acetato de etilo:pentano (20:80, en volumen) cambiando a acetato de etilo:metanol 0,88 (90:10, en volumen) y después diclorometano:metanol:amoniaco (90:10:1 y después 80:20:1, en volumen), proporcionando el compuesto del título (170 mg) como un sólido amarillo.

^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,10 (m, 6H), 2,39 (q, 2H), 2,49

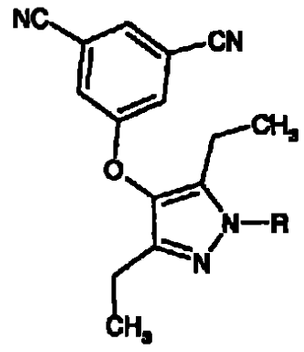
(q, 2H), 3,80 (s, 3H), 7,40 (s, 2H), 7,56 (s, 1H).

LRMS (electronebulización) : m/z [MH^+] 281.

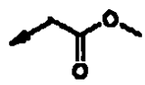
Microanálisis: Encontrado C, 68,41; H, 5,71; N, 19,93. $C_{16}H_{16}N_4O$ requiere C, 68,55; H, 5,75; N, 19,99%.

EJEMPLOS 178-180

Los compuestos de los siguientes Ejemplos indicados en la tabla, de formula general:



se prepararon por un procedimiento similar al del Ejemplo 177 usando el apropiado haluro de alquilo como el material de partida.

Ejemplo No (No de Ejemplo del Material de Partida)	R	Datos Analíticos
178 (122)		^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,08 (t, 3H), 1,12 (t, 3H), 2,40 (q, 2H), 2,54 (q, 2H), 3,34 (s, 3H), 3,75 (t, 2H), 4,17 (t, 2H), 7,38 (s, 2H), 7,56 (s, 1H). LRMS (electronebulización) : m/z [MH^+] 325, [MNa^+] 347. Microanálisis: Encontrado C, 65,73; H, 6,17; N, 17,08. $C_{18}H_{20}N_4O_3.0.25H_2O$ requiere C, 65,74; H, 6,28; N, 17,04%.
179[1,2] (122)		^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,10 (m, 6H), 1,98 (m, 2H), 2,38 (q, 2H), 2,51 (q, 2H), 2,76 (t, 2H), 4,09 (t, 2H), 7,38 (s, 2H), 7,57 (s, 1H). LRMS (electronebulización) : m/z [MH^+] 324. Microanálisis: Encontrado C, 64,86; H, 6,51; N, 20,79. $C_{18}H_{21}N_5O.0.57H_2O$ requiere C, 64,79; H, 6,69; N, 20,99%.
180[1] (122)		^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,09 (t, 3H), 1,14 (t, 3H), 2,41 (q, 2H), 2,47 (q, 2H), 3,79 (s, 3H), 4,82 (s, 2H), 7,40 (s, 2H), 7,57 (s, 1H). LRMS (electronebulización) : m/z [MH^+] 339. Microanálisis: Encontrado C, 63,58; H, 5,35; N, 16,35. $C_{19}H_{19}N_5O_3.0.10H_2O$ requiere C, 63,56; H, 5,39; N, 16,47%.

[1] Los dos reactivos se calentaron conjuntamente como un fundido a 160°C durante 24 horas y la reacción se preparó repartiéndose entre diclorometano y una solución de bicarbonato sódico, se extrajo la fase orgánica con ácido clorhídrico 2 M y la fase acuosa se basificó con carbonato sódico. Después de la extracción con diclorometano, las fase orgánica se secó y se concentró, dando el producto bruto.

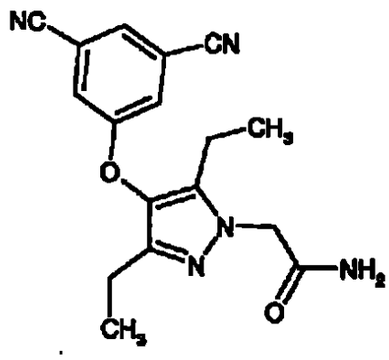
[2] El eluyente usado para la purificación por cromatografía en columna ultrarrápida de este compuesto fue diclorometano:metanol:amoniaco 0,88 (95:5:0,5 cambiando a 80:20:1), en volumen).

[3] El eluyente usado para la purificación por cromatografía en columna ultrarrápida de este compuesto fue pentano:acetato de etilo (75:25 cambiando a 66:34 y después a 50:50, en volumen).

[4] Se usó sal clorhidrato del haluro de alquilo de partida.

EJEMPLO 181

2-[4-(3,5-Dicianofenoxi)-3,5-dietil-1*H*-pirazol-1-il]acetamida



Se disolvió el éster del Ejemplo 180 (200 mg, 0,59 mmol) en una solución de amoniaco 2M en metanol (5 ml) y la reacción se agitó en una atmósfera de nitrógeno a 75°C durante 18 horas. La mezcla se concentró a presión reducida y el residuo se purificó por cromatografía ultrarrápida sobre gel de sílice, eluyendo con un gradiente de disolvente de diclorometano:metanol:amoniaco 0,88 (95:5:0,5, en volumen),

proporcionando el compuesto del título (6 mg).

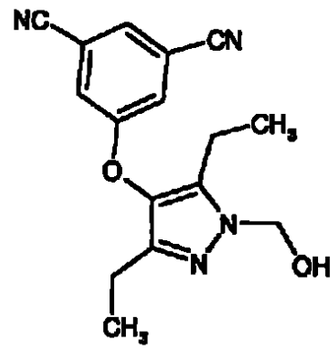
^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,10 (t, 3H), 1,15 (t, 3H), 2,44 (q, 2H), 2,54 (q, 2H), 4,69 (s, 2H), 5,55 (s a, 1H), 6,22 (s a, 1H), 7,38 (s, 2H), 7,59 (s, 1H).

LRMS (electronebulización): m/z [M-H$^+$] 322.

Microanálisis: Encontrado: C, 68,41; H, 5,71; N, 19,93. $C_{16}H_{16}N_4O$ requiere C, 68,55; H, 5,75; N, 19,99%.

EJEMPLO 182

5-{[3,5-Dietil-1-(hidroximetil)-1*H*-pirazol-4-il]oxi}isoftalonitrilo



Se añadió formaldehído (solución en agua al 37%, 253 µl, 3,14 mmol) a una solución del pirazol del Ejemplo 122 (440 mg, 1,65 mmol) en etanol (5 ml) y la reacción se agitó a 80°C durante 18 horas. Después de la refrigeración a temperatura ambiente, el disolvente se retiró a presión reducida y el sólido amarillo residual se repartió entre acetato de etilo (15 ml) y agua (10 ml) y la fase orgánica se retiró. La fase acuosa se lavó con acetato de etilo (2x15 ml) y los extractos

orgánicos reunidos se secaron sobre sulfato de magnesio y se concentraron a presión reducida, proporcionando el compuesto del título (490 mg) en forma de un sólido blanco.

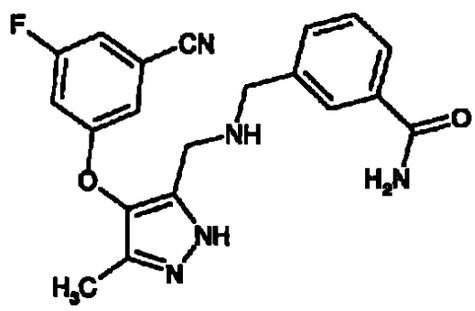
^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,13 (t, 3H), 1,14 (t, 3H), 2,39 (q, 2H), 2,61 (q, 2H), 5,49 (s, 2H), 5,68 (s a, 1H), 7,40 (s, 2H), 7,56 (s, 1H).

LRMS (termonebulización) : m/z [MH^+] 267.

Microanálisis: Encontrado C, 64,28; H, 5,52; N, 18,47. $C_{16}H_{16}N_4O_2.0,15H_2O$ requiere C, 64,27; H, 5,49; N, 18,24%.

EJEMPLO 183

3-[({[4-(3-Ciano-5-fluorofenoxi)-3-metil-1*H*-pirazol-5-il]metil}amino)metil]benzamida



El pirazol de la Preparación 75 (320 mg, 0,91 mmol) y la amina de la Preparación 80 (680 mg, 4,61 mmol) se calentaron a reflujo en isopropanol (5 ml) durante 1,5 horas. El disolvente se retiró a presión reducida y el residuo se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco 0,88 (95:5:0,5, en volumen), dando el producto, que se purificó

adicionalmente por HPLC preparativa usando una columna de 3 µm Develosil combi-rp C30 de 50x4,6 mm, eluyendo con un gradiente de disolventes de 5:95 de ácido trifluoroacético acuoso al 0,1% en acetonitrilo:acetonitrilo (0-6 min 95:5 cambiando a 50-50; 6-7 min 50:50; 7-7,1 min 50:50 cambiando a 5:95; 7,1-8 min 5:95), proporcionando el compuesto del título (38 mg).

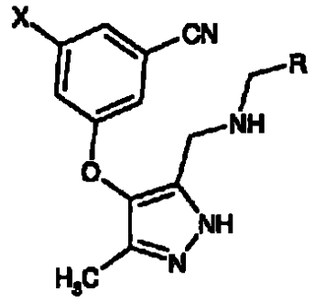
^{1}H-RMN (400 MHz, CD_3OD_3): δ = 2,14 (s, 3H), 4,10 (s, 2H), 4,34 (s, 2H), 7,03 (m, 1H), 7,10 (s, 1H), 7,25 (m, 1H), 7,54 (t, 1H), 7,64 (d, 1H), 7,92 (d, 1H), 7,97 (s, 1H).

LRMS (electronebulización) : m/z [MH^+] 380.

Microanálisis: Encontrado C, 51,32; H, 3,91; N, 13,69. $C_{20}H_{18}N_5O_2F.1,00CF_3CO_2H1,10H_2O$ requiere C, 51,49; H, 4,16; N, 13,65%.

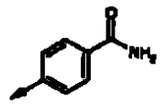
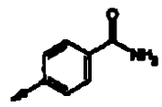
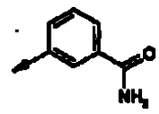
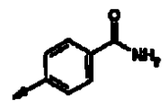
EJEMPLOS 184-188

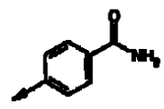
Los compuestos de los siguientes Ejemplos indicados en la tabla, de formula general:



se prepararon por un procedimiento similar al del Ejemplo 183 usando como materiales de partida los apropiados pirazoles

(P) y aminas (A).

Ej. No.	No. de Prep. P	No. de Prep. A	X	R	Datos Analíticos
184[1]	75	55	F		^{1}H-RMN (400 MHz, $CDCl_3$): δ = 2.09 (s, 3H), 3.65 (s, 2H), 3.79 (s, 2H), 6.80 (d, 1H), 6.93 (s, 1H), 6.97 (d, 1H), 7.31 (d, 2H), 7.72 (d, 2H). LRMS (termonebulización): m/z [MH$^+$] 380.
185[1]	76	55	CN		p.f. 114-116°C ^{1}H-RMN (400 MHz, $CDCl_3$): δ = 2.08 (s, 3H), 3.62 (s, 2H), 3.77 (s, 2H), 7.34 (d, 2H), 7.55 (s, 1H), 7.77 (d, 2H), 7.79 (s, 1H). LRMS (termonebulización): m/z [MH$^+$] 387.
186[1]	18	80	Cl		p.f. 98-101°C. ^{1}H-RMN (400 MHz, $CDCl_3$): δ = 2.04 (s, 3H), 3.62 (s, 2H), 3.74 (s, 2H), 6.97 (s, 1H), 7.07 (s, 1H), 7.20 (s, 1H), 7.22 (d, 1H), 7.29 (t, 1H), 7.62 (s, 1H), 7.81 (s, 1H). LRMS (termonebulización) : m/z [MH$^+$] 396. Microanálisis: Encontrado C, 56.98; H, 4.58; N, 17.69. $C_{20}H_{18}ClN_3O_3.0.40CH_2Cl_2$ requiere C, 57.01; H, 4.41; N, 16.29%.
187[1-13]	77	55	Me		^{1}H-RMN (400 MHz, $CDCl_3$): δ = 2.10 (s, 3H), 2.30 (s, 3H), 3.65 (s, 2H), 3.80 (s, 2H), 6.85 (s, 1H), 6.95 (s, 1H), 7.10 (s, 1H), 7.30 (d, 2H), 7.70 (d, 2H). LRMS (electronebulización) : m/z [MH$^+$] 376, [M-H$^+$] 374 Microanálisis: Encontrado C, 65.59; H, 5.65; N, 18.19. $C_{21}H_{21}N_3O_2.0.50H_2O$ requiere C, 65.51; H, 5.77; N, 18.22%.

188[4]	78	55	H		^{1}H-RMN (400 MHz, $CDCl_3$): δ = 2,15 (s, 3H), 4,10 (s, 2H), 7,20 (m, 2H), 7,40 (m, 1H), 7,50 (m, 1H), 7,55 (d, 2H), 7,90 (d, 2H). Microanálisis: Encontrado C, 53,51; H, 4,13; N, 13,59. $C_{20}H_{19}N_5O_2$.1,25TFA requiere C, 53,63; H, 4,05; N, 13,90%.

[1] No se requirió HPLC preparativa para la purificación de este compuesto.

[2] El eluyente usado para la purificación por cromatografía en columna ultrarrápida de este compuesto fue diclorometano:metanol:amoniaco 0,88 (95:5:0,5 cambiando a 90:10:1, en volumen).

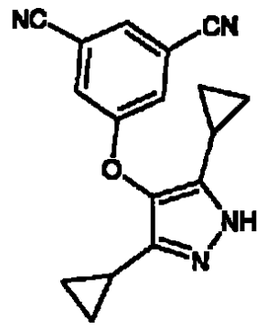
[3] El producto se trituró con diclorometano que contenía una traza de metanol - cristalizó un sólido que era una impureza. Este se retiró por filtración y el filtrado se concentró a presión reducida y el residuo se purificó por cromatografía ultrarrápida, eluyendo con diclorometano:metanol:amoniaco 0,88 (90:10:1, en volumen), dando el compuesto del título.

[4] La columna usada para la HPLC preparativa fue una LUNA C18

10 μm 150x21,2 mm.

EJEMPLO 189

5-[(3,5-Dicloropropil-1*H*-pirazol-4-il)oxi]isoftalonitrilo



Se añadió hidrato de hidrazina (133 μl, 2,75 mmol) a una solución de la dicetona de la Preparación 82 (735 mg, 2,50 mmol) en ácido acético (25 ml) en una atmósfera de nitrógeno a temperatura ambiente. Después de agitar durante 64 horas, la mezcla se concentró a presión reducida y el residuo se repartió entre diclorometano (25 ml) y una solución acuosa saturada de bicarbonato sódico (25 ml). La fase orgánica se secó sobre sulfato de magnesio, se concentró a presión reducida y el residuo se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol (98:2 cambiando a 96:4, en volumen), proporcionando el compuesto del título (473 mg) en forma de un sólido blanco, p.f. 168-170°C.

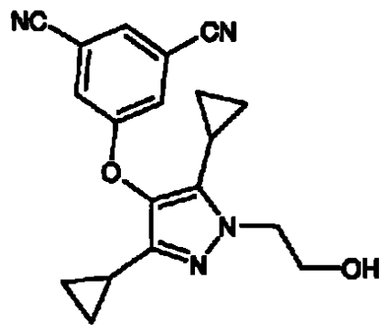
^{1}H-RMN (400 MHz, $CDCl_3$): δ = 0,77 (m, 4H), 0,85 (m, 4H), 1,59 (m, 2H), 7,44 (s, 2H), 7,59 (s, 1H).

LRMS (termonebulización) : m/z [MH^+] 291.

Microanálisis: Encontrado C, 69,90; H, 4,85; N, 19,18. $C_{17}H_{14}N_4O.0,10H_2O$ requiere C, 69,90; H, 4,90; N, 19,18%.

EJEMPLO 190

5-{[3,5-Dicloropropil-1-(2-hidroxietil)-1*H*-pirazol-4-il]oxi}isoftalonitrilo



Se añadió 2-hidroxietilhidrazina (84 mg, 1,10 mmol) a una solución de la dicetona de la Preparación 82 (294 mg, 1,00 mmol) en ácido acético (10 ml) en una atmósfera de nitrógeno a temperatura ambiente. Después de agitar durante 64 horas, la mezcla se concentró a presión reducida y el residuo se repartió entre diclorometano (25 ml) y una solución acuosa saturada de bicarbonato sódico (25 ml). La fase orgánica se secó sobre sulfato de magnesio, se concentró a presión reducida y el residuo se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol (99:1 cambiando a 95:5, en volumen), proporcionando el compuesto del título (137 mg) en forma de

un sólido blanco, p.f. 115-117°C.

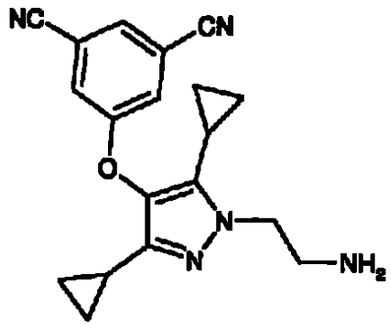
^{1}H-RMN (400 MHz, $CDCl_3$): δ = 0,67 (m, 2H), 0,80 (m, 4H), 0,85 (m, 2H), 1,52 (m, 2H), 3,39 (s a, 1H), 4,05 (m, 2H), 4,22 (t, 2H), 7,42 (s, 2H), 7,58 (s, 1H).

LRMS (termonebulización) : m/z [MH^+] 355.

Microanálisis: Encontrado C, 67,63; H, 5,55; N, 16,35. $C_{19}H_{18}N_4O_2.0,17H_2O$ requiere C, 67,63; H, 5,48; N, 16,60%.

EJEMPLO 191

5-{[1-(2-Aminoetil)-3,5-dicicopropil-1*H*-pirazol-4-il]oxi}isoftalonitrilo



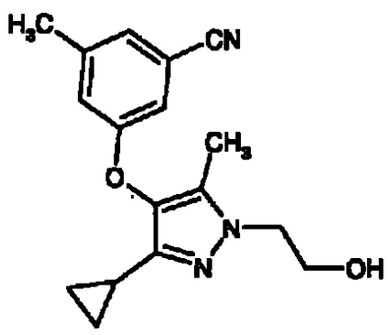
Se calentaron clorhidrato de 2-cloroetilamina (192 mg, 1,65 mmol) y el pirazol del Ejemplo 189 (440 mg, 1,50 mmol) como un fundido a 160°C durante 18 horas y el residuo se repartió entre diclorometano (25 ml) y una solución acuosa al 10% de carbonato potásico (25 ml). La fase orgánica se secó sobre sulfato de magnesio, se concentró a presión reducida y el residuo se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con

diclorometano:metanol:amoniaco 0,88 (95:5:0 cambiando a 95:5:0,5, en volumen), proporcionando el compuesto del título (9,2 mg) en forma de un sólido blanco, p.f. 175-177°C.

^{1}H-RMN (400 MHz, $CDCl_3$): δ = 0,70 (m, 2H), 0,79 (m, 4H), 0,88 (m, 2H), 1,57 (m, 1H), 1,66 (m, 1H), 3,46 (t, 2H), 4,41 (t, 2H), 7,62 (s, 2H), 7,58 (s, 1H).

EJEMPLO 192

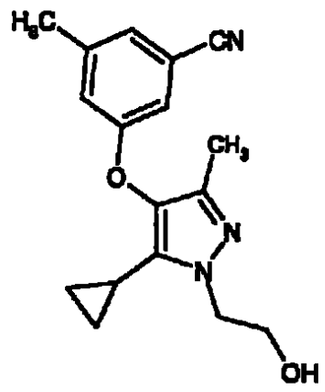
3-{[3-Ciclopropil-1-(2-hidroxietil)-5-metil-1*H*-pirazol-4-iloxi}-5-metilbenzonitrilo



y

EJEMPLO 193

3-{[5-Ciclopropil-1-(2-hidroxietil)-3-metil-1*H*-pirazol-4-iloxi}-5-metilbenzonitrilo



Se añadió 2-hidroxi-etil-hidrazina (326 µl, 4,80 mmol) a una solución de la dicetona de la Preparación 86 (1,00 g, 4,37 mmol) en ácido acético (10 ml) en una atmósfera de nitrógeno a temperatura ambiente. Después de agitar durante 18 horas, la mezcla se concentró a presión reducida y el aceite naranja residual se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con acetato de etilo:pentano (50:50 cambiando a 100:0, en volumen), proporcionando dos aceites amarillo pálido.

Fracción menos polar (Ejemplo 192) - 419 mg

^{1}H-RMN (400 MHz, $CDCl_3$): δ = 0,69 (m, 2H), 0,82 (m, 2H), 1,54 (m, 1H), 2,00 (s, 3H), 2,35 (s, 3H), 3,46 (s a, 1H), 4,05 (t, 2H), 4,22 (t, 2H), 6,88 (s, 1H), 6,94 (s, 1H), 7,08 (s, 1H).

LRMS (termonebulización) : m/z [MH^+] 298.

Microanálisis: Encontrado C, 68,29; H, 6,51; N, 13,92. $C_{17}H_{19}N_3O_2$ requiere C, 68,67; H, 6,44; N, 14,13%.

Fracción más polar (Ejemplo 193) - 201 mg

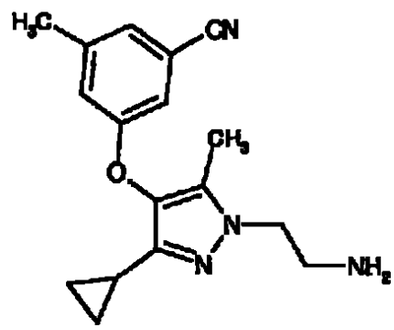
^{1}H-RMN (400 MHz, $CDCl_3$): δ = 0,75 (m, 4H), 1,58 (m, 1H), 2,07 (s, 3H), 2,35 (s, 3H), 3,45 (s a, 1H), 4,00 (m, 4H), 6,92 (s, 1H), 7,00 (s, 1H), 7,10 (s, 1H).

LRMS (termonebulización) : m/z [MH^+] 298,

Microanálisis: Encontrado C, 68,44; H, 6,49; N, 13,95. $C_{17}H_{19}N_3O_2$ requiere C, 68,67; H, 6,44; N, 14,13%.

EJEMPLO 194

3-[3-Ciclopropil-1-(2-amino-etil)-5-metil-1*H*-pirazol-4-iloxi]-5-metil-benzonitrilo



Se disolvieron el alcohol del Ejemplo 192 (140 mg, 0,47 mmol), trifenilfosfina (309 mg, 1,18 mmol) y ftalimida (174 mg, 1,18 mmol) en tetrahidrofurano (9 ml) a 0°C en una atmósfera de nitrógeno y se añadió durante 10 minutos azodicarboxilato de diisopropilo (232 μl, 1,18 mmol) disuelto en tetrahidrofurano (2 ml). La reacción se dejó calentar a temperatura ambiente y se agitó durante 18 horas. El disolvente se retiró a presión reducida, el residuo se disolvió en etanol (11 ml) y se añadió hidrato de hidrazina

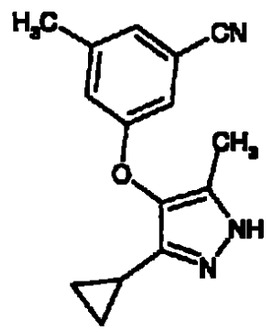
(114 µl, 2,35 mmol). La solución blanca espesa se agitó durante 18h a temperatura ambiente en una atmósfera de nitrógeno, se añadió metanol (10 ml) y la mezcla se filtró. El filtrado se concentró a presión reducida y el residuo se disolvió en diclorometano (20 ml). La fase orgánica se extrajo con ácido clorhídrico acuoso 2 M (20 ml) y la fase acuosa se lavó con diclorometano (5x10 ml), se basificó con hidróxido sódico acuoso 1 M y se extrajo con diclorometano (50 ml). La fase orgánica se secó sobre sulfato de magnesio y se concentró a presión reducida, proporcionando el compuesto del título (135 mg) en forma de un aceite amarillo. ^{1}H-RMN (400 MHz, $CDCl_3$): δ = 0,70 (m, 4H), 1,56 (m, 1H), 2,06 (s, 3H), 2,30 (s, 3H), 3,10 (t, 2H), 3,97 (t, 2H), 6,87 (s, 1H), 6,92 (s, 1H), 7,05 (s, 1H).

LRMS (electronebulización) : m/z [MH^+] 297.

Microanálisis: Encontrado C, 63,81; H, 6,51; N, 17,30. $C_{17}H_{20}N_4O.0,36CH_2Cl_2$ requiere C, 63,78; H, 6,39; N, 17,14%.

EJEMPLO 195

3-[(3-Ciclopropil-5-metil-1*H*-pirazol-4-il)oxi]-5-metilbenzonitrilo



Se añadió hidrato de hidrazina (31 µl, 0,64 mmol) a una solución de la dicetona de la Preparación 86 (150 mg, 0,58 mmol) en ácido acético (1,3 ml) en una atmósfera de nitrógeno a temperatura ambiente. Después de agitar durante 24 horas, la mezcla se concentró a presión reducida y el residuo se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con pentano:acetato de etilo (60:40 cambiando a 40:60, en volumen), proporcionando el compuesto del título (140 mg).

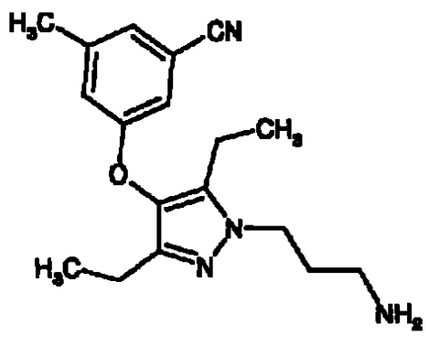
^{1}H-RMN (400 MHz, $CDCl_3$): δ = 0,60 (m, 4H), 1,69 (m, 1H), 2,09 (s, 3H), 2,34 (s, 3H), 6,95 (s, 1H), 6,99 (s, 1H), 7,10 (s, 1H).

LRMS (termonebulización) : m/z [MH^+] 254.

Microanálisis: Encontrado C, 68,35; H, 6,13; N, 15,10. $C_{15}H_{15}N_3O.0,29EtOAc$ requiere C, 68,72; H, 6,32; N, 14,88%.

EJEMPLO 196

3-{[1-(3-Aminopropil)-3,5-dietil-1*H*-pirazol-4-il]oxi}-5-metilbenzonitrilo



Se calentaron clorhidrato de 3-cloropropilamina (62 mg, 0,48 mmol) y el pirazol del Ejemplo 123 (113 mg, 0,44 mmol) como un fundido a 150°C durante 18 horas. Después de la refrigeración el residuo se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco 0,88 (98:2:0 cambiando a 95:5:0,5, en volumen). Quedaba una impureza por lo que el aceite se disolvió en acetona (3 ml) y se añadió ácido (L)-tartárico (54 mg, 0,44 mmol). La mezcla se calentó para conseguir la disolución y se enfrió. El precipitado resultante se aisló por filtración y se lavó con acetona (10 ml), proporcionando el compuesto del título (127 mg) en forma de un sólido blanco que fue la sal tartrato.

^{1}H-RMN (400 MHz, CD_3OD): δ = 1,05 (m, 6H), 2,07 (m, 2H), 2,37 (q, 2H), 2,53 (s, 3H), 2,57 (q, 2H), 2,99 (t, 2H), 4,15 (t, 2H), 4,38 (s, 2H), 6,89 (s, 1H), 7,01 (s, 1H), 7,19 (s,1H).

LRMS (termonebulización) : m/z [MH^+] 313.

Microanálisis: Encontrado C, 56,81; H, 6,57; N, 12,06.

$C_{22}H_{30}N_4O_7$ requiere C, 57,13; H, 6,54; N, 12,11%.

EJEMPLO 197

3-{[3,5-Dietil-1-(2-hidroxietil)-1*H*-pirazol-4-il]oxi}-4-metoxibenzonitrilo



Se añadió carbonato de cesio (700 mg, 2,14 mmol) a una solución agitada de 2-metoxi-5-cianofenol (285 mg, 2,15 mmol) y la diona de la Preparación 2 (348 mg, 2,15 mmol) en acetona (20 ml) a temperatura ambiente. La reacción se calentó a 50°C durante 3 horas y después se enfrió a temperatura ambiente. La mezcla se concentró a presión reducida, se disolvió en diclorometano (5 ml) y se lavó con agua (5 ml). La fase orgánica se aisló usando un cartucho vitrificado 5 µM Whatman PTFE y después se concentró a presión reducida. El residuo se disolvió en ácido acético (5,4 ml) y se añadió 2-hidroxi-etil-hidrazina (160 µl, 2,15 mmol) en una atmósfera de nitrógeno a temperatura ambiente. Después de agitar durante 18 horas, la mezcla se concentró a presión reducida y el aceite naranja residual se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con una gradiente

de disolventes de acetato de etilo:pentano (25:75 cambiando a 50:50, en volumen), proporcionando el compuesto del título (182 mg).

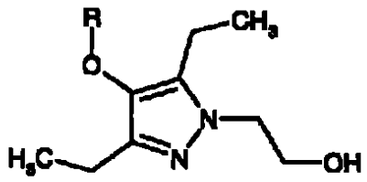
^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,10 (m, 6H), 2,39 (q, 2H), 2,51 (q, 2H), 3,71 (s a, 1H), 4,00 (s, 3H), 4,08 (m, 2H), 4,09 (m, 2H), 6,89 (s, 1H), 6,99 (d, 1H), 7,32 (d, 1H).

LRMS (termonebulización) : m/z [MH^+] 316.

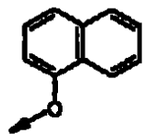
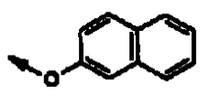
Microanálisis: Encontrado C, 64,57; H, 6,73; N, 13,15. $C_{17}H_{21}N_3O_3$ requiere C, 64,74; H, 6,71; N, 13,32%.

EJEMPLOS 198-199

Los compuestos de los siguientes Ejemplos indicados en la tabla, de formula general:

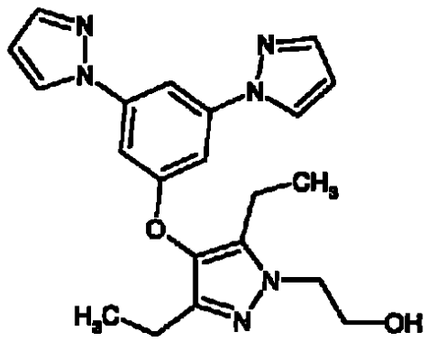


se prepararon por un procedimiento similar al del Ejemplo 197 usando la β-dicetona de la Preparación 2 y el apropiado alcohol arílico como los materiales de partida.

Ejemplo No.	R	Datos Analíticos
198		^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,04 (m, 6H), 2,42 (q, 2H),2,51 (q,2H), 4,07 (m, 2H), 4,12 (m, 2H), 6,60 (d, 1H), 7,25 (t, 1H), 7,49 (d, 1H), 7,53 (m, 2H), 7,82 (m, 1H), 8,41 (m, 1H). LRMS (termonebulización): m/z [MH$^+$] 311.
199		^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,19 (m, 6H), 2,48 (q, 2H), 2,51 (q,2H), 4,03 (m, 2H), 4,10 (m, 2H), 7,06 (s: 1H), 7,22 (m, 1H), 7,38 (t, 1H), 7,42 (m, 1H), 7,69 (d, 1H), 7,79 (s, 1H), 7,80 (s, 1H). ¡LRMS (termonebulización) : m/z [MH$^+$] 311. Microanálisis: Encontrado C, 72,16; H, 7,20; N, 8,95. $C_{19}H_{22}N_2O_2$.0.10EtOAc requiere C, 72,45; H, 7,19; N, 8,63.

EJEMPLO 200

2-{4-[3,5-Di(1*H*-pirazol-1-il)fenoxi]-3,5-dietil-1*H*-pirazol-1-il}etanol



Se disolvieron el alcohol protegido de la Preparación 88 (254 mg, 0,53 mmol) y ácido p-tolueno-sulfónico (10 mg, 0,05 mmol) en metanol (4 ml) y se agitó en una atmósfera de nitrógeno a temperatura ambiente durante 18 horas. El disolvente se retiró a presión reducida y el residuo se

repartió entre una solución acuosa saturada de bicarbonato sódico (20 ml) y diclorometano (20 ml). La fase acuosa se extrajo con diclorometano (10 ml) y los extractos orgánicos reunidos se secaron sobre sulfato de magnesio, se concentraron a presión reducida y se purificaron por cromatografía ultrarrápida sobre gel de sílice eluyendo con un gradiente de disolventes de diclorometano:metanol (100:0 cambiando a 93:7, en volumen), proporcionando el compuesto del título (56 mg) en forma de un sólido blanco, p.f. 108-110°C.

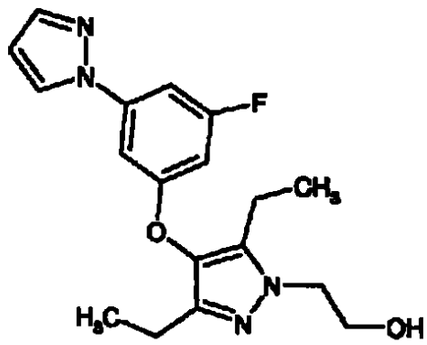
^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,11 (m, 6H), 2,46 (q, 2H), 2,53 (q, 2H), 4,01 (t,2H), 4,07 (t, 2H), 6,44 (s, 2H), 7,16 (s, 2H), 7,68 (s, 3H), 7,92 (s, 2H).

LRMS (electronebulización) : m/z [MH^+] 393, [MNa^+] 415.

Microanálisis: Encontrado C, 63,62; H 6,11; N, 21,11. $C_{21}H_{24}N_6O_2.0,06CH_2Cl_2$ requiere C, 63,63; H, 6,12; N, 21,14%.

EJEMPLO 201

2-{3,5-Dietil-4-[3-fluoro-5-(1*H*-pirazol-1-il)fenoxi]-1*H*-pirazol-1-il}etanol



Se disolvieron el alcohol protegido de la Preparación 89 (38,6 mg, 0,09 mmol) y ácido p-tolueno-sulfónico (3,5 mg, 0,01 mmol) en metanol (1 ml) y se agitaron en una atmósfera de nitrógeno a temperatura ambiente durante 18 horas. El disolvente se retiró a presión reducida y el residuo se repartió entre una solución acuosa al 10% de carbonato potásico (4 ml) y diclorometano (4 ml). La fase acuosa se extrajo con diclorometano (10 ml) y los extractos orgánicos reunidos se secaron sobre sulfato de magnesio, se concentraron a presión reducida y se purificaron por cromatografía ultrarrápida sobre gel de sílice eluyendo con un gradiente de disolventes de diclorometano:metanol (99:1 cambiando a 98:2, en volumen), proporcionando el compuesto del título (23 mg) en forma de un sólido blanco, p.f. 120-122°C.

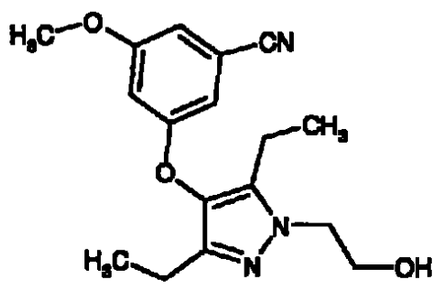
^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,14 (m, 6H), 2,46 (q, 2H), 2,55 (q, 2H), 4,06 (m, 2H), 4,09 (m, 2H), 6,47 (s, 1H), 6,49 (s, 1H), 7,09 (s, 1H), 7,12 (s, 1H), 7,71 (s, 1H), 7,86 (s, 1H).

LRMS (electronebulización) : m/z [MNa^+] 367.

HRMS: [MH^+] Encontrado 345,1717. $C_{18}H_{22}FN_4O_2$ requiere 345,1722.

EJEMPLO 202

3-{[3,5-Dietil-1-(2-hidroxietil)-1*H*-pirazol-4-il]oxi}-5-metoxibenzonitrilo



Se disolvieron el alcohol protegido de la Preparación 90 (400 mg, 1,00 mmol) y ácido p-tolueno-sulfónico (19 mg, 0,10 mmol) en metanol (10 ml) y se agitaron en una atmósfera de nitrógeno a temperatura ambiente durante 18 horas. El disolvente se retiró a presión reducida y el residuo se repartió entre una solución acuosa saturada de bicarbonato sódico (20 ml) y diclorometano (20 ml). La fase acuosa se extrajo con diclorometano (40 ml) y los extractos orgánicos reunidos se secaron sobre sulfato de magnesio, se concentraron a presión reducida y se purificaron por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol (97:3, en volumen), proporcionando el compuesto del título (174 mg) en forma de un aceite.

^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,09 (m, 6H), 2,40 (q, 2H), 2,49

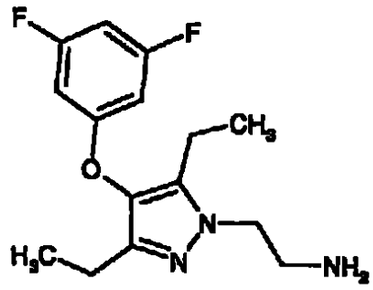
(q, 2H), 3,78 (s, 3H), 4,04 (m, 2H), 4,08 (m, 2H), 6,66 (s, 1H), 6,71 (s, 1H), 6,79 (s, 1H).

LRMS (electronebulización) : m/z [MH^+] 316.

Microanálisis: Encontrado C, 63,63; H, 6,76; N, 13,06. $C_{17}H_{21}N_3O_3.0,08CH_2Cl_2$ requiere C, 63,68; H, 6,68; N, 13,04%.

EJEMPLO 203

2-[4-(3,5-Difluorofenoxi)-3,5-dietil-1*H*-pirazol-1-il]etilamina



Se disolvieron el alcohol del Ejemplo 38 (371 mg, 1,25 mmol), trifenilfosfina (984 mg, 3,75 mmol) y ftalimida (552 mg, 3,75 mmol) en tetrahidrofurano (20 ml) a 0°C en una atmósfera de nitrógeno y se añadió durante 10 minutos azodicarboxilato de diisopropilo (738 µl, 3,75 mmol) disuelto en tetrahidrofurano (2 ml). La reacción se dejó calentar a temperatura ambiente y se agitó durante 18 horas. El disolvente se retiró a presión reducida, el residuo se disolvió en etanol (25 ml) y se añadió hidrato de hidrazina (303 µl, 6,25 mmol). La suspensión se agitó durante 4 horas

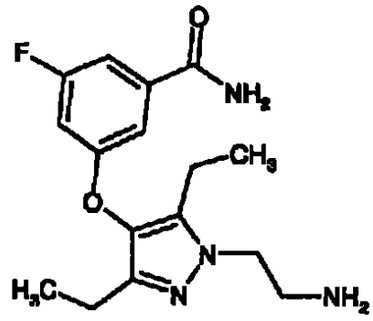
a 45°C en una atmósfera de nitrógeno, se concentró a presión reducida y el residuo se disolvió en metanol. La solución después se pasó a través de una columna SCX, eluyendo con metanol para retirar las impurezas y después con una solución 2 M de amoniaco en metanol para eluir el producto. Después, el producto se purificó por cromatografía en columna ultrarrápida eluyendo con diclorometano:metanol:amoniaco 0,88 (90:10:1, en volumen), proporcionando el compuesto del título (212 mg) en forma de un aceite.

^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,12 (m, 6H), 2,43 (q, 2H), 2,54 (q, 2H), 3,21 (t,2H), 4,07 (t, 2H), 6,43 (m, 3H).

Microanálisis: Encontrado C, 59,78; H, 6,50; N, 14,35. $C_{15}H_{19}F_2N_3O.0,26H_2O$ requiere C, 60,05; H, 6,56; N, 14,01%.

EJEMPLO 204

3-{[1-(2-Aminoetil)-3,5-dietil-1*H*-pirazol-4-il]oxi}-5-fluorobenzamida



Se disolvieron el alcohol del Ejemplo 163 (142 mg, 0,44 mmol), trifenilfosfina (346 mg, 1,32 mmol) y ftalimida (194 mg, 1,32 mmol) en tetrahidrofurano (8 ml) a 0°C en una

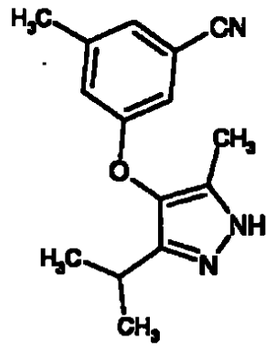
atmósfera de nitrógeno y se añadió durante 10 minutos azodicarboxilato de diisopropilo (260 µl, 1,32 mmol) disuelto en tetrahidrofurano (1 ml). La reacción se dejó calentar a temperatura ambiente y se agitó durante 18 horas. El disolvente se retiró a presión reducida, el residuo se disolvió en etanol (9 ml) y se añadió hidrato de hidrazina (107 µl, 2,2 mmol). La suspensión se agitó durante 4 horas a 45°C en una atmósfera de nitrógeno, se concentró a presión reducida y el residuo se disolvió en metanol. La solución después se pasó a través de una columna de ácido sulfónico soportada en polímero para eluir el producto. Después, el producto se purificó por cromatografía ultrarrápida sobre alúmina, eluyendo con diclorometano:metanol:amoniaco 0,88 (90:10:1, en volumen), proporcionando el compuesto del título (60 mg) en forma de un aceite.

^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,11 (m, 6H), 2,43 (q, 2H), 2,53 (q, 2H), 3,17 (t, 2H) 4,05 (t, 2H), 6,01 (s a, 1H), 6,25 (s a, 1H), 6,75 (d, 1H), 7,16 (m, 2H).

HRMS: [MH^+] Encontrado 321,1718, $C_{16}H_{21}FN_4O_2$ requiere 321,1722.

EJEMPLO 205

3-[(3-Isopropil-5-metil-1*H*-pirazol-4-il)oxi]-5-metilbenzonitrilo



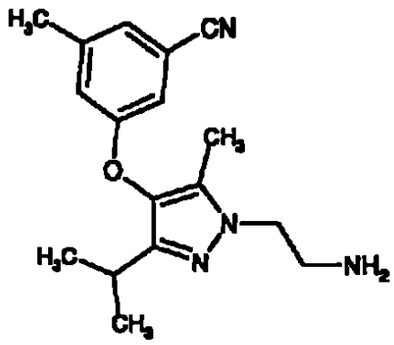
Se añadió hidrato de hidrazina (100 µl, 2,10 mmol) a una solución de la dicetona de la Preparación 91 (544 mg, 2,10 mmol) en ácido acético (10 ml) en una atmósfera de nitrógeno a temperatura ambiente. Después de agitar durante 64 horas, la mezcla se concentró a presión reducida y el residuo se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con pentano:acetato de etilo (66:34, en volumen), proporcionando el compuesto del título (308 mg) en forma de un aceite amarillo pálido.

^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,22 (d, 6H), 2,09 (s, 3H), 2,56 (s, 3H), 2,84 (m, 1H), 6,91 (s, 1H), 6,94 (s, 1H), 7,11 (s, 1H).

LRMS (termonebulización) : m/z [MH^+] 256.

EJEMPLO 206

3-{[1-(2-Aminoetil)-3-isopropil-5-metil-1*H*-pirazol-4-il]oxi}-5-metilbenzonitrilo



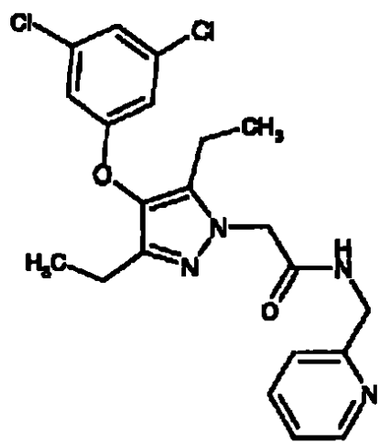
Se calentaron el pirazol del Ejemplo 205 (70 mg, 0,27 mmol) y clorhidrato de 2-cloroetilamina (38 mg, 0,33 mmol) como un fundido a 150°C durante 18 horas. El residuo se enfrió y se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco 0,88 (95:5:0,5, en volumen), dando el compuesto del título (25 mg).

^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,18 (m, 6H), 2,06 (s, 3H), 2,35 (s, 3H), 2,79 (m, 1H), 3,19 (m, 2H), 4,04 (m, 2H), 6,89 (s, 1H), 6,97 (s, 1H), 7,12 (s, 1H).

LRMS (electronebulización) : m/z [MH^+] 300.

EJEMPLO 207

2-[4-(3,5-Diclorofenoxi)-3,5-dietil-1*H*-pirazol-1-il]-*N*-(2-piridinilmetil)acetamida

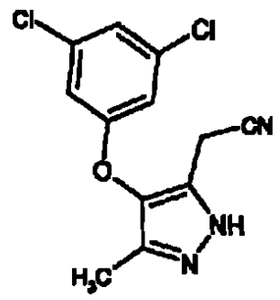


Soluciones convencionales: Se disolvieron por separado el ácido de la Preparación 4 (800 mg, 2,33 mmol), hexafluorofosfato de 1*H*-(benzotriazol-1-il)-*N*,*N*,*N'*,*N'*-tetrametiluronio (822 mg, 3,50 mmol) y diisopropiletilamina (603 mg, 4,66 mmol) en *N*,*N*-dimetilformamida (3x13 ml). Se trató 2-(metilamino)piridina (3 mg, 0,029 mmol) con las soluciones convencionales del ácido y los reactivos de acoplamiento (3x170 µl) en una placa de 96 pocillos y la mezcla se agitó durante 14 horas a temperatura ambiente. El disolvente se retiró a presión reducida y la mezcla se disolvió en dimetilsulfóxido (500 µl) y se purificó por HPLC (columna Magellen C_8(2) 150x10mm); se usó una fase móvil de gradiente, 5:95 (en volumen) a 95:5 (en volumen) acetonitrilo:(ácido trifluoroacético al 0,1% en agua). Tiempo de retención: 5,69 minutos.

LRMS (electronebulización) : m/z [MH^+] 434.

EJEMPLO 208

[4-(3,5-Diclorofenoxi)-3-metil-1*H*-pirazol-5-il]acetonitrilo



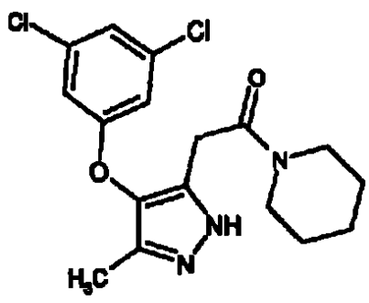
Se añadió en una porción el pirazol de la Preparación 8 (1,00 g, 2,60 mmol) en tetrahidrofurano (10 ml) a una solución de cianuro de cesio (284 mg, 5,20 mmol) en agua (10 ml) a temperatura ambiente. La reacción se calentó a 80°C durante 14 horas y se enfrió a temperatura ambiente. El disolvente se retiró a presión reducida y el sólido pardo resultante se disolvió en diclorometano (50 ml) y agua (50 ml). La capa orgánica se separó, se lavó con agua (50 ml) y salmuera (30 ml), se secó sobre sulfato de magnesio, se filtró y el disolvente se retiró a presión reducida, dando un sólido pardo. El producto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con pentano:acetato de etilo (50:50, en volumen), dando el compuesto del título como un sólido amarillo (500 mg), p.f. 150-152°C.

^{1}H-RMN (400 MHz, $CDCl_3$): δ = 2,17 (s, 3H), 3,56 (s, 2H), 6,77 (s, 2H), 7,02 (s, 1H).

LRMS (termonebulización) : m/z [MH^+] 282.

EJEMPLO 209

1-{[4-(3,5-Diclorofenoxi)-3-metil-1*H*-pirazol-5-il]acetil}piperidina



Soluciones convencionales: Se disolvieron por separado el ácido de la Preparación 92 (680 mg, 2,16 mmol) y hexafluorofosfato de 1*H*-(benzotriazol-1-il)-*N*,*N*,*N*',*N*'-tetrametiluronio (761 mg, 3,23 mmol) en *N*,*N*-dimetilacetamida:trietilamina (96:4) (2x17 ml).

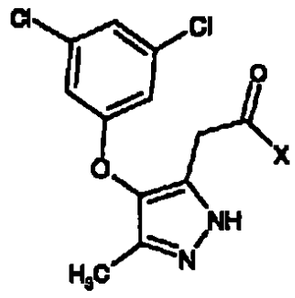
Se trató piperidina (3 mg, 0,031 mmol) con las soluciones convencionales del ácido y los reactivos de acoplamiento (250 µl de cada una) en una placa de 96 pocillos y la mezcla se agitó durante 14 horas a 80°C. El disolvente se retiró a presión reducida y la mezcla se disolvió en dimetilsulfóxido (500 µl) y se purificó por HPLC (columna Magellen C_8(2) 150x10mm); se usó una fase móvil de gradiente, 5:95 (en volumen) a 95:5 (en volumen) acetonitrilo:(ácido trifluoroacético al 0,1% en agua).

Tiempo de retención: 4,7 minutos.

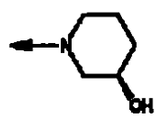
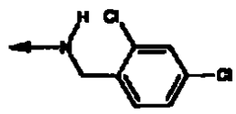
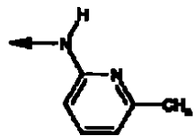
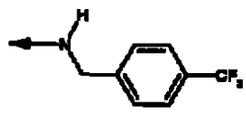
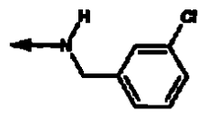
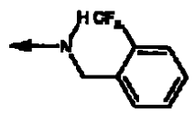
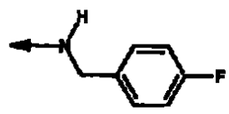
LRMS (electronebulización) : m/z [MH^+] 368.

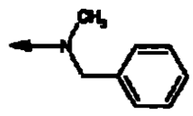
EJEMPLOS 210-217

Los compuestos de los siguientes Ejemplos indicados en la tabla, de formula general:



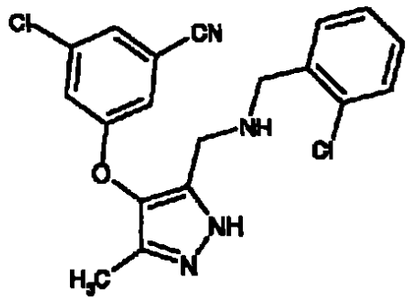
se prepararon por un procedimiento similar al del Ejemplo 209 usando la amina apropiada.

Ejemplo No.	X	Tiempos de retención de HPLC/min	LRMS (electronebulización) m/z [MH⁺]
210		3.9	384
211		5.5	459
212		5.4	476
213		5.3	458
214		5.1	424
215		5.3	458
216		4.9	408

217		5,2	404

EJEMPLO 218

3-Cloro-5-[(5-{[(2-clorobencil)amino]metil}-3-metil-1*H*-pirazol-4-il)oxi]benzonitrilo



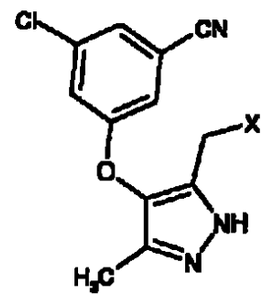
Soluciones convencionales: Se disolvió el bromuro de la Preparación 18 (850 mg, 2,30 mmol) en *N*-metilpirrolidinona (43 ml).

En una placa de 96 pocillos se trató 2-clorobencilamina (19 mg, 0,13 mmol) con la solución del bromuro de la Preparación 18 (500 µl) y la mezcla se agitó durante 14 horas a 80°C. El disolvente se retiró a presión reducida y la mezcla se disolvió en dimetilsulfóxido (500 µl) y se purificó por HPLC (columna Magellen C_8(2) 150x10 mm); se usó una fase móvil de gradiente, 5:95 (en volumen) a 95:5 (en volumen) acetonitrilo:(ácido trifluoroacético al 0,1% en agua), Tiempo de retención: 5,3 minutos.

LRMS (electronebulización) : m/z [MH^+] 386.

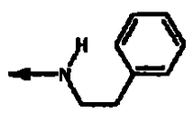
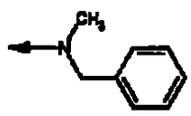
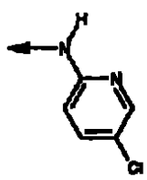
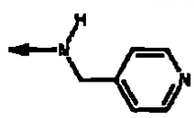
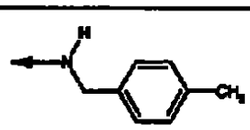
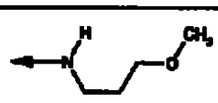
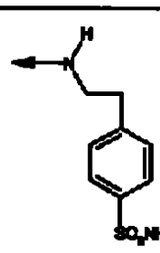
EJEMPLOS 219-249

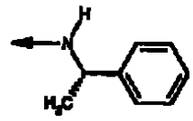
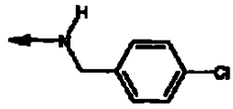
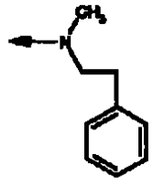
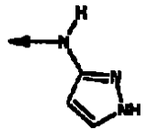
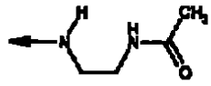
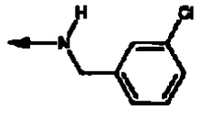
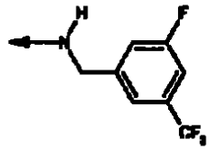
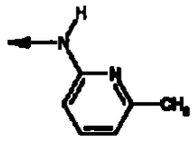
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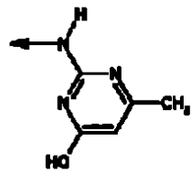
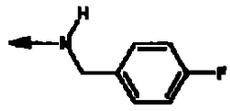
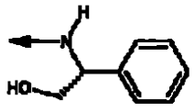
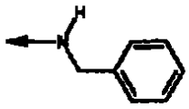
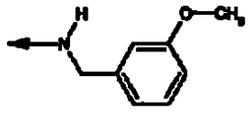
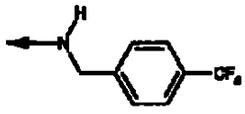
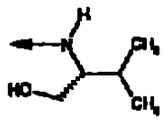
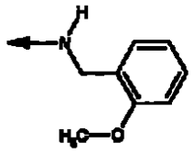


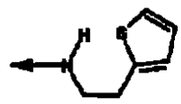
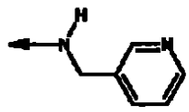
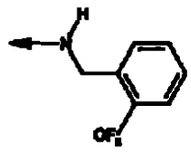
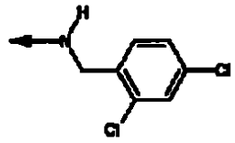
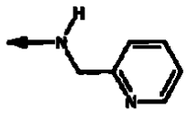
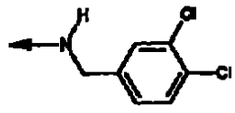
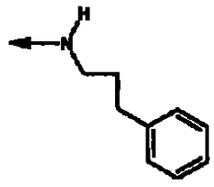
se prepararon por un procedimiento similar al del Ejemplo 218 usando la amina apropiada.

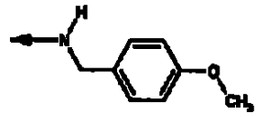
406 #03

Ejemplo No.	X	Tiempos de retención de HPLC/min	LRMS (electronebulización) m/z [MH⁺]
219		4.2	367
220		4.1	366
221		3.8	374
222		3.2	353
223		4.2	366
224		3.7	334
225		3.7	445

226		4.1	366
227		4.3	387
228		4.2	380
229		3.6	328
230		3.5	347
231		4.3	387
232		4.5	438
233		3.8	353

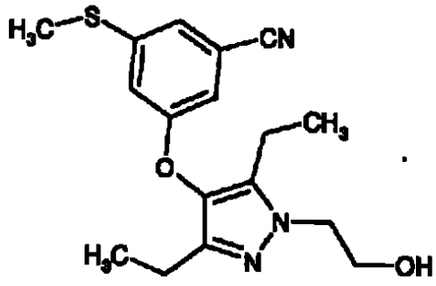
234		3.7	370
235		4.1	370
236		4.1	396
237		4.1	352
238		4.1	382
239		4.4	420
240		4.0	362
241		4.1	382

242		4.2	372
243		3.2	353
244		4.2	420
245		4.4	421
246		3.7	353
247		4.4	421
248		4.1	382

249		4.1	382

EJEMPLO 250

3-{[3,5-Dietil-1-(2-hidroxietil)-1*H*-pirazol-4-iloxi}-5-(metilsulfanil)benzonitrilo



Se disolvieron el alcohol protegido de la Preparación 93 (687 mg, 1,65 mmol) y ácido p-tolueno-sulfónico (32 mg, 0,17 mmol) en metanol (16 ml) y se agitaron en una atmósfera de nitrógeno a temperatura ambiente. Después de 4 horas se añadió una segunda porción de ácido p-tolueno-sulfónico (32 mg, 0,17 mmol). Después de 18 horas, el disolvente se retiró a presión reducida y el residuo se repartió entre una solución acuosa saturada de bicarbonato sódico (20 ml) y diclorometano (20 ml). La fase acuosa se extrajo con diclorometano (40 ml) y los extractos orgánicos reunidos se

secaron sobre sulfato de magnesio, se concentraron a presión reducida y se purificaron por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol (97:31 en volumen), proporcionando el compuesto del título (487 mg) como un sólido blanco p.f. 72°C.

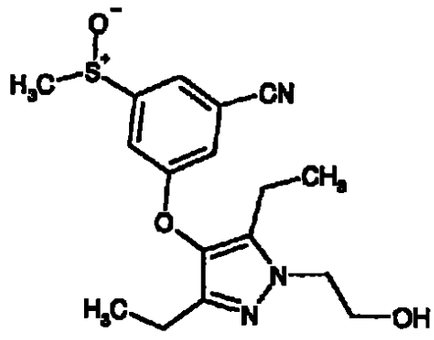
^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,14 (m, 6H), 2,44 (q, 2H), 2,49 (s, 3H), 2,53 (q, 3H), 4,08 (m, 2H),4,14 (m, 2H), 6,84 (s, 1H), 7,00 (s, 1H), 7,10 (s, 1H).

LRMS (electronebulización) : m/z [MH^+] 332.

Microanálisis: Encontrado C, 61,36; H, 6,43; N, 12,55. $C_{17}H_{21}N_3O_2S$ requiere C, 61,61; H, 6,39; N, 12,68%.

EJEMPLO 251

3-{[3,5-Dietil-1-(2-hidroxietil)-1*H*-pirazol-4-il]oxi}-5-(metilsulfonil)benzonitrilo



Se preparó alúmina húmeda por la adición de agua (1 ml) a alúmina Brockman de calidad I (5 g). A una solución agitada del sulfuro del Ejemplo 250 (134 mg, 0,40 mmol) en

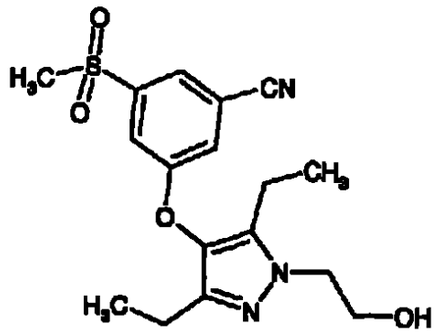
diclorometano (2 ml) se le añadió la alúmina húmeda (400 mg) seguido de Oxone® (123 mg, 0,4 mmol) y la mezcla se calentó a reflujo. Después de 1 hora, se añadió una segunda porción de oxone (123 mg, 0,40 mmol) y la mezcla se calentó durante 2 horas más. Después de enfriar a temperatura ambiente, la mezcla de reacción se filtró y los sólidos resultantes se lavaron con diclorometano (20 ml). El filtrado se concentró y se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol (un gradiente de 99:1 a 90:10, en volumen), proporcionando el compuesto del título (92 mg) en forma de un aceite.

^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,12 (m, 6H), 2,44 (q, 2H), 2,53 (q, 2H), 2,73 (s, 3H), 4,06 (m, 2H), 4,18 (m, 2H), 7,24 (s, 1H), 7,45 (s, 1H), 7,49 (s, 1H).

LRMS (electronebulización) : m/z [M+Na$^+$] 370.

EJEMPLO 252

3-{[3,5-Dietil-1-(2-hidroxietil)-1*H*-pirazol-4-il]oxi}-5-(metilsulfonil)benzonitrilo



A una solución agitada del sulfuro del Ejemplo 250 (133 mg, 0,4 mmol) en diclorometano (2 ml) a -78°C se le añadió una solución de ácido meta-cloroperoxibenzoico (138 mg de una mezcla al 50% en peso 0,4 mmol) en diclorometano (2 ml). El baño de refrigeración se retiró y la solución se agitó a temperatura ambiente durante 4 horas. La mezcla se inactivó por adición de una solución acuosa saturada de bicarbonato sódico (6 ml) y se extrajo con diclorometano (3x5 ml). Los componentes orgánicos reunidos se secaron sobre sulfato de magnesio y se concentraron. El análisis de la ^{1}H-RMN (400 MHz, $CDCl_3$) sugirió una mezcla del producto deseado y el sulfóxido del Ejemplo 251. La mezcla de producto bruto se disolvió en diclorometano (2 ml), se enfrió a -78°C y a esto se le añadió ácido meta-cloroperoxibenzoico (138 mg de una mezcla al 50% en peso, 0,4 mmol) en diclorometano (2 ml). El baño de refrigeración se retiró y la mezcla se agitó a temperatura ambiente durante 1 hora. La mezcla se inactivó por adición de una solución acuosa saturada de bicarbonato sódico (6 ml) y se extrajo con diclorometano (3x5 ml). Los componentes orgánicos reunidos se secaron sobre sulfato de magnesio y se concentraron. La mezcla de producto bruto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol (98:2, en volumen), proporcionando el compuesto del título contaminado con ácido meta-cloroperoxibenzoico. A una solución de este producto

bruto en diclorometano a -78°C se le añadió dimetilsulfóxido (30 µl, 0,4 mmol). El baño de refrigeración se retiró y la mezcla se agitó a temperatura ambiente durante 15 minutos. La mezcla se inactivó por adición de una solución acuosa al 10% de carbonato potásico (10 ml) y el diclorometano se evaporó. La mezcla acuosa restante después se extrajo con dietil éter (2x10 ml) y acetato de etilo (10 ml). Los componentes orgánicos se combinaron, se secaron sobre sulfato de magnesio y se concentraron, dando la mezcla de producto bruto que se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol (98:2, en volumen), proporcionando el compuesto del título (26 mg) en forma de un sólido blanco, p.f. 133°C.

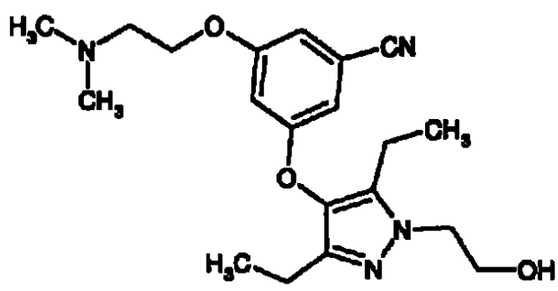
^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,10 (m, 6H), 2,39 (q, 2H), 2,51 (q, 2H), 3,06 (s, 3H), 4,05 (m, 2H), 4,10 (m, 2H), 7,39 (s, 1H), 7,67 (s, 1H), 7,84 (s, 1H).

LRMS (electronebulización) : m/z [$M+Na^+$] 385.

HRMS: [MH^+] 364,1329, $C_{18}H_{20}N_6O_2$ requiere 364,1326.

EJEMPLO 253

3-{[3,5-Dietil-1-(2-hidroxietil)-1*H*-pirazol-4-il]oxi}-5-[2-(dimetilamino)etoxi]benzonitrilo



A una solución agitada del alcohol protegido de la Preparación 94 (180 mg, 0,39 mmol) en metanol (4 ml) se le añadió ácido para-toluenosulfónico (89 mg, 0,47 mmol). Después de 18 horas a temperatura ambiente, el disolvente se evaporó a presión reducida y el residuo se repartió entre diclorometano (5 ml) y una solución acuosa al 10% de carbonato potásico (5 ml). La fase acuosa se separó y se extrajo con diclorometano (3 ml). Los componentes orgánicos se combinaron, se secaron sobre sulfato de magnesio y se concentraron a presión reducida. La mezcla de producto bruto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol (95:5, en volumen) seguido de diclorometano:metanol:amoniaco (80:20:1, en volumen), proporcionando el compuesto del título (63 mg) en forma de un aceite.

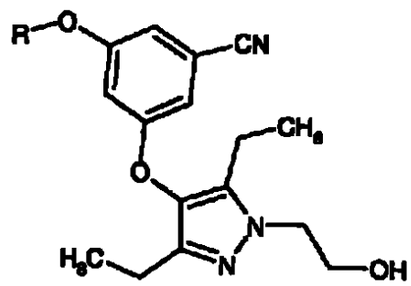
^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,13 (m, 6H), 2,43 (m, 8H), 2,52 (q, 2H), 2,85 (m, 2H), 3,81 (s ancho, 1H), 4,08 (m, 6H) 6,70 (s, 1H), 6,78 (s, 1H), 6,81 (s, 1H).

LRMS (APCI) : m/z [MH^+] 373.

HRMS: [MH$^+$] 373,2234, $C_{20}H_{29}N_4O_3$ requiere 373,2234.

EJEMPLOS 254-256

Los compuestos de los siguientes Ejemplos indicados en la tabla, de formula general:



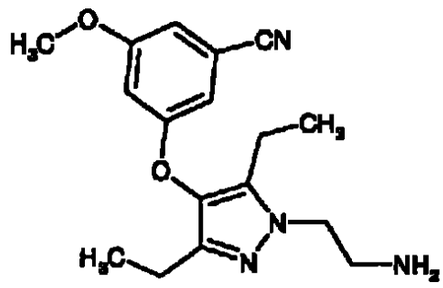
se prepararon por un procedimiento similar al del Ejemplo 253 usando como material de partida el apropiado alcohol protegido (PA) de las Preparaciones 95-97.

Ejemplo No.	No de Prep. PA	R	Datos Analíticos
254	95	CH_2CH_2NHMe	^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,13 (m, 6H), 2,42 (q, 2H), 2,53 (q, 2H), 2,59 (s, 3H), 3,12 (t, 2H), 4,05 (m, 2H), 4,09 (m, 2H), 4,16 (t, 2H), 6,75 (s, 1H), 6,81 (s, 1H), 6,82 (s, 1H). LRMS (APCI): m/z [MH$^+$] 359. HRMS: [MH$^+$] 359,2083, $C_{19}H_{27}N_4O_3$ requiere 359,2078.
255	96	CH_2CONH_2	^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,11 (m, 6H), 2,41 (q, 2H), 2,52 (q, 2H), 4,05 (t, 2H), 4,09 (t, 2H), 4,46 (s, 2H), 5,74 (s ancho, 1H), 6,42 (s ancho, 1H), 6,69 (s, 1H), 6,85 (s, 2H). LRMS (APCI): m/z 359 (MH$^+$).

256	97	$CH_3CH_2OCH_3$	^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,12 (m, 6H), 2,42 (q, 2H), 2,51 (q, 2H), 3,44 (s, 3H), 3,73 (t, 2H), 4,09 (m, 6H), 6,71 (s, 1H), 6,77 (s, 1H), 6,83 (s, 1H). LRMS (electronebulización): m/z 360 (MH^+) HRMS: [MH^+] 360,1920. $C_{19}H_{26}N_3O_4$ requiere 360,1918.

EJEMPLO 257

3-{[1-(2-Aminoetil)-3,5-dietil-1*H*-pirazol-4-il]oxi}-5-metoxibenzonitrilo



Se disolvieron el alcohol del Ejemplo 202 (87 mg, 0,28 mmol), trifenilfosfina (220 mg, 0,84 mmol) y ftalimida (124 mg, 0,84 mmol) en tetrahidrofurano (5 ml) a 0°C en una atmósfera de nitrógeno y se añadió gota a gota azodicarboxilato de diisopropilo (165 µl, 0,84 mmol) disuelto en tetrahidrofurano (1 ml). La reacción se dejó calentar a temperatura ambiente y se agitó durante 18 horas. El disolvente se retiró a presión reducida, el residuo se disolvió en etanol (6 ml) y se añadió hidrato de hidrazina

(68 µl, 1,40 mmol). La suspensión se agitó durante 48 horas a temperatura ambiente en una atmósfera de nitrógeno, se concentró a presión reducida y el residuo se disolvió en metanol. Después, la solución se pasó a través de una columna SCX eluyendo con metanol para retirar las impurezas y después con una solución 2 M de amoniaco en metanol para eluir el producto. Después, el producto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol (95:5) y después con diclorometano:metanol:amoniaco 0,88 (90:10:1, en volumen), proporcionando el compuesto del título (67 mg) en forma de un aceite.

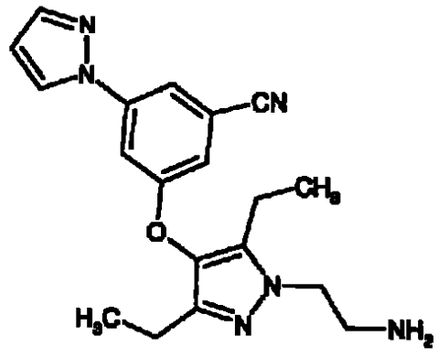
^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,13 (m, 6H), 2,19 (s ancho, 2H), 2,43 (q, 2H), 2,54 (q, 2H), 3,19 (t, 2H), 3,60 (s, 3H), 4,06 (t, 2H), 6,68 (s, 1H), 6,73 (s, 1H), 6,80 (s, 1H).

LRMS (electronebulización): m/z 315 (MH^+)

HRMS: [MH^+] 315,1819. $C_{17}H_{23}N_4O_2$ requiere 315,1816.

EJEMPLO 258

3-{[1-(2-Aminoetil)-3,5-dietil-1*H*-pirazol-4-il]oxi}-5-(1*H*-pirazol-1-il)benzonitrilo



El alcohol del Ejemplo 164 (162 mg, 0,46 mmol), trifenilfosfina (362 mg, 1,38 mmol) y ftalimida (203 mg, 1,38 mmol) se disolvieron en tetrahidrofurano (8 ml) a 0°C en una atmósfera de nitrógeno y se añadió gota a gota azodicarboxilato de diisopropilo (272 µl, 1,38 mmol) disuelto en tetrahidrofurano (1 ml). La reacción se dejó calentar a temperatura ambiente y se agitó durante 18 horas. El disolvente se retiró a presión reducida, el residuo se disolvió en etanol (9 ml) y se añadió hidrato de hidrazina (112 µl, 2,3 mmol). La suspensión se agitó durante 48 horas a temperatura ambiente en una atmósfera de nitrógeno, se concentró a presión reducida y el residuo se disolvió en metanol. Después, la solución se pasó a través de una columna SCX, eluyendo con metanol para retirar las impurezas y después con una solución 2 M de amoniaco en metanol para eluir el producto. Después, el producto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol (95:5) y después con

diclorometano:metanol:amoniaco 0,880 (90:10:1, en volumen), proporcionando el compuesto del título (62 mg) en forma de un aceite.

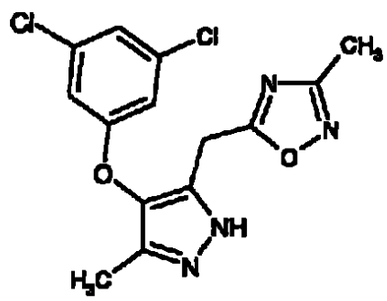
^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,15 (m, 6H), 2,46 (q, 2H), 2,63 (q, 2H), 3,13 (t, 2H), 4,13 (t, 2H), 6,54 (s, 1H), 7,17 (s, 1H), 7,69 (s, 1H), 7,72 (s, 1H), 7,82 (s, 1H), 8,32 (s, 1H).

LRMS (APCI): m/z 351 (MH^+)

HRMS: [MH^+] 351,1929. $C_{19}H_{22}N_4O_2$ requiere 351,1928.

EJEMPLO 259

3,4-Diclorofenil-3-metil-5-[(3-metil-1,2,4-oxadiazol-5-il)metil]-1*H*-pirazol-4-il éter



A una solución agitada del ácido (100 mg, 0,33 mmol) de la Preparación 92 en dimetilformamida (2 ml) se añadió en una porción carbonildiimidazol (59 mg, 0,36 mmol). Después de 30 minutos a temperatura ambiente, se añadió (1*Z*)-*N'*-hidroxietanimidamida (27 mg, 0,36 mmol) y la mezcla de reacción se agitó a temperatura ambiente durante 3 horas. Se añadió una segunda porción de carbonildiimidazol (59 mg, 0,36

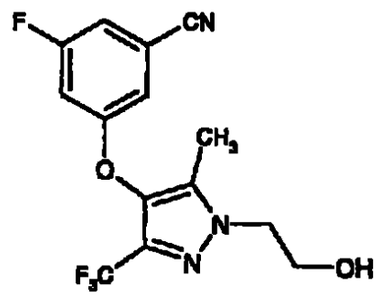
mmol) y la mezcla se calentó a 100°C durante 12 horas. Después de enfriar a temperatura ambiente, se añadió agua (30 ml) y la mezcla se extrajo con acetato de etilo (3 x 20 ml). Los componentes orgánicos reunidos se secaron sobre sulfato de magnesio y se concentraron a presión reducida, dando un aceite pardo. La mezcla de producto bruto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con acetato de etilo:pentano (30:70, en volumen), proporcionando el compuesto del título (40 mg) en forma de un aceite amarillo pálido.

^{1}H-RMN (400 MHz, $CDCl_3$): δ = 4,12 (s, 3H), 2,29 (s, 3H), 4,08 (s, 2H), 6,74 (s, 2H), 6,98 (s, 1H).

LRMS (electronebulización): m/z 339 (MH^+).

EJEMPLO 260

3-Fluoro-5-{[1-(2-hidroxietil)-5-metil-3-(trifluorometil)-1*H*-pirazol-4-il]oxi}benzonitrilo



A una solución agitada del alcohol protegido (85 mg, 0,21 mmol) de la Preparación 99 en metanol (0,5 ml) se le añadió ácido para-toluenosulfónico (4 mg, 0,02 mmol). Después

de 5 horas, la mezcla de reacción se concentró a presión reducida, se disolvió en diclorometano (20 ml), se lavó con una solución saturada de bicarbonato sódico (20 ml), se secó sobre sulfato de magnesio y se concentró a presión reducida. La mezcla de producto bruto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con pentano:acetato de etilo (60:40 seguido de 40:60, en volumen), proporcionando el compuesto del título (54 mg) en forma de un sólido blanco.

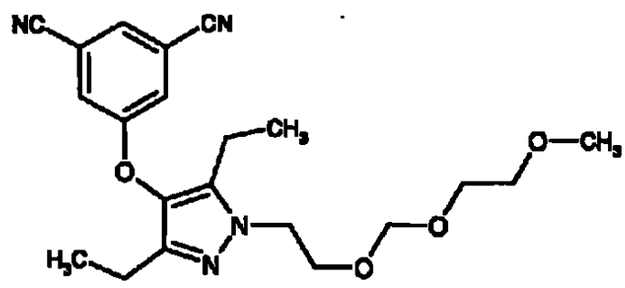
^{1}H-RMN (400 MHz, $CDCl_3$): δ = 2,19 (s, 3H), 2,45 (t, 1H), 4,10 (m, 2H), 4,20 (m, 2H), 6,87 (d, 1H), 6,96 (s, 1H), 7,05 (d, 1H).

LRMS (APCI): m/z 330 (MH^+)

Microanálisis: Encontrado C, 51,38; H, 3,52; N, 12,37. $C_{14}H_{11}F_4N_3O_2$ requiere C, 51,07; H, 3,37; N, 12,76%.

EJEMPLO 261

5[(3,5-Dietil-1-{2-[(2-metoxietoxi)metoxi]etil}-1*H*-pirazol-4-il)oxi]isoftalonitrilo



A una solución agitada del alcohol (5,0 g, 16,11 mmol) del Ejemplo 119 en tetrahidrofurano (65 ml) a 0°C se le

añadió cloruro de 2-metoxietoximetilo (2,39 ml, 20,94 mmol) seguido de hidruro sódico (838 mg de una dispersión en aceite al 60% en peso, 20,94 mmol). Después de 10 minutos, la mezcla de reacción se calentó a 50°C durante 18 horas. Después de enfriar a temperatura ambiente, la mezcla se diluyó gota a gota con una solución acuosa saturada de cloruro amónico (3 ml). La mezcla se concentró a presión reducida y el residuo se repartió entre diclorometano (250 ml) y agua (200 ml). La fase acuosa se separó y se extrajo con diclorometano (150 ml). Los componentes orgánicos se combinaron, se secaron sobre sulfato de magnesio y se concentraron a presión reducida. La mezcla de producto bruto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano, seguido de diclorometano:metanol (99:1, en volumen), proporcionando el compuesto del título (5,38 g) en forma de un aceite incoloro.

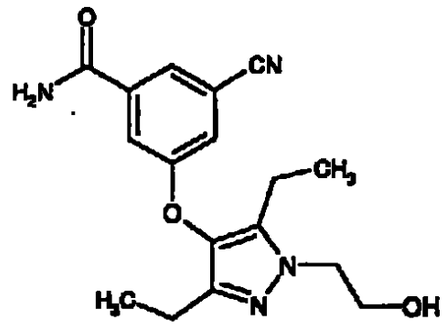
^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,10 (m, 6H), 2,39 (q, 2H), 2,55 (q, 2H), 3,38 (s, 3H), 3,51 (m, 2H), 3,56 (m, 2H), 3,93 (t, 2H), 4,20 (t, 2H), 4,66 (s, 2H), 7,38 (s, 2H), 7,56 (s, 1H).

LRMS (APCI): m/z 399 (MH^+).

Microanálisis: Encontrado C, 62,11; H, 6,67; N, 13,51. $C_{21}H_{26}N_4O_4$+0,43H_2O requiere C, 62,09; H, 6,67; N, 13,79%.

EJEMPLO 262

3-Ciano-5-{[3,5-dietil-1-(2-hidroxietil)-1*H*-pirazol-4-iloxi}benzamida



A una solución agitada del pirazol (60 mg) de la Preparación 100 en diclorometano (4 ml) se le añadió tricloruro de aluminio (134 mg, 1 mmol). Después de 18 horas, se añadió hielo, la mezcla se neutralizó usando una solución acuosa saturada de bicarbonato sódico, se diluyó con agua (30 ml) y se extrajo con diclorometano (2x40 ml). Los componentes orgánicos se combinaron, se secaron sobre sulfato de magnesio y se concentraron a presión reducida. La mezcla de producto bruto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol (95:5, en volumen), proporcionando el compuesto del título (27 mg) en forma de un cristal incoloro.

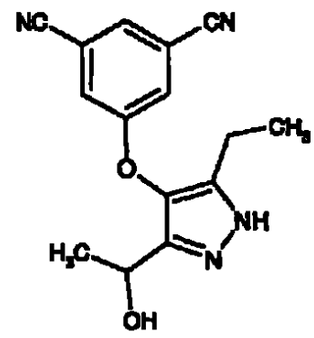
^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,10 (m, 6H), 2,40 (q, 2H), 2,52 (q, 2H), 4,07 (m, 4H), 7,25 (s, 1H), 7,60 (s, 1H), 7,65 (s, 1H).

LRMS (APCI): m/z 329 (MH^+).

EJEMPLO 263

5-{[5-Etil-3-(1-hidroxietil)-1*H*-pirazol-4-il]oxi}-

isoftalonitrilo



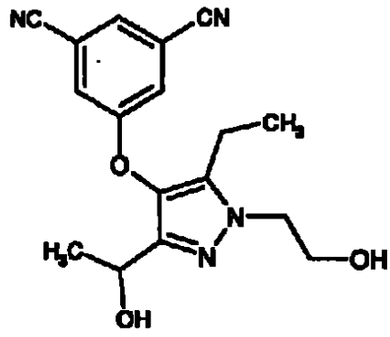
A una solución agitada del pirazol de la Preparación 102 (219 mg, 0,57 mmol) en tetrahidrofurano (2,5 ml) se le añadió una solución acuosa saturada de carbonato sódico (0,5 ml). La mezcla de reacción se agitó a temperatura ambiente durante 4 horas y después se calentó a reflujo durante 18 horas. La mezcla de reacción se concentró a presión reducida y el residuo se repartió entre diclorometano (20 ml) y agua (20 ml). La fase orgánica se secó sobre sulfato de magnesio y se concentró a presión reducida. La mezcla de producto bruto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol (un gradiente de 100:0 a 90:10, en volumen), proporcionando el compuesto del título (68 mg) en forma de un sólido blanco.

^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,21 (t, 3H), 1,51 (d, 3H), 2,54 (q, 2H), 4,89 (q, 1H), 7,25 (s, 2H), 7,43 (s, 1H).

LRMS (APCI): m/z 283 (MH^+).

EJEMPLO 264

5-{[5-Etil-3-(1-hidroxietil)-1-(2-hidroxietil)-1*H*-pirazol-4-iloxi}isoftalonitrilo



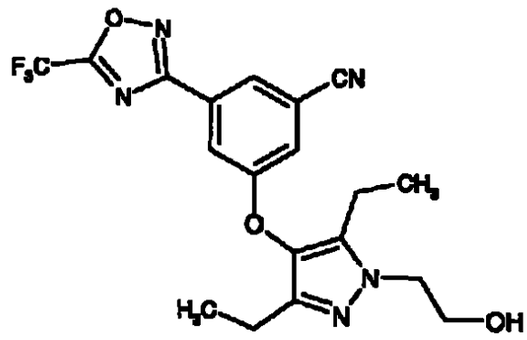
A una solución agitada del pirazol de la Preparación 103 (80 mg, 0,19 mmol) en metanol (1 ml) se le añadió ácido para-toluenosulfónico (4 mg, 0,02 mmol). Después de 5 horas a temperatura ambiente, la mezcla de reacción se concentró a presión reducida y el residuo se repartió entre diclorometano (20 ml) y agua (20 ml). El componente orgánico se secó sobre sulfato de magnesio y se concentró a presión reducida. La mezcla de producto bruto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol (un gradiente de 100:0 a 95:5, en volumen), proporcionando el compuesto del título (44 mg) en forma de un sólido blanco.

^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,11 (t, 3H), 1,46 (d, 3H), 2,54 (q, 2H), 4,10 (q, 2H), 4,17 (q, 2H), 4,79 (q, 1H), 7,44 (S, 2H), 7,57 (s, 1H).

LRMS (APCI): m/z 327 (MH^+).

EJEMPLO 265

3-{[3,5-Dietil-1-(2-hidroxietil)-1*H*-pirazol-4-il]oxi}-5-(5-trifluorometil-1,2,4-oxadiazol-3-il)benzonitrilo



A una solución agitada del pirazol de la Preparación 105 (235 mg, 0,46 mmol) en diclorometano (2 ml) se le añadió tricloruro de aluminio (373 mg, 2,8 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 48 horas, se diluyó con agua (6 ml) y se extrajo con diclorometano (6 ml). El componente orgánico se concentró a presión reducida y se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol (un gradiente de 99:1 a 80:20, en volumen) seguido de diclorometano:metanol:amoniaco 0,88 (80:20:1, en volumen), proporcionando una muestra impura del compuesto del título (44 mg) en forma de un sólido blanco. El producto se purificó adicionalmente por HPLC usando una columna Phenomenex Luna C_{18} 150x21,2 mm, eluyendo con un gradiente de disolventes de 5:95 ácido trifluoroacético acuoso al 0,1% en

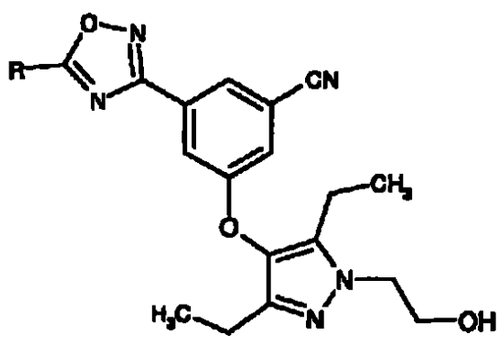
acetonitrilo:acetonitrilo (0-1 min 80:20; 1-7 min 80:20 cambiando a 0:100; 7-12 min 0:100; 12-12,1 min 0:100 cambiando a 80:20; 12,1-15 min 80:20), proporcionando el compuesto del título (38 mg) en forma de un sólido blanco.

Tiempo de retención 5,7 minutos.

LRMS (electronebulización): m/z 422 (MH^+).

EJEMPLOS 266-268

Los compuestos de los siguientes Ejemplos indicados en la tabla, de formula general:



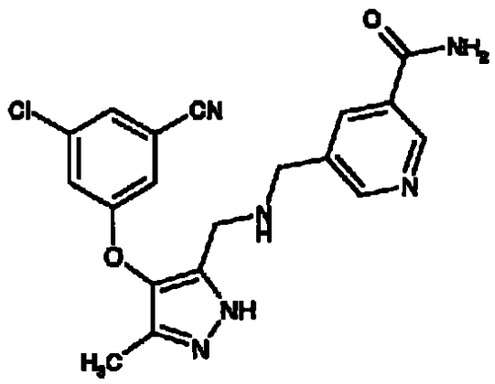
se prepararon por un procedimiento similar al del Ejemplo 265 usando el apropiado alcohol protegido (PA) de las Preparaciones 106-108.

Ejemplo No.	No de Prep. PA	R	Datos Analíticos
266	106	Me	Tiempo de retención 4,8 minutos LRMS (electronebulización): m/z [MH⁺] 368.
267	107	Et	Tiempo de retención 5,3 minutos LRMS (electronebulización): m/z [MH⁺] 382

268	108	^{i}Pr	Tiempo de retención 5,7 minutos LRMS (electronebulización): m/z 396 (MH^+)

EJEMPLO 269

5-[({[4-(3-Cloro-5-cianofenoxi)-3-metil-1*H*-pirazol-5-il]metil}amino)metil]nicotinamida



A una solución agitada de la amina de la Preparación 111 (650 mg, 1,70 mmol) en alcohol iso-propílico (6 ml) se le añadió el pirazol de la Preparación 18 (210 mg, 0,57 mmol) seguido de carbonato potásico (240 mg, 1,70 mmol). La mezcla de reacción se calentó a reflujo durante 1,5 horas. Después de enfriar a temperatura ambiente, la mezcla se concentró a presión reducida y la mezcla de producto bruto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco 0,88 (95:5:0,5, después 90:10:1 y después 80:20:1, en volumen) que dio una muestra impura del producto deseado. Se repitió la cromatografía

ultrarrápida eluyendo con diclorometano:metanol:amoniaco 0,88 (100:0:0, después 95:5:0,5 y después 90:10:1, en volumen), proporcionando el compuesto del título (10 mg) en forma de un sólido amarillo pálido.

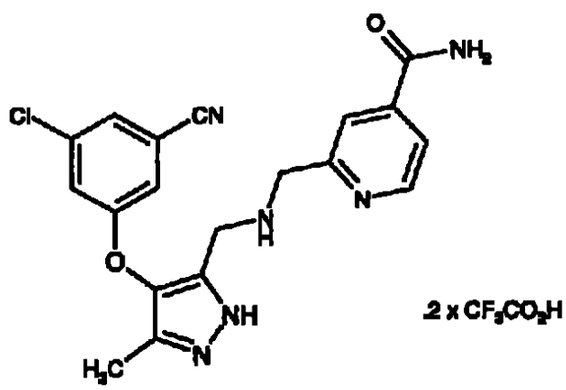
^{1}H-RMN (400 MHz, $CDCl_3$): δ = 2,05 (s, 3H), 3,62 (s, 2H), 3,79 (s, 2H), 7,16 (m, 1H), 7,18 (m, 1H), 7,38 (s, 1H), 8,15 (s, 1H), 8,54 (s, 1H), 8,84 (s, 1H).

LRMS (APCI): m/z 419 ($M+Na^+$).

HRMS: [MH^+] 397,1173, $C_{19}H_{18}N_6O_2Cl$ requiere 397,1175.

EJEMPLO 270

2-[({[4-(3-Cloro-5-cianofenoxi)-3-metil-1*H*-pirazol-5-il]metil}amino)metil]isonicotinamida



A una solución agitada de la amina de la Preparación 115 (250 mg, 1,66 mmol) y el pirazol de la Preparación 18 (155 mg, 0,42 mmol) en isopropanol (6 ml) se le añadió tetrahidrofurano (2 ml). La mezcla se calentó a reflujo durante 2 horas, después de lo cual la mezcla de reacción se

concentró a presión reducida. La mezcla de producto bruto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco 0,88 (85:15:1, en volumen), proporcionando una muestra impura del compuesto del título. El producto se purificó adicionalmente por HPLC, usando una columna Phenomenex Luna C_8(II) 10 µM 150x21,2 mm, eluyendo con un gradiente de disolventes de 5:95 de ácido trifluoroacético acuoso al 0,1% en acetonitrilo:acetonitrilo (0-6 min 95:5 cambiando a 0:100; 6-10 min 0:100), proporcionando el compuesto del título (65 mg) en forma de un sólido blanquecino.

Tiempo de retención: 3,40 minutos.

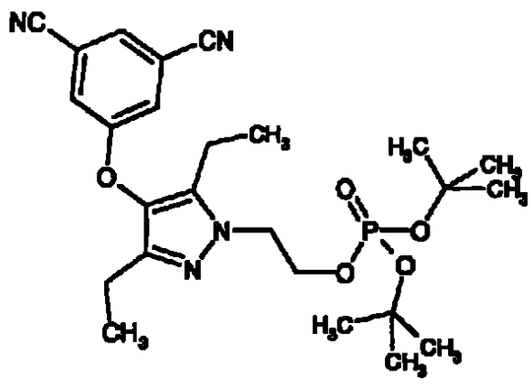
^{1}H-RMN (400 MHz, CD_3OD_3): δ = 2,14 (s, 3H), 4,21 (s, 2H), 4,50 (s, 2H), 7,19 (s, 1H), 7,27 (m, 1H), 7,43 (m, 1H), 7,48 (m, 1H), 7,78 (m, 1H), 8,68 (d, 1H).

LRMS (electronebulización): m/z 397 (MH^-)

Microanálisis: Encontrado C, 44,56; H, 3,41; N, 14,07. $C_{19}H_{17}N_6O_2Cl+1,9CF_3CO_2H$ requiere C, 44,64; H, 3,11; N, 13,70%.

EJEMPLO 271

2-[4-(3,5-Dicianofenoxi)-3,5-dietil-1*H*-pirazol-1-il]etil fosfato de di(*terc*-butilo)



A una solución agitada del alcohol del Ejemplo 119 (500 mg, 1,60 mmol) en diclorometano (5 ml) se le añadió tetrazol (226 mg, 3,20 mmol) seguido de di-*terc*-butil-*N,N*-diisopropilfosforamidita (1,02 ml, 3,20 mmol). Después de agitar durante 4 horas a temperatura ambiente, la mezcla de reacción se enfrió a 0°C y se añadió por porciones ácido meta-cloroperoxibenzoico (1,0 g de una mezcla al 50% en peso, 3 mmol) (CUIDADO, EXOTERMIA). Después de 10 minutos, la mezcla se calentó a temperatura ambiente y se diluyó con diclorometano (50 ml). La solución se lavó con una solución acuosa saturada de carbonato sódico (20 ml) y el componente acuoso se separó y se extrajo con diclorometano (20 ml). Los componentes orgánicos reunidos se lavaron con salmuera (20 ml), se secaron sobre sulfato de magnesio y se concentraron a presión reducida. La mezcla de producto bruto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco 0,88 (100:0:0, después

99:1:0,1 y después 98:2:0,2, en volumen), proporcionando una muestra del compuesto del título (660 mg).

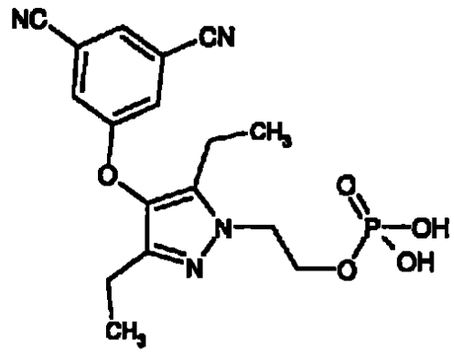
^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,10 (m, 6H), 1,43 (s, 18H), 2,38 (q, 2H), 2,55 (q, 2H), 4,26 (m, 4H), 7,38 (s, 2H), 7,54 (s, 1H).

LRMS (electronebulización): m/z 525 (MH^+).

Microanálisis: Encontrado C, 57,77; H, 7,38; N, 10,33. $C_{25}H_{33}N_4O_5P+H_2O$ requiere C, 57,68; H, 7,16; N, 10,76%.

EJEMPLO 272

Fosfato ácido de 2-[4-(3,5-dicianofenoxi)-3,5-dietil-1*H*-pirazol-1-il]etilo



A una solución agitada del éster de fostato del Ejemplo 271 (250 mg, 0,48 mmol) en diclorometano (10 ml) a 0°C se le añadió ácido trifluoroacético (0,5 ml). La mezcla de reacción se dejó calentar a temperatura ambiente y después de 4 horas se concentró a presión reducida. El residuo se purificó por HPLC usando una columna Phenomenex Luna C_8(II) 10 μM 150x21,2 mm, eluyendo con un gradiente de disolventes de 5:95 de ácido

trifluoroacético acuoso al 0,1% en acetonitrilo:acetonitrilo (0-1,9 min 95:5; 2-10 min 90:10 cambiando a 30:70; 10,0-13,8 min 30:70; 13,8-13,9 min 30:70 cambiando a 95:5; 13,9-15 min 95:5), dando una muestra del producto deseado. Esta muestra se purificó adicionalmente por recristalización usando acetonitrilo/agua, dando el compuesto del título en forma de un sólido blanco, p.f.198-199 °C.

Tiempo de retención: 2,31 minutos.

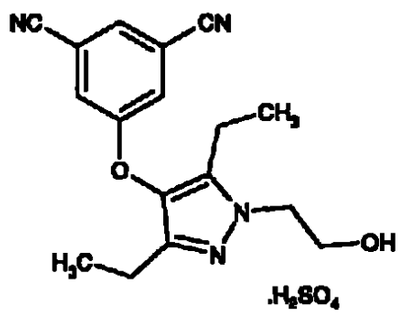
^{1}H-RMN (400 MHz, CD_3OD): δ = 1,09 (m, 6H), 2,35 (q, 2H), 2,61 (q, 2H), 4,28 (m, 4H), 7,55 (s, 2H), 7,79 (s, 1H).

LRMS (APCI): m/z 391 (MH^+).

Microanálisis: Encontrado C, 50,99; H, 4,92; N, 14,06. $C_{17}H_{19}N_4O_5P+0,5H_2O$ requiere C, 51,13; H, 5,05; N, 14,03%.

EJEMPLO 273

Sal sulfato de 5-{[3,5-dietil-1-(2-hidroxietil)-1*H*-pirazol-4-il]oxi}isoftalonitrilo



A una solución agitada del pirazol del Ejemplo 119 (200 mg, 0,65 mmol) en acetona (5 ml) se le añadió ácido sulfúrico

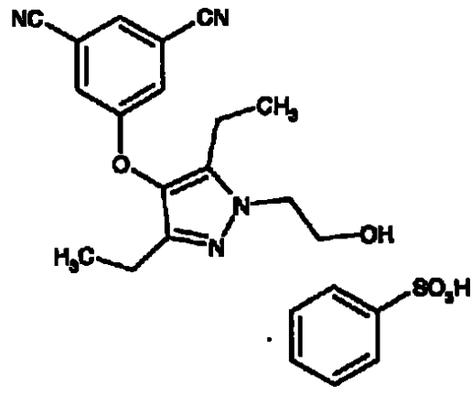
(0,32 ml de una solución acuosa 2 M, 0,64 mmol) y la mezcla se agitó a temperatura ambiente y el disolvente se dejó evaporar. El residuo se recristalizó (tolueno/acetona), dando el compuesto del título (160 mg) en forma de un polvo blanco, p.f. 105-110°C.

^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,22 (m, 6H), 2,70 (m, 4H), 4,12 (s a, 1H), 4,59 (m, 2H), 4,75 (s a, 1H), 7,66 (s, 1H), 7,69 (m, 1H), 7,72 (s, 1H).

Microanálisis: Encontrado C, 50,29; H, 4,90; N, 13,48. $C_{17}H_{18}N_4O_2.H_2SO_4$ requiere C, 49,99; H, 4,93; N, 13,72%.

EJEMPLO 274

Sal del ácido bencenosulfónico 5-{[3,5-dietil-1-(2-hidroxietil)-1*H*-pirazol-4-il]oxi}isoftalonitrilo



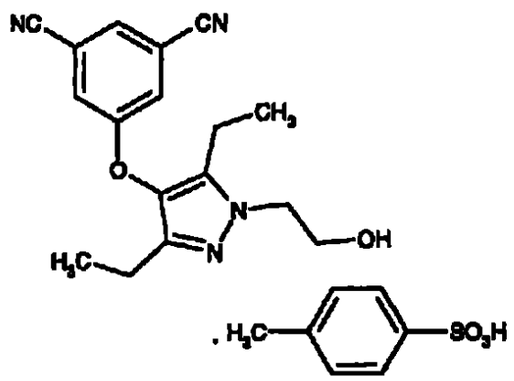
A una solución agitada del pirazol del Ejemplo 119 (20 g, 65 mmol) en acetona (200 ml) se le añadió ácido bencenosulfónico (10,7 g, 68 mmol) y la mezcla se agitó a temperatura ambiente durante 10 minutos. La mezcla de

reacción se concentró a presión reducida y el residuo se recristalizó dos veces (acetona), dando el compuesto del título (16,2 g) en forma de un polvo blanco, p.f. 142-144°C. ^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,05-1,08 (m, 6H), 2,59 (q, 2H), 2,68 (q, 2H), 4,04 (t, 2H), 4,54 (t, 2H), 7,35-7,42 (m, 3H), 7,55 (s, 1H), 7,64 (s, 1H), 7,86 (d, 2H).

Microanálisis: Encontrado C, 58,86; H, 5,13; N, 11,88. $C_{23}H_{24}N_4O_5S$ requiere C, 58,96; H,5,16;N,11,96%.

EJEMPLO 275

Sal tosilato de 5-{[3,5-dietil-1-(2-hidroxietil)-1*H*-pirazol-4-il]oxi}isoftalonitrilo



A una suspensión agitada del pirazol del Ejemplo 119 (300 mg, 1,00 mmol) en etanol (2 ml) se le añadió ácido p-toluenosulfónico (202 mg, 1,10 mmol) y la mezcla se calentó en un baño de aceite hasta que se disolvieron los sólidos. La mezcla de reacción se enfrió a temperatura ambiente y se

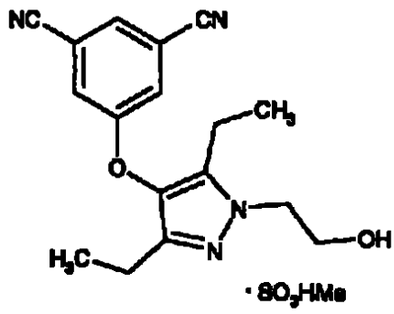
concentró a presión reducida. El residuo se cristalizó (dietil éter), se filtró y se recristalizó (alcohol isopropílico), dando el compuesto del título (200 mg) en forma de un sólido blanco, p.f. 120°C.

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 1,00 (m, 6H), 2,24 (m, 5H), 2,49 (m, 2H), 4,00 (m, 2H), 7,11 (d, 2H), 7,45 (d, 2H), 7,73 (s, 2H), 8,09 (s, 1H).

Microanálisis: Encontrado C, 59,64; H, 5,46; N, 11,60. $C_{24}H_{26}N_4O_5S$ requiere C, 59,74; H, 5,43; N, 11,61%.

EJEMPLO 276

Sal mesilato de 5-{[3,5-dietil-1(2-hidroxietil)-1*H*-pirazol-4-il]oxi}isoftalonitrilo



A una suspensión agitada del pirazol del Ejemplo 119 (250 mg, 0,83 mmol) en alcohol isopropílico (3 ml) se le añadió ácido metanosulfónico (52 µl, 0,91 mmol) y la mezcla se calentó en un baño de aceite hasta que se disolvieron los sólidos. La mezcla de reacción se enfrió a temperatura ambiente y se concentró a presión reducida hasta un volumen

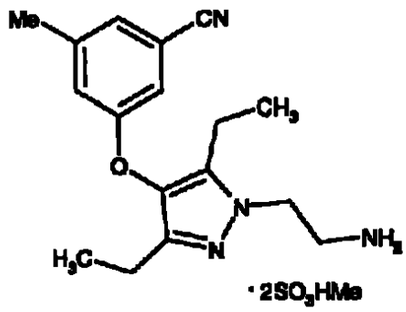
de 1 ml. Se formó un precipitado sólido blanco que se lavó con alcohol isopropílico frío, dando el compuesto del título (239 mg) en forma de un sólido blanco, p.f. 144-146°C.

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 1,02 (m, 6H), 2,32 (q, 2H), 2,43 (s, 3H), 2,52 (m, 2H), 3,73 (m, 2H), 4,02 (m, 2H), 7,75 (s, 2H), 8,11 (s, 1H).

Microanálisis: Encontrado C, 53,20; H, 5,52; N, 13,68. $C_{18}H_{22}N_4O_5S$ requiere C, 53,19; H, 5,46; N, 13,78%.

EJEMPLO 277

Sal bis-mesilato de 3-{[1-(2-aminoetil)-3,5-dietil-1*H*-pirazol-4-il]oxi}-5-metilbenzonitrilo



A una solución agitada de la amina del Ejemplo 125 (119 mg, 0,40 mmol) en etanol (2 ml) se le añadió ácido metanosulfónico (1,00 ml de una solución 0,84 M en etanol). La mezcla de reacción se concentró a presión reducida para retirar parte del etanol. Se añadió una mezcla de dietil éter y acetona y se formó un precipitado sólido blanco que se filtró y se lavó (éter dietílico/acetona), dando el compuesto

del título (153 mg) en forma de un sólido blanco, p.f. 146-148°C.

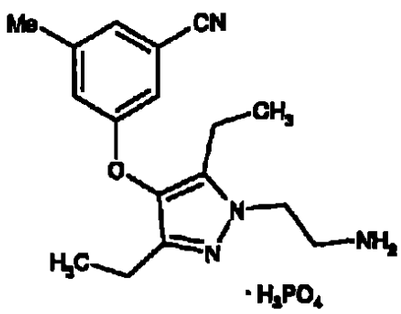
^{1}H-RMN (400 MHz, CD_3OD): δ = 1,09 (m, 6H), 2,33 (s, 3H), 2,39 (q, 2H), 2,55 (q, 2H), 2,68 (s, 6H), 3,42 (t, 2H), 4,29 (t, 2H), 6,93 (s, 1H), 7,06 (s, 1H), 7,19 (s, 1H).

LRMS (termonebulización): m/z [base libre+H^+] 299.

Microanálisis: Encontrado C, 45,83; H, 6,12; N, 11,27. $C_{19}H_{30}N_4O_7S_2.0,50H_2O$ requiere C, 45,68; H, 6,25; N, 11,21%.

EJEMPLO 278

Sal fosfato de 3-{[1-(2-aminoetil)-3,5-dietil-1*H*-pirazol-4-iloxi}-5-metilbenzonitrilo



A un solución agitada de la amina del Ejemplo 125 (251 mg, 0,84 mmol) en etanol (5 ml) se le añadió ácido fosfórico (63 µl, 0,93 mmol). El precipitado resultante se filtró, se lavó (etanol y después dietil éter) y se secó, dando el compuesto del título (265 mg) en forma de un sólido blanco, p.f. 210-211°C.

^{1}H-RMN (400 MHz, CD_3OD): δ = 1,08 (m, 6H), 2,32 (s, 3H), 2,39

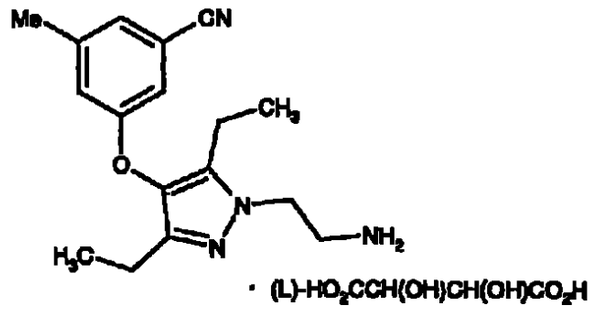
(q, 2H), 2,56 (q, 2H), 3,39 (m, 2H), 4,29 (m, 2H), 6,93 (s, 1H), 7,05 (s, 1H), 7,18 (s, 1H).

LRMS (termonebulización): m/z [base libre+H^+] 299.

Microanálisis: Encontrado C, 51,26; H, 6,36; N, 14,08. $C_{17}H_{25}N_4O_5P$ requiere C, 51,51; H, 6,36; N, 14,14%.

EJEMPLO 279

Sal (L) tartrato de 3-{[1-(2-aminoetil)-3,5-dietil-1*H*-pirazol-4-il]oxi}-5-metilbenzonitrilo



A una solución agitada de la amina del Ejemplo 125 (500 mg, 1,68 mmol) en acetona (15 ml) se le añadió ácido (L)-tartárico (252 mg, 1,68 mmol) y la mezcla se calentó sobre un baño de aceite hasta que se produjo la disolución completa. La mezcla se enfrió a temperatura ambiente y se formó un precipitado blanco, que se filtró y se lavó (acetona), dando el compuesto del título (515 mg) en forma de un polvo blanco, p.f. 159-161°C.

^{1}H-RMN (400 MHz, CD_3OD): δ = 1,05-1,10 (m, 6H), 2,32 (s, 3H), 2,34-2,41 (m, 2H), 2,53-2,57 (m, 2H), 3,40 (m, 2H), 4,27 (m,

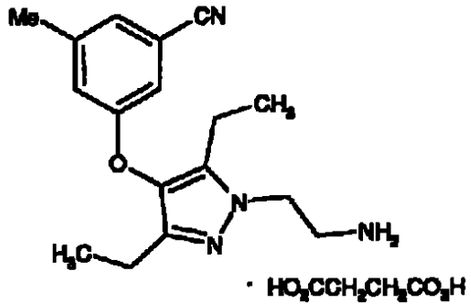
2H), 4,35 (s, 2H), 6,93 (s, 1H), 7,05 (s, 1H), 7,17(s, 1H).

LRMS (electronebulización): m/z [base libre+H^+] 299.

Microanálisis: Encontrado C, 54,80; H, 6,38; N, 12,11. $C_{21}H_{28}N_4O_7.0,65H_2O$ requiere C, 54,81; H, 6,42; N, 12,10%.

EJEMPLO 280

Sal succinato de 3-{[1-(2-aminoetil)-3,5-dietil-1*H*-pirazol-4-iloxi}-5-metilbenzonitrilo



A una solución agitada de la amina del Ejemplo 125 (235 mg, 0,79 mmol) en acetona (7 ml) se añadió ácido succínico (93 mg, 0,79 mmol). Después de dos minutos, la mezcla se concentró a ~3 ml usando una corriente de gas nitrógeno que produjo la formación de cristales blancos. El precipitado se filtró y se lavó (acetona), dando el compuesto del título (172 mg) en forma de cristales blancos, p.f. 155°C.

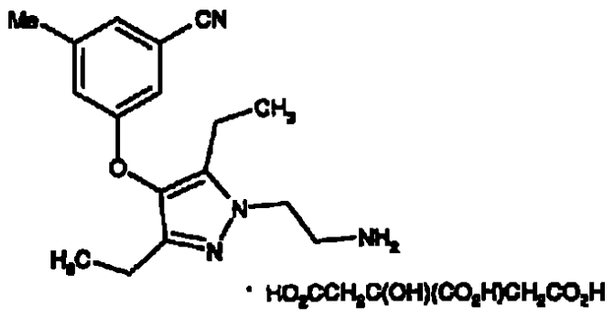
^{1}H-RMN (400 MHz, CD_3OD): δ = 1,03-1,07 (m, 6H), 2,34 (s, 3H), 2,40 (q, 2H), 2,50 (s, 4H), 2,59 (q, 2H), 3,34 (t, 2H), 4,23 (t, 2H), 6,95 (s, 1H), 7,06 (s, 1H), 7,22 (s, 1H).

LRMS (electronebulización): m/z [base libre+H^+] 299.

Microanálisis: Encontrado C, 60,47; H, 6,77; N, 13,39. $C_{21}H_{28}N_4O_5$ requiere C, 60,56; H, 6,78; N, 13,45%.

EJEMPLO 281

Sal (L)-citrato de 3-{[1-(2-Aminoetil)-3,5-dietil-1*H*-pirazol-4-iloxi}-5-metilbenzonitrilo



A una solución agitada de la amina del Ejemplo 125 (140 mg, 0,47 mmol) en acetona (3 ml) se añadió ácido cítrico (90 mg, 0,47 mmol). La mezcla se agitó hasta que se produjo la completa disolución. La mezcla se concentró a ~1 ml usando una corriente de gas nitrógeno y se enfrió en un congelador durante 1,5 horas. Se recogió un precipitado, que se filtró, dando el compuesto del título (149 mg) en forma de un polvo blanco, p.f. 180-182°C.

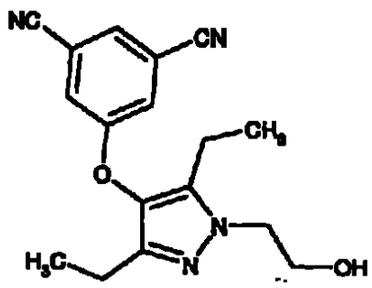
^{1}H-RMN (400 MHz, CD_3OD): δ = 1,04-1,07 (m, 6H), 2,35 (s, 3H), 2,40 (q, 2H), 2,58 (q, 2H), 2,73 (d, 2H), 2,80 (d, 2H), 3,42 (t, 2H), 4,30 (t, 2H), 6,95 (s, 1H), 7,08 (s, 1H), 7,21 (s, 1H).

LRMS (electronebulización): m/z [base libre+H^+] 299.

Microanálisis: Encontrado C, 56,19; H, 6,20; N, 11,31. $C_{23}H_{30}N_4O_8$ requiere C, 56,32; H, 6,16; N, 11,42%.

EJEMPLO 282

5-{[3,5-Dietil-1-(2-hidroxietil)-1*H*-pirazol-4-iloxi}isoftalonitrilo



Se añadió gota a gota 2-hidroxietilhidrazina (8,43 ml, 124 mmol) a una solución de la dicetona de la Preparación 45 (30,5 g, 113 mmol) en ácido acético (300 ml) a temperatura ambiente en una atmósfera de nitrógeno. La reacción se agitó a temperatura ambiente durante 90 minutos y el disolvente se retiró a presión reducida, dando un sólido naranja. Éste se combinó con un sólido naranja de otra reacción realizada de una forma idéntica esta. El producto bruto reunido se purificó por cromatografía en columna ultrarrápida sobre gel de sílice eluyendo con acetato de etilo:pentano (75:25 en volumen), proporcionando el compuesto del título en forma de un sólido blanco. El análisis de la RMN de protón mostró que había impurezas minoritarias, por lo que el producto se purificó por cromatografía en columna ultrarrápida sobre gel

de sílice eluyendo con acetato de etilo:pentano (50:50 en volumen), proporcionando el compuesto del título (50 g) en forma de un sólido blanco, p.f. 125°C.

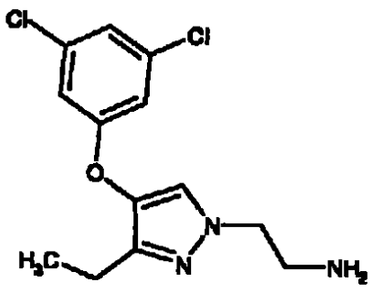
^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,13 (6H, m), 2,40 (2H, q), 2,53 (2H, q), 3,53 (1H, m), 4,11 (4H, m), 7,40 (2H, s), 7,58 (1H, s).

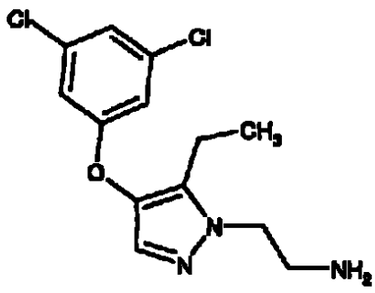
LRMS (electronebulización): m/z [MH^+] 311.

Microanálisis: Encontrado: C, 65,62; H, 5,85; N, 18,04. $C_{17}H_{18}N_4O_2$ requiere C, 65,64; H, 5,84; N, 18,05%.

EJEMPLO 283

2-[4-(3,5-Diclorofenoxi)-3-etil-1*H*-pirazol-1-il]etilamina y 2-[4-(3,5-Diclorofenoxi)-5-etil-1*H*-pirazol-1-il]etilamina





El pirazol del Ejemplo 42 (1,03 g, 4,00 mmol) y clorhidrato de 2-cloroetilamina (510 mg, 4,40 mmol) se calentaron como un fundido a 150°C durante 24 horas. La reacción se enfrió y una solución del residuo en diclorometano (100 ml) se lavó con una solución acuosa 1 M de carbonato potásico (50 ml) y salmuera (50 ml), se secó sobre sulfato de magnesio, se filtró y se concentró a presión

reducida. El producto bruto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco (93:7:1, en volumen), produciendo los compuestos del título (768 mg) en una relación de regioisómeros de 85:15 en forma de un aceite amarillo.

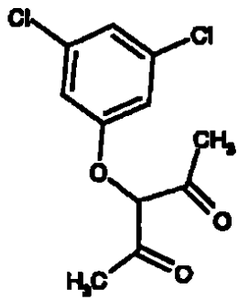
^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,16 (principal, t, 3H), 1,16 (minoritario, t, 3H), 2,47 (principal, q, 2H), 2,60 (minoritario, q, 2H), 3,13 (principal, m, 2H), 3,13 (minoritario, m, 2H), 4,10 (principal, m, 2H), 4,10 (minoritario, m, 2H), 4,24 (principal, t, 2H), 4,24 (minoritario, t, 2H), 6,85 (principal, s, 2H), 6,85 (minoritario, s, 2H), 7,02 (principal, s, 1H), 7,02 (minoritario, s, 1H), 7,27 (principal, s, 1H), 7,31 (minoritario, s, 1H).

LRMS (termonebulización): m/z [MH^+] 300.

Las siguientes preparaciones describen la preparación de ciertos intermedios usados en los Ejemplos precedentes.

PREPARACIÓN 1

3-(3,5-Diclorofenoxi)-2,4-pentanodiona



Se añadió 3-cloro-2,4-pentanodiona (183 µl, 1,53 mmol) a una suspensión agitada de 3,5-diclorofenol (250 mg, 1,53 mmol) y carbonato potásico (233 mg, 1,69 mmol) en acetona (7,7 ml) a temperatura ambiente en una atmósfera de nitrógeno. La mezcla se agitó durante 30 minutos y después se calentó a reflujo durante 3,5 horas. Después de la refrigeración, se añadió yoduro sódico (230 mg, 1,53 mmol) y se continuó a reflujo durante 3,5 horas más. Después de enfriar de nuevo, la mezcla se diluyó con agua (5 ml) y se concentró a presión reducida en una campana de ventilación (precaución: posible resto de gas lacrimógeno) para retirar la acetona. La solución acuosa roja resultante se diluyó con ácido clorhídrico 2 M (5 ml) y se extrajo con diclorometano (3x10 ml). Las capas orgánicas reunidas se lavaron con una solución acuosa saturada de sulfito sódico (10 ml) y salmuera (10 ml), se secaron sobre sulfato de magnesio, se filtraron y se evaporaron a presión reducida, dando un aceite rojo (344 mg). El producto bruto se purificó por cromatografía

ultrarrápida sobre gel de sílice eluyendo con pentano:acetato de etilo (20:1, en volumen), dando el compuesto del título (118 mg) en forma de un sólido de color crema, p.f. 91- 92°C.

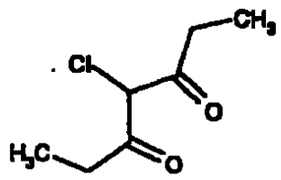
^{1}H-RMN (400 MHz, $CDCl_3$): δ = 2,04 (s, 6H), 6,84 (s, 2H), 7,06 (s, 1H), 14,38 (s a, 1H).

LRMS (termonebulización): m/z [MNH_4^+] 278.

Microanálisis: Encontrado: C, 50,43; H, 3,84. $C_{11}H_{10}Cl_2O_3$ requiere C, 50,60; H, 3,86%.

PREPARACIÓN 2

4-Cloro-3,5-heptanodiona



Se añadió gota a gota clorotrimetilsilano (29,7 ml, 0,234 mol) a una solución amarilla pálida de bromuro de tetrabutilamonio (1,26 g, 3,9 mmol) en acetonitrilo seco (116 ml) a temperatura ambiente en una atmósfera de nitrógeno. La solución resultante se enfrió en hielo y 3,5-heptanodiona (10,6 ml, 78,0 mmol) y después se añadió gota a gota durante 5 minutos dimetilsulfóxido seco (16,6 ml, 0,234 mol) produciendo una solución amarilla que se dejó calentar lentamente a temperatura ambiente, con agitación, durante 4 horas. La mezcla se diluyó con agua (1 litro), se agitó durante 10 minutos y después se extrajo con éter (1x500 ml,

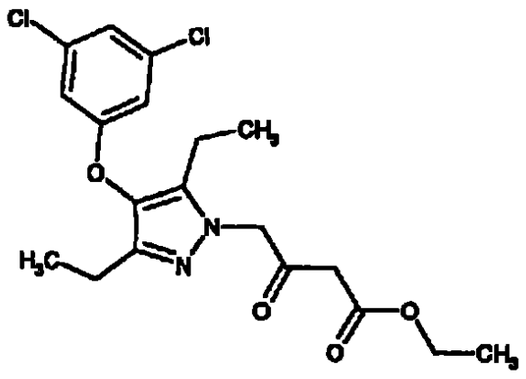
2x250 ml). Las capas de éter reunidas se secaron sobre sulfato de magnesio, se filtraron y se concentraron a presión reducida, dando un aceite amarillo. El producto bruto se purificó por destilación a presión reducida, produciendo el compuesto del título (5,5 g) en forma de un aceite amarillo pálido, p.e. 102-105°C/54 mm de Hg que contenía aproximadamente un 10% de 4,4-dicloro-3,5-heptanodiona según se estimó por microanálisis.

^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,12 (t, 6H), 2,59 (q, 4H), 4,77 (s, 0,2H, dicetona), 15,50 (s, 0,8H, enol).

LRMS (termonebulización): m/z [MNH_4^+] 180 para el compuesto del título y 214 para la impureza diclorada.

PREPARACIÓN 3

4-[4-(3,5-diclorofenoxi)-3,5-dietil-1*H*-pirazol-1-il]-3-oxobutanoato de etilo



Se añadió hidruro sódico (dispersión en aceite al 60%, 250 mg, 6,17 mmol) a una solución agitada de 4-(3,5-

diclorofenoxi)-3,5-dietil-1*H*-pirazol (800 mg, 2,81 mmol, Ejemplo 3) en *N*,*N*-dimetilformamida seca (5 ml) a 0°C en una atmósfera de nitrógeno. La mezcla se agitó durante 5 minutos tiempo durante el cual se desprendió hidrógeno y después se añadió 4-cloroacetoacetato de etilo (0,42 ml, 3,09 mmol). Después de 30 minutos, la mezcla de reacción se inactivó por la adición de agua (0,5 ml) y se concentró a presión reducida. Una solución del residuo en acetato de etilo (50 ml) se lavó con una solución acuosa saturada de cloruro amónico (20 ml) y agua (20 ml), se secó sobre sulfato de magnesio y se concentró a presión reducida. El producto bruto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con acetato de etilo:pentano (30:70, en volumen), proporcionando el compuesto del título (1,1 g) en forma de un sólido blanco, p.f. 82-84°C.

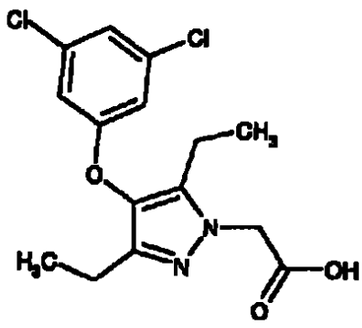
^{1}H-RMN (300 MHz, $CDCl_3$): δ = 1,40 (6H, m), 1,26 (3H, t), 2,44 (4H, q), 3,47 (2H, s), 4,22 (2H, q), 4,96 (2H, s), 6,82 (2H, s), 7,02 (1H, s).

LRMS (termonebulización): m/z [MH^+] 413.

Microanálisis: Encontrado: C, 55,13; H, 5,34; N, 6,98. $C_{15}H_{15}Cl_2N_3O$ requiere C, 55,22; H, 5,37; N, 6,78%.

PREPARACIÓN 4

Ácido [4-(3,5-diclorofenoxi)-3,5-dietil-1*H*-pirazol-1-il]acético



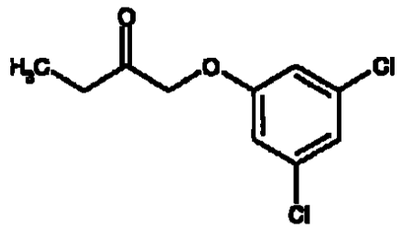
Se añadió gota a gota una solución acuosa de hidróxido sódico (1 N, 6,2 ml, 6,2 mmol) a una solución agitada del éster (2 g, 5,6 mmol) del Ejemplo 9 en tetrahidrofurano (20 ml) a 0°C. Después de 1 hora, el disolvente se retiró a presión reducida y se añadió ácido clorhídrico acuoso (20 ml) con agitación vigorosa. El precipitado blanco resultante se recogió por filtración, se lavó con éter (3x30 ml) y se secó en una pistola de vacío a 60°C/10 mm de Hg, produciendo el compuesto del título en forma de un sólido blanco (1,5 g), p.f.157-158°C.

^{1}H-RMN (300 MHz, $CDCl_3$): δ = 1,13 (6H, m), 2,52 (2H, q), 2,60 (2H, q), 5,03 (2H, s), 6,95 (2H, s), 7,14 (1H, s).

LRMS (electronebulización): m/z [M-H$^+$] 341.

PREPARACIÓN 5

1-(3,5-Diclorofenoxi)-2-butanona



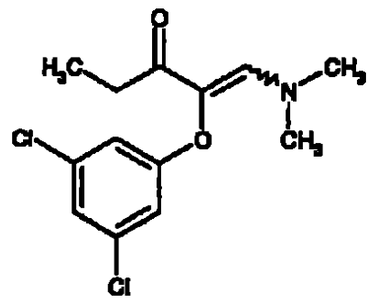
Se añadió en una porción carbonato de cesio (108 g, 0,33 mol) a una solución agitada de 3,5-diclorofenol (49 g, 0,30 mol) en acetona (900 ml) a temperatura ambiente en una atmósfera de nitrógeno. A esta suspensión se le añadió gota a gota una solución de 1-bromo-2-butanona (30,6 ml, 0,30 mol) en acetona (300 ml) y la suspensión resultante se calentó a reflujo durante 2 horas. La suspensión se enfrió a temperatura ambiente, se añadió agua (200 ml) y la acetona se retiró a presión reducida. La mezcla se extrajo con diclorometano (2x300 ml) y las fases orgánicas reunidas se secaron sobre sulfato de magnesio, se filtraron y se concentraron a presión reducida, dando un aceite transparente. El producto bruto se purificó por cromatografía en columna ultrarrápida sobre gel de sílice eluyendo con diclorometano:ciclohexano (50:50, en volumen), proporcionando el compuesto del título (65 g) en forma de un aceite amarillo.

^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,13 (t, 3H), 2,60 (q, 2H), 4,58 (s, 2H), 6,78 (s, 2H), 7,01 (s, 1H).

LRMS (termonebulización): m/z [MNH_4^+] 250.

PREPARACIÓN 6

2-(3,5-Diclorofenoxi)-1-(dimetilamino)-1-penten-3-ona



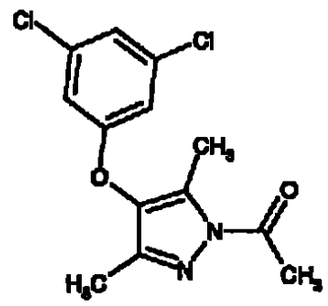
Una solución de la cetona de la Preparación 5 (65 g, 0,28 mol) en dimetilacetal de *N*,*N*-dimetilformamida (75 ml, 0,56 mol) se calentó a 100°C usando un aparato Dean-Stark durante 10 horas. La reacción se enfrió y se concentró a presión reducida, dando un aceite pardo. El producto bruto se purificó por cromatografía en columna ultrarrápida sobre gel de sílice eluyendo con pentano:acetato de etilo (90:10, en volumen) y después con pentano:acetato de etilo (60:40, en volumen), proporcionando el compuesto del título (55 g) en forma de un aceite amarillo que solidificó tras reposo. El sólido amarillo resultante se lavó con pentano (100 ml) y se secó, proporcionando el compuesto del título (28 g) en forma de un sólido amarillo, p.f. 96-97°C.

^{1}H-RMN (400 MHz, $CDCl_3$): δ = 0,98 (t, 3H), 2,30 (s a, 2H), 2,94 (s, 6H), 6,77 (s, 2H), 6,95 (s, 1H), 7,24 (s, 1H).

LRMS (termonebulización): m/z [MNH_4^+] 288.

PREPARACIÓN 7

1-Acetil-4-(3,5-diclorofenoxi)-3,5-dimetil-1*H*-pirazol



Se añadió hidruro sódico (dispersión en aceite al 60%, 684 mg, 17,1 mmol) a una solución agitada de cloruro de acetilo (1,21 ml, 17,1 mmol) y el pirazol del Ejemplo 53 (4,00 g, 15,6 mmol) en *N*,*N*-dimetilformamida (20 ml) a 0°C en una atmósfera de nitrógeno. La reacción se agitó a 0°C durante 1 hora y después se inactivó por la adición de agua (100 ml). La fase acuosa se extrajo con éter (2x50 ml). Las fases orgánicas reunidas se lavaron con agua (30 ml) y salmuera (30 ml), se secaron sobre sulfato de magnesio, se filtraron y se concentraron a presión reducida, dando un sólido amarillo. El producto bruto se purificó por cromatografía en columna ultrarrápida sobre gel de sílice eluyendo con pentano:éter (90: 10, en volumen), proporcionando el compuesto del título (3,0 g) en forma de un sólido blanco, p.f. <60°C.

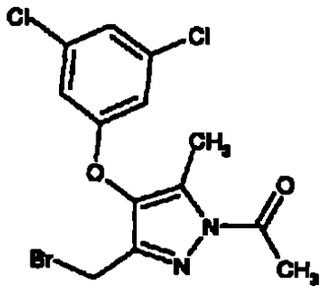
^{1}H-RMN (300 MHz, $CDCl_3$): δ = 2,11 (s, 3H), 2,43 (s, 3H), 2,70

(s, 3H), 6,78 (s, 2H), 7,03 (s, 1H).

LRMS (termonebulización): m/z [MH^+] 299.

PREPARACIÓN 8

1-Acetil-3-(bromometil)-4-(3,5-diclorofenoxi)-5-metil-1*H*-pirazol



Se añadió N-bromosuccinimida (2,70 g, 15,0 mmol) a una solución agitada del pirazol de la Preparación 7 (3,00 g, 10,0 mmol) en 1,1,1-tricloroetano (40 ml) a temperatura ambiente en una atmósfera de nitrógeno. La reacción se calentó a 80°C durante 1 hora y después se añadió azobisisobutironitrilo (2 mg) y la mezcla de reacción se calentó durante 3 horas más. La reacción se enfrió a temperatura ambiente y se retiró un sólido por filtración. El filtrado se concentró a presión reducida y el aceite amarillo resultante se disolvió en acetato de etilo (100 ml). El acetato de etilo se lavó con una solución acuosa 1 M de carbonato sódico (30 ml), agua (30 ml) y salmuera (30 ml), se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida, dando un sólido amarillo. El producto

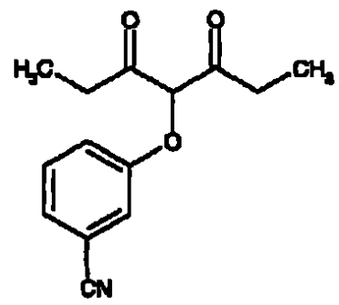
bruto se purificó por cromatografía en columna ultrarrápida sobre gel de sílice eluyendo con pentano:acetato de etilo (90:10, en volumen), proporcionando un sólido amarillo que se lavó con éter enfriado con hielo (20 ml), proporcionando el compuesto del título (2,3 g) en forma de un sólido blanco, p.f. 111-113°C.

^{1}H-RMN (300 MHz, $CDCl_3$): δ = 2,10 (s, 3H), 2,73 (s, 3H), 4,73 (s, 2H), 6,86 (s, 2H), 7,11 (s, 1H).

LRMS (termonebulización): m/z [MH^+] 379.

PREPARACIÓN 9

4-(3-Cianofenoxi)-3,5-heptanodiona



Una mezcla de la β-dicetona de la Preparación 2 (1,79 g, 11,0 mmol), 3-cianofenol (1,31 g, 11,0 mmol), carbonato de cesio (3,58 g, 11,0 mmol) y acetona (44 ml) se calentó a reflujo durante 2 horas. Después de la refrigeración, la mezcla se concentró a presión reducida y el residuo se repartió entre diclorometano (50 ml) y agua (25 ml). La capa orgánica se separó, se lavó con salmuera (25 ml), se secó sobre sulfato de magnesio, se filtró y se concentró a presión

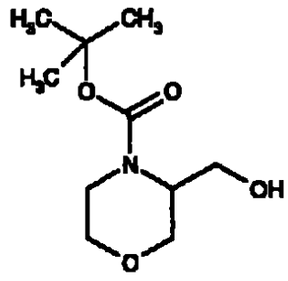
reducida, dando un aceite amarillo. El producto bruto se purificó por cromatografía en columna ultrarrápida sobre gel de sílice eluyendo con acetato de etilo:pentano (10:90, en volumen), proporcionando el compuesto del título (1,10 g) en forma de un aceite amarillo.

^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,04 (t, 6H), 2,49 (q, 4H), 7,16 (m, 2H), 7,30 (d, 1H), 7,39 (t, 2H), 14,51 (s, 1H).

LRMS (termonebulización): m/z [MNH_4^+] 263.

PREPARACIÓN 10

3-(Hidroximetil)-4-morfolinocarboxilato de *terc*-butilo



Se añadió gota a gota borano (38,1 ml de una solución 1,0 M en tetrahidrofurano, 38,1 mmol) a una suspensión agitada de ácido 3-morfolinocarboxílico (1,00 g, 7,63 mmol) en tetrahidrofurano (50 ml) a temperatura ambiente en una atmósfera de nitrógeno. La reacción se calentó a reflujo y la reacción se hizo homogénea y se continuó agitando durante 12 horas. La reacción se enfrió a temperatura ambiente y se concentró a presión reducida, dando un aceite pardo. El residuo se disolvió en una solución acuosa 1 M de hidróxido

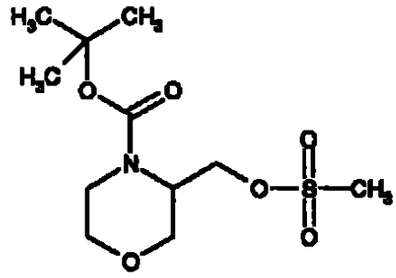
sódico y se agitó a temperatura ambiente durante 5 días. Después de este tiempo, se añadió dicarbonato de di-*terc*-butilo (1,66 g, 7,63 mmol) y la reacción se agitó durante 12 horas. La reacción se diluyó con éter (100 ml). La capa orgánica se separó, se lavó con salmuera (10 ml), se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida. El producto bruto se purificó por cromatografía en columna ultrarrápida sobre gel de sílice eluyendo con pentano:acetato de etilo (50:50, en volumen) y después con acetato de etilo, proporcionando el compuesto del título (1,30 g) en forma de un aceite incoloro.

^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,48 (s, 9H), 2,05 (s, 1H), 3,19 (t a, 1H), 3,47 (td, 1H), 3,60 (dd, 1H), 3,87 (m, 6H).

LRMS (termonebulización): m/z [MH^+] 218.

PREPARACIÓN 11

3-{[(Metilsulfonil)oxi]metil}-4-morfolinocarboxilato de *terc*-butilo



Se añadió gota a gota trietilamina (1,15 ml, 8,29 mmol) a una solución agitada del alcohol de la Preparación 10 (1,20

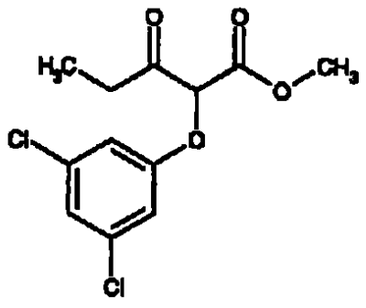
g, 5,52 mmol) y anhídrido metanosulfónico (1,44 g, 5,52 mmol) en diclorometano (50 ml) a temperatura ambiente en una atmósfera de nitrógeno. La reacción se agitó durante 1 hora y después se vertió en agua (50 ml). La capa orgánica se separó, se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida. El producto bruto se purificó por cromatografía en columna ultrarrápida sobre gel de sílice eluyendo con pentano:acetato de etilo (50:50, en volumen), proporcionando el compuesto del título (1,20 g) en forma de un aceite incoloro.

^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,49 (s, 9H), 3,06 (s, 3H), 3,50 (td, 1H), 3,60 (dd, 1H), 3,80 (m, 4H), 4,26 (s a, 1H), 4,39 (m, 2H).

LRMS (termonebulización): m/z [MNH_4^+] 313.

PREPARACIÓN 12

2-(3,5-Diclorofenoxi)-3-oxopentanoato de metilo



Una mezcla de 2-cloro-3-pentanoato de metilo (25,0 g, 152 mmol), 3,5-diclorofenol (24,6 g, 152 mmol), carbonato de

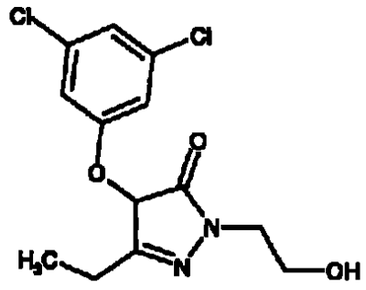
cesio (54,4 g, 167 mmol) y acetona (500 ml) se calentó a reflujo durante 2 horas. Después de la refrigeración, la mezcla se concentró a presión reducida y el residuo se repartió entre diclorometano (100 ml) y agua (50 ml). La capa orgánica se separó, se lavó con salmuera (25 ml), se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida, dando un aceite naranja. El producto bruto se purificó por cromatografía en columna ultrarrápida sobre gel de sílice eluyendo con pentano:tolueno (90:10, en volumen), proporcionando el compuesto del título (40,0 g) en forma de un aceite rosa.

^{1}H-RMN (300 MHz, $CDCl_3$): δ = 1,16 (t, 3H), 2,60 (m, 2H), 3,77 (s, 3H), 5,13 (s, 1H), 6,84 (s, 2H), 7,10 (s, 1H).

LRMS (termonebulización): m/z [MNH_4^+] 308.

PREPARACIÓN 13

4-(3,5-Diclorofenoxi)-5-etil-2(2-hidroxietil)-2,4-dihidro-3*H*-pirazol-3-ona



Se añadió una solución de 2-hidroxietilhidrazina (4,30 g, 56,7 mmol) en ácido acético glacial (2,0 ml) a una

solución agitada del cetoéster de la Preparación 12 (15,0 g, 51,5 mol) en ácido acético glacial (100 ml) y la solución resultante se agitó a temperatura ambiente durante 48 horas. La mezcla se concentró a presión reducida y el producto bruto se purificó por cromatografía en columna ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol (95:5, en volumen), proporcionando el compuesto del título (10,1 g) en forma de un aceite incoloro.

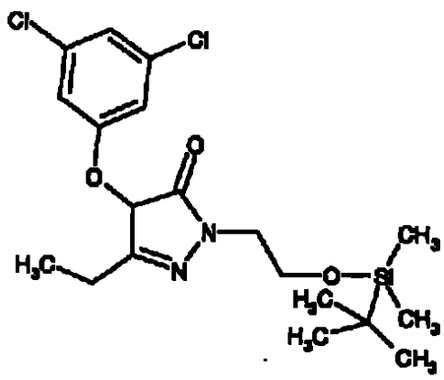
^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,02 (t, 3H), 2,29 (m, 2H), 3,63 (m, 2H), 3,80 (m, 2H), 6,92 (s, 2H), 7,21 (s, 1H).

LRMS (termonebulización): m/z [MH^+] 317.

Microanálisis: Encontrado: C, 48,86; H, 4,44; N, 9,01. $C_{13}H_{14}N_2O_3Cl_2$ requiere C, 49,23; H, 4,45; N, 8,83%.

PREPARACIÓN 14

2-(2-{[*terc*-Butil(dimetil)silil]oxi}etil)-4-(3,5-diclorofenoxi)-5-etil-2,4-dihidro-3*H*-pirazol-3-ona



Se añadió en una porción cloruro de *terc*-

butildimetilsililo (8,14 g, 54,0 mmol) a una solución agitada del pirazol de la Preparación 13 (14,3 g, 45,0 mmol) e imidazol (3,98 g, 58,5 mmol) en *N,N*-dimetilformamida (90 ml) y la solución resultante se agitó a temperatura ambiente durante 48 horas. La mezcla se repartió entre acetato de etilo (100 ml) y agua (300 ml). La capa orgánica se separó, se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida. El producto bruto se purificó por cromatografía en columna ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol (95:5, en volumen), proporcionando el compuesto del título (9,56 g) en forma de un aceite incoloro.

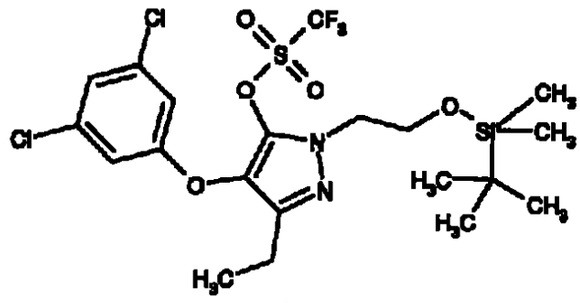
^{1}H-RMN (400 MHz, $CDCl_3$): δ = 0,15 (s, 6H), 0,94 (s, 9H), 1,16 (t, 3H), 2,45 (m, 2H), 3,94 (m, 4H), 6,85 (s, 2H), 6,97 (s, 1H).

LRMS (termonebulización): m/z [MH^+] 431.

Microanálisis: Encontrado: C, 52,87; H, 6,52; N, 6,46. $C_{19}H_{28}N_2O_3Cl_2Si$ requiere C, 52,90; H, 6,54; N, 6,49%.

PREPARACIÓN 15

<u>Trifluorometanosulfonato de 1-(2-{[*terc*-butil(dimetil)silil]oxi}etil)-4-(3,5-diclorofenoxi)-3-etil-1*H*-pirazol-5-ilo</u>



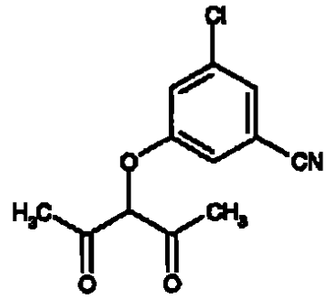
Se añadió en una porción feniltriflamida (3,70 g, 10,5 mmol) a una solución agitada del pirazol de la Preparación 14 (4,10 g, 9,50 mmol) y trietilamina (1,60 ml, 11,4 mmol) en diclorometano (20 ml) a temperatura ambiente en una atmósfera de nitrógeno. La reacción se agitó durante 2 horas y después se vertió en agua (50 ml). La capa orgánica se separó, se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida. El producto bruto se purificó por cromatografía en columna ultrarrápida sobre gel de sílice eluyendo con diclorometano, proporcionando el compuesto del título (5,10 g) en forma de un aceite púrpura.

^{1}H-RMN (300 MHz, $CDCl_3$): δ = 0,01 (s, 6H), 0,86 (s, 9H), 1,17 (t, 3H), 2,45 (q, 2H), 4,01 (m, 2H), 4,14 (m, 2H), 6,84 (s, 2H), 7,08 (s, 1H).

LRMS (termonebulización): m/z [MH^+] 563.

PREPARACIÓN 16

3-(1-Acetil-2-oxopropoxi)-5-clorobenzonitrilo



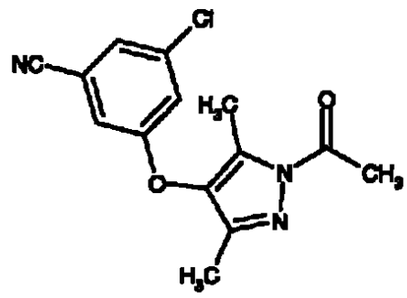
Una mezcla de 3-cloro-2,4-pentanodiona (6,73 g, 50,0 mmol), el fenol de la Preparación 36 (7,67 g, 50,0 mmol), carbonato de cesio (18,0 g, 55,4 mmol) y acetona (40 ml) se calentó a reflujo durante 2 horas. La reacción se enfrió a temperatura ambiente, se añadieron *N,N*-dimetilformamida (6 ml) y acetona (30 ml) y la reacción se calentó a 70°C durante 12 horas más. Después de la refrigeración, el sólido se retiró por filtración y se disolvió en ácido clorhídrico acuoso 1 M (150 ml). La solución resultante se extrajo con diclorometano (3x100 ml) y las fases orgánicas reunidas se lavaron con salmuera (30 ml), se secaron sobre sulfato de magnesio, se filtraron y se concentraron a presión reducida, proporcionando el compuesto del título (5,50 g) en forma de un sólido pardo, p.f. 105-108°C.

^{1}H-RMN (300 MHz, $CDCl_3$): δ = 2,04 (s, 6H), 7,13 (s, 1H), 7,19 (s, 1H), 7,35 (s, 1H), 14,40 (s, 1H).

PREPARACIÓN 17

3-[(1-Acetil-3,5-dimetil-1*H*-pirazol-4-il)oxi]-5-

clorobenzonitrilo



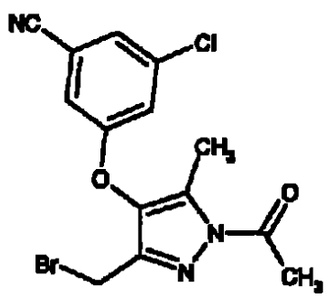
Se añadió hidruro sódico (dispersión en aceite al 60%, 840 mg, 21,0 mmol) a una solución agitada de cloruro de acetilo (1,50 ml, 21,0 mmol) y el pirazol del Ejemplo 76 (4,80 g, 19,4 mmol) en *N,N*-dimetilformamida (20 ml) a 0°C en una atmósfera de nitrógeno. La reacción se agitó a 0°C durante 15 minutos y después se inactivó por la adición de agua (200 ml). La mezcla de reacción se extrajo con acetato de etilo (3x120 ml). Las fases orgánicas reunidas se lavaron con agua (50 ml) y salmuera (50 ml), se secaron sobre sulfato de magnesio, se filtraron y se concentraron a presión reducida, dando un sólido amarillo. El producto bruto se purificó por cromatografía en columna ultrarrápida sobre gel de sílice eluyendo con diclorometano, proporcionando el compuesto del título (5,00 g) en forma de un sólido blanco, p.f. <60°C.

^{1}H-RMN (400 MHz, $CDCl_3$): δ = 2,06 (s, 3H), 2,38 (s, 3H), 2,65 (s, 3H), 6,99 (m, 1H), 7,08 (m, 1H), 7,29 (m, 1H).

LRMS (termonebulización): m/z [MH^+] 290.

PREPARACIÓN 18

3-{[1-Acetil-3-(bromometil)-5-metil-1*H*-pirazol-4-il]oxi}-5-clorobenzonitrilo

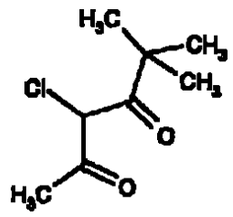


Se añadió *N*-bromosuccinimida (4,60 g, 25,6 mmol) a una solución agitada del pirazol de la Preparación 17 (5,00 g, 17,3 mmol) en 1,1,1-tricloroetano (70 ml) y azobisisobutironitrilo (20 mg) a temperatura ambiente en una atmósfera de nitrógeno. La reacción se calentó a 80°C durante 3 horas y después se enfrió a temperatura ambiente. Se añadió una segunda porción de *N*-bromosuccinimida (2,00 g, 11,2 mmol) y la mezcla de reacción se calentó a 80°C durante 4 horas más. La reacción se enfrió a temperatura ambiente y se concentró a presión reducida y el aceite amarillo resultante se purificó por cromatografía en columna ultrarrápida sobre gel de sílice eluyendo con pentano:diclorometano (25:75, en volumen), proporcionando el compuesto del título (2,30 g) en forma de un sólido blanco, p.f. 122- 123°C.

^{1}H-RMN (300 MHz, $CDCl_3$): δ = 2,10 (s, 3H), 2,74 (s, 3H), 4,73 (s, 2H), 7,12 (s, 1H), 7,22 (s, 1H), 7,39 (s, 1H).

PREPARACIÓN 19

3-Cloro-5,5-dimetil-2,4-hexanodiona



Se añadió gota a gota clorotrimetilsilano (26,8 ml, 0,21 mol) a una solución amarilla pálida agitada de bromuro de tetrabutilamonio (1,13 g, 3,50 mmol) en acetonitrilo seco (100 ml) a temperatura ambiente en una atmósfera de nitrógeno. La solución resultante se enfrió en hielo y se añadieron gota a gota durante 5 minutos 5,5-dimetilhexano-2,4-diona (10,0 g, 70,4 mmol) y después dimetilsulfóxido seco (14,7 ml, 0,21 mol), produciendo una solución amarilla que se dejó calentar lentamente a temperatura ambiente con agitación durante 3 horas. La mezcla se diluyó con agua (1000 ml) y se agitó durante 10 min y después se extrajo con éter (1x500 ml, 2x250 ml). Las capas de éter reunidas se secaron sobre sulfato de magnesio, se filtraron y se concentraron a presión reducida, dando un aceite amarillo. El producto bruto se purificó por destilación a presión reducida, proporcionando el compuesto del título (10,0 g) en forma de un aceite amarillo pálido, p.e. 220-225°C/60 mm de Hg.

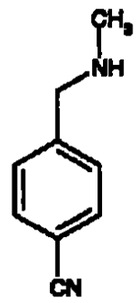
^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,25 (s, 9H), 2,39 (s, 3H), 5,10

(s, 1H).

LRMS (termonebulización): m/z [MNH_4^+] 194.

PREPARACIÓN 20

4-[(Metilamino)metil]benzonitrilo



4-Cianobenzaldehído (12,0 g, 92,0 mmol), metilamina (69 ml de una solución 2,0 M en tetrahidrofurano, 137 mmol) y sulfato de magnesio (45 g) se agitaron en diclorometano (300 ml) a temperatura ambiente durante 5 días. La mezcla se filtró y el filtrado se concentró a presión reducida, dando un aceite amarillo. El aceite se disolvió en metanol (200 ml) y se añadió cuidadosamente borohidruro sódico (4,10 g, 109 mmol) con agitación vigorosa. Una vez completada la adición, la reacción se agitó durante 1 hora y la mezcla se concentró a presión reducida. El residuo se disolvió en una solución acuosa 1 M de hidróxido sódico (200 ml) y la mezcla se agitó a temperatura ambiente durante 1 hora. La solución resultante se extrajo con diclorometano (2x200 ml) y las fases orgánicas reunidas se secaron sobre sulfato de magnesio, se filtraron y se concentraron a presión reducida, proporcionando el

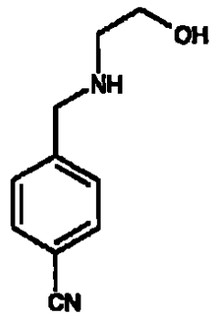
compuesto del título (13,4 g) en forma de un aceite amarillo pálido.

^{1}H-RMN (300 MHz, $CDCl_3$): δ = 1,46 (s, 1H), 2,46 (s, 3H), 3,82 (s, 2H), 7,47 (d, 2H), 7,64 (d, 2H).

LRMS (electronebulización): m/z [MH^+] 147.

PREPARACIÓN 21

4-{[(2-Hidroxietil)amino]metil}benzonitrilo



Una mezcla de 4-cianobenzaldehído (14,1 g, 107 mmol), etanolamina (6,56 g, 107 mmol) y tolueno (100 ml) se calentó a reflujo durante 14 horas usando un aparato Dean-Stark para retirar agua. La reacción se enfrió a temperatura ambiente y se concentró a presión reducida, dando un aceite amarillo. El aceite se disolvió en diclorometano (200 ml), se enfrió a 0°C y se añadieron gota a gota trietilamina (16,3 ml, 117 mmol) y clorotrimetilsilano (14,9 ml, 117 mmol). Se formó un precipitado blanco y después de agitar durante 1 hora la mezcla se filtró. El filtrado se concentró a presión reducida, dando un sólido naranja (25,0 g). El sólido naranja

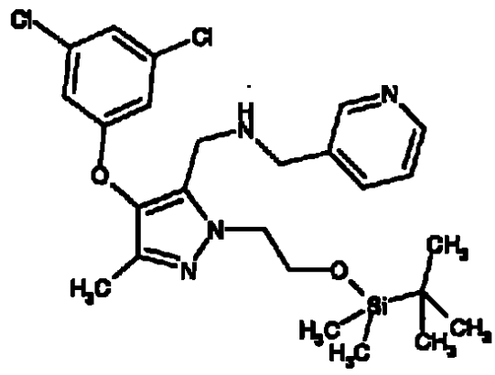
se disolvió en metanol (200 ml) y se añadió cuidadosamente con agitación vigorosa borohidruro sódico (4,50 g, 122 mmol). Una vez completada la adición, la reacción se agitó durante 1 hora y la mezcla después se concentró a presión reducida. El residuo se disolvió en una solución acuosa 1 M de hidróxido sódico (200 ml) y la mezcla se agitó a temperatura ambiente durante 1 hora. La solución resultante se extrajo con diclorometano (3x200 ml) y las fases orgánicas reunidas se secaron sobre sulfato de magnesio, se filtraron y se concentraron a presión reducida. El producto bruto se purificó por cromatografía en columna ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco (95:4:1, en volumen), proporcionando el compuesto del título (12,0 g) en forma de un aceite amarillo pálido que solidificó tras reposo, dando un sólido amarillo, p.f. <60°C.

^{1}H-RMN (300 MHz, $CDCl_3$): δ = 1,84 (s, 2H), 2,84 (t, 2H), 3,68 (t, 2H), 3,89 (s, 2H), 7,45 (d, 2H), 7,65 (d, 2H).

LRMS (termonebulización): m/z [MH^+] 177.

PREPARACIÓN 22

N-{[1-(2-{[terc-Butil(dimetil)silil]oxi}etil)-4-(3,5-diclorofenoxi)-3-metil-1*H*-pirazol-5-il]metil}-*N*-(3-piridinilmetil)amina



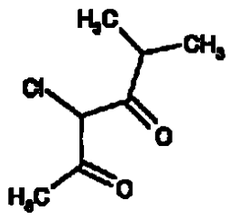
Se añadió en una porción 3-(metilamino)piridina (327 mg, 3,04 mmol) a una solución agitada del bromuro de la Preparación 28 (300 mg, 0,610 mmol) en isopropanol (5 ml) a temperatura ambiente. La mezcla se calentó a 50°C durante 1 hora, se enfrió a temperatura ambiente y se concentró a presión reducida, dando un aceite naranja. El producto bruto se purificó por cromatografía en columna ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco (95:4:1, en volumen), produciendo el compuesto del título (50 mg) en forma de un aceite incoloro.

^{1}H-RMN (400 MHz, $CDCl_3$): δ = 0,15 (s, 6H), 0,77 (s, 9H), 2,02 (s, 3H), 3,64 (s, 2H), 3,70 (s, 2H), 3,95 (t, 2H), 4,17 (t, 2H), 6,75 (s, 2H), 6,97 (s, 1H), 7,15 (dd, 1H), 7,53 (d, 1H), 8,47 (m, 2H).

LRMS (termonebulización): m/z [MH^+] 521.

PREPARACIÓN 23

3-Cloro-5-metil-2,4-hexanodiona



Se añadió gota a gota clorotrimetilsilano (13,4 ml, 105 mmol) a una solución amarilla pálida agitada de yoduro de tetrabutilamonio (566 mg, 1,53 mmol) en acetonitrilo seco (100 ml) a temperatura ambiente en una atmósfera de nitrógeno. La solución resultante se enfrió en hielo y se añadieron gota a gota durante 5 minutos 5-metilhexano-2,4-diona (4,50 g, 35,1 mmol) y después dimetilsulfóxido seco (7,47 ml, 105 mmol), produciendo una solución amarilla que se dejó calentar lentamente a temperatura ambiente con agitación durante 1 hora. Después se añadió en una porción bromuro de tetrabutilamonio (566 mg, 1,75 mmol) y la reacción se agitó a temperatura ambiente durante 2 horas. La mezcla se diluyó con agua (200 ml), se agitó durante 10 minutos y después se extrajo con éter (3x100 ml). Las capas de éter reunidas se secaron sobre sulfato de magnesio, se filtraron y se concentraron a presión reducida, dando un aceite amarillo. El producto bruto se purificó por cromatografía en columna ultrarrápida sobre gel de sílice eluyendo con pentano:acetato de etilo (98:2, en volumen), proporcionando el compuesto del título (2,00 g) en forma de un aceite

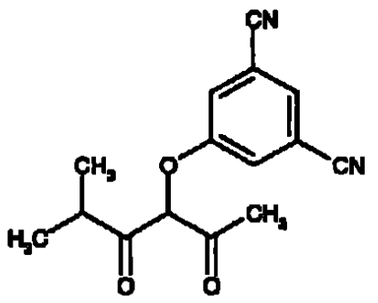
incoloro.

^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,15 (d, 6H), 2,29 (s, 3H), 3,25 (sept, 1H), 15,60 (s, 1H).

LRMS (termonebulización): m/z [MNH_4^+] 180.

PREPARACIÓN 24

5-(1-Acetil-3-metil-2-oxobutoxi)isoftalonitrilo



Una mezcla de la diona de la Preparación 23 (1,12 g, 6,94 mmol), el fenol de la Preparación 39 (1,00 g, 6,94 mmol), carbonato de cesio (2,25 g, 6,94 mmol) y acetona (30 ml) se calentó a reflujo durante 4 horas. La reacción se enfrió a temperatura ambiente y se concentró a presión reducida, dando un sólido pardo. El sólido se disolvió en ácido clorhídrico acuoso 1 M (50 ml) y la solución se extrajo con diclorometano (3x30 ml). Las fases orgánicas reunidas se lavaron con salmuera (30 ml), se secaron sobre sulfato de magnesio, se filtraron y se concentraron a presión reducida. El producto bruto se purificó por cromatografía en columna ultrarrápida sobre gel de sílice eluyendo con pentano:acetato de etilo (90:10, en volumen), proporcionando el compuesto del

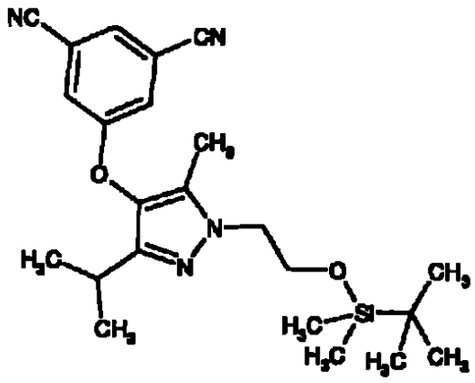
título (580 mg) en forma de un sólido amarillo.

^{1}H-RMN (300 MHz, $CDCl_3$): δ = 1,08 (d, 6H), 2,02 (s, 3H), 2,24 (sept, 1H), 7,47 (s, 2H), 7,63 (s, 1H), 14,71 (s, 1H).

LRMS (electronebulización): m/z [M-H$^+$] 269.

PREPARACIÓN 25

5-{[1-(2-{[terc-Butil(dimetil)silil]oxi}etil)-3-isopropil-5-metil-1*H*-pirazol-4-il]oxi}isoftalonitrilo



Se añadió hidruro sódico (dispersión en aceite al 60%, 45 mg, 1,12 mmol) a una solución agitada de 2-bromoetoxi-t-butildimetilsilano (270 mg, 1,12 mmol) y el pirazol del Ejemplo 95 (250 mg, 0,930 mmol) en *N*,*N*-dimetilformamida (5 ml) a 0°C en una atmósfera de nitrógeno. La reacción se calentó a temperatura ambiente y se agitó durante 12 horas. La mezcla de reacción se inactivó por la adición de agua (50 ml) y la fase acuosa se extrajo con acetato de etilo (3x30 ml). Las fases orgánicas reunidas se secaron sobre sulfato de magnesio, se filtraron y se concentraron a presión

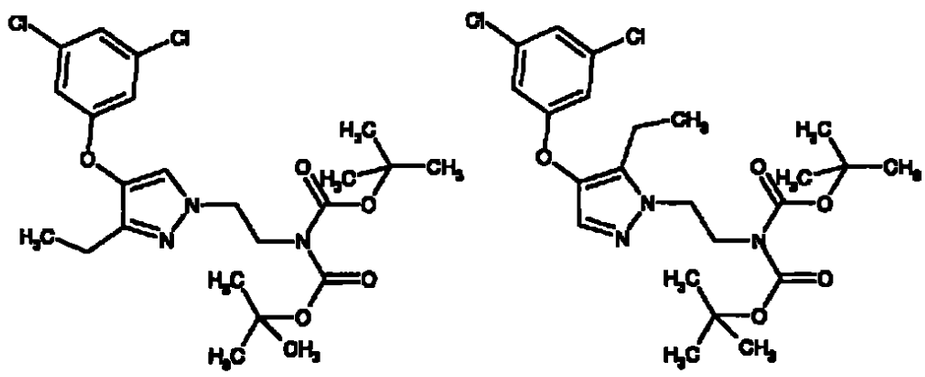
reducida, dando un aceite pardo. El producto bruto se purificó por cromatografía en columna ultrarrápida sobre gel de sílice eluyendo pentano:acetato de etilo (80:20, en volumen), proporcionando el compuesto del título (60 mg) en forma de un aceite incoloro.

^{1}H-RMN (400 MHz, $CDCl_3$): δ = 0,02 (s, 6H), 0,85 (s, 9H), 1,19 (d, 6H), 2,09 (s, 3H), 2,79 (sept, 1H), 3,99 (m, 2H), 4,10 (m, 2H), 7,39 (s, 2H), 7,57 (s, 1H).

LRMS (electronebulización): m/z [MH^+] 425.

PREPARACIÓN 26

2-[4-(3,5-Diclorofenoxi)-3-etil-1*H*-pirazol-1-il]etilimidodicarbonato de di(*terc*-butilo) y 2-[4-(3,5-diclorofenoxi)-5-etil-1*H*-pirazol-1-il]etilimidodicarbonato de di(*terc*-butilo)



Se añadieron en porciones dicarbonato de di-t-butilo (14,0 g, 64,2 mmol) y 4,4-dimetilaminopiridina (630 mg, 5,14 mmol) a una solución agitada de las aminas del Ejemplo 283

(7,72 g, 25,7 mmol) en acetonitrilo (128 ml) a temperatura ambiente en una atmósfera de nitrógeno. La reacción se agitó durante 14 horas y se concentró a presión reducida. Una solución del residuo en diclorometano (300 ml) se lavó con agua (100 ml), se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida. El producto bruto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol (99:1, en volumen), produciendo los compuestos del título (12,3 g) en una relación de regioisómeros de 85:15 en forma de un aceite incoloro.

^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,15 (principal, t, 3H), 1,15 (minoritario, t, 3H), 1,52 (principal, s, 18H), 1,52 (minoritario, s, 18H), 2,47 (principal, q, 2H), 2,56 (minoritario, q, 2H), 4,00 (principal, t, 2H), 4,00 (minoritario, t, 2H), 4,24 (principal, t, 2H), 4,24 (minoritario, t, 2H), 6,85 (principal, s, 2H), 6,85 (minoritario, s, 2H), 7,00 (principal, s, 1H), 7,00 (minoritario, s, 1H), 7,21 (principal, s, 1H), 7,25 (minoritario, s, 1H).

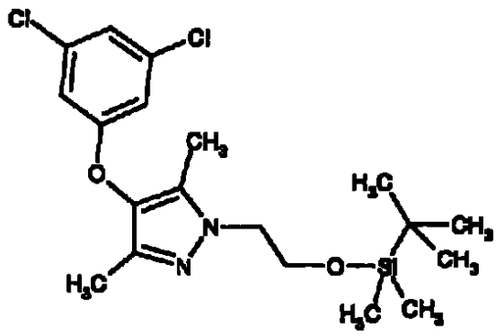
LRMS (termonebulización): m/z [MH^+] 500.

Microanálisis: Encontrado: C, 54,94; H, 6,26; N, 8,27. $C_{23}H_{31}Cl_2N_3O_5$ requiere C, 55,20; H, 6,24; N, 8,40%.

PREPARACIÓN 27

1-(2-{[*terc*-Butil(dimetil)silil]oxi}etil)-4-(3,5-

diclorofenoxi)-3,5-dimetil-1*H*-pirazol



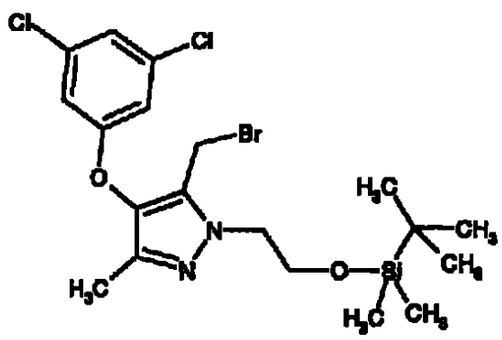
Se añadió en una porción cloro-t-butildimetilsilano (1,93 g, 12,8 mmol) a una solución agitada del pirazol del Ejemplo 1 (3,50 g, 11,6 mmol) e imidazol (1,03 g, 15,1 mmol) en *N,N*-dimetilformamida (23 ml) a temperatura ambiente en una atmósfera de nitrógeno. La reacción se agitó durante 2 días y se añadió agua (200 ml). La fase acuosa se extrajo con dietil éter (3x200 ml) y las fases orgánicas reunidas se lavaron con agua (2x50 ml) y salmuera (2x50 ml), se secaron sobre sulfato de magnesio, se filtraron y se concentraron a presión reducida. El producto bruto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con pentano:acetato de etilo (80:20, en volumen), proporcionando el compuesto del título (4,82 g) en forma de un aceite incoloro.

^{1}H-RMN (400 MHz, $CDCl_3$): δ = 0,09 (s, 6H), 0,78 (s, 9H), 2,01 (s, 3H), 2,05 (s, 3H), 3,88 (q, 2H), 4,02 (q, 2H), 6,76 (s, 2H), 6,88 (s, 1H).

LRMS (termonebulización): m/z [MH^+] 415.

PREPARACIÓN 28

5-(Bromometil)-1-(2-{[*terc*-butil(dimetil)silil]oxi}etil)-4-(3,5-diclorofenoxi)-3-metil-1*H*-pirazol.



Se añadió N-bromosuccinimida (640 mg, 3,60 mmol) a una solución agitada del pirazol de la Preparación 27 (1,00 g, 2,40 mmol) en tetracloruro de carbono (15 ml) y azobisisobutironitrilo (20 mg) a temperatura ambiente en una atmósfera de nitrógeno. La reacción se calentó a reflujo durante 5 horas, después se enfrió a temperatura ambiente y se filtró. El filtrado se concentró a presión reducida y el producto bruto se purificó por cromatografía en columna ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco (97:2,5:0,5, en volumen), proporcionando el compuesto del título (300 mg) en forma de un aceite incoloro.

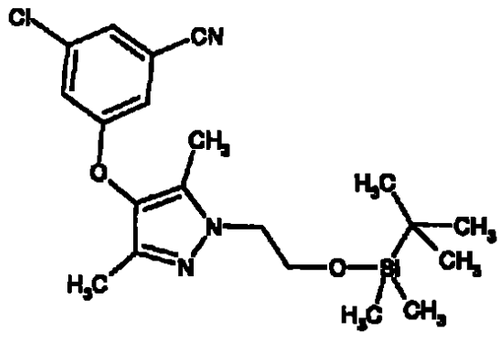
^{1}H-RMN (300 MHz, $CDCl_3$): δ = 0,04 (s, 6H), 0,82 (s, 9H), 2,02 (s, 3H), 3,96 (m, 2H), 4,22 (m, 2H), 4,41 (s, 2H), 6,81 (s,

2H), 7,01 (s, 1H).

LRMS (termonebulización): m/z [MH^+] 495.

PREPARACIÓN 29

3-{[1-(2-{[*terc*-Butil(dimetil)silil]oxi}etil)-3,5-dimetil-1*H*-pirazol-4-il]oxi}-5-clorobenzonitrilo



Se añadió en una porción cloro-t-butildimetilsilano (2,78 g, 18,5 mmol) a una solución agitada del pirazol del Ejemplo 114 (4,89 g, 16,8 mmol) e imidazol (1,48 g, 21,8 mmol) en *N*,*N*-dimetilformamida (30 ml) a temperatura ambiente en una atmósfera de nitrógeno. La reacción se agitó durante 3 días y se añadió agua (200 ml). La fase acuosa se extrajo con dietil éter (3x200 ml) y las fases orgánicas reunidas se lavaron con agua (2x50 ml) y salmuera (2x50 ml), se secaron sobre sulfato de magnesio, se filtraron y se concentraron a presión reducida. El producto bruto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano, proporcionando el compuesto del título (5,60 g) en forma de un aceite amarillo.

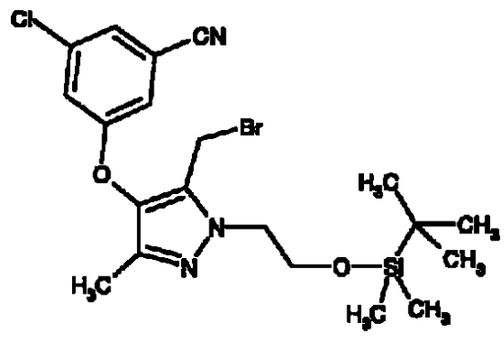
^{1}H-RMN (400 MHz, $CDCl_3$): δ = -0,02 (s, 6H), 0,82 (s, 9H), 2,02 (s, 3H), 2,12 (s, 3H), 3,97 (q, 2H), 4,06 (m, 2H), 7,02 (s, 1H), 7,11 (s, 1H), 7,24 (s, 1H).

LRMS (termonebulización): m/z [MH^+] 408.

Microanálisis: Encontrado: C, 58,95; H, 6,96; N, 10,22. $C_{20}H_{28}N_3O_2ClSi$ requiere C, 59,13; H, 6,95: N, 10,35%.

PREPARACIÓN 30

3-{[5-(Bromometil)-1-(2-{[*terc*-butil(dimetil)silil]oxi}etil)-3-metil-1*H*-pirazol-4-il]oxi}-5-clorobenzonitrilo



Se añadió *N*-bromosuccinimida (2,44 g, 13,7 mmol) a una solución agitada del pirazol de la Preparación 29 (5,56 g, 13,7 mmol) en tetracloruro de carbono (50 ml) y azobisisobutironitrilo (20 mg) a temperatura ambiente en una atmósfera de nitrógeno. La reacción se calentó a reflujo durante 1 hora, se enfrió a temperatura ambiente y se concentró a presión reducida. El producto bruto se purificó por cromatografía en columna ultrarrápida sobre gel de sílice eluyendo con pentano:acetato de diclorometano (75:25, en

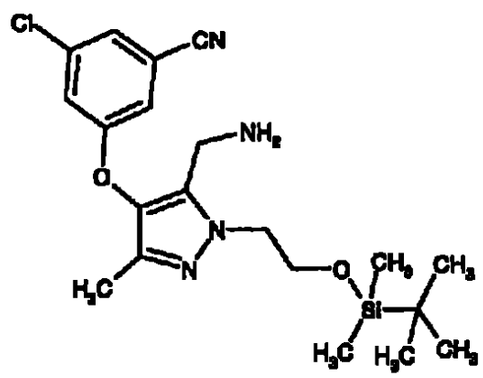
volumen), proporcionando el compuesto del título (3,00 g) en forma de un aceite incoloro.

^{1}H-RMN (300 MHz, $CDCl_3$): δ = -0,02 (s, 6H), 0,83 (s, 9H), 2,04 (s, 3H), 3,97 (q, 2H), 4,25 (m, 2H), 4,43 (s, 2H), 7,09 (s, 1H), 7,18 (s, 1H), 7,33 (s, 1H).

LRMS (termonebulización): m/z [MH^+] 486.

PREPARACIÓN 31

3-{[5-(Aminometil)-1-(2-{[*terc*-butil(dimetil)silil]oxi}etil)-3-metil-1*H*-pirazol-4-il]oxi}-5-clorobenzonitrilo



Se añadió el bromuro de la Preparación 30 (1,58 g, 3,26 mmol) se añadió a una solución saturada de amoniaco en isopropanol (50 ml) a 0°C. La reacción se agitó durante 6 horas y se dejó calentar lentamente a temperatura ambiente. La mezcla se concentró a presión reducida y el aceite amarillo resultante se disolvió en diclorometano (50 ml). La solución se lavó con una solución acuosa 1 M de carbonato sódico (2x20 ml) y salmuera (20 ml), se secó sobre sulfato

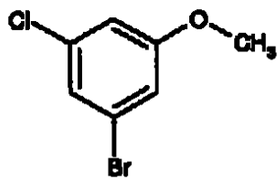
de magnesio, se filtró y se concentró a presión reducida, proporcionando el compuesto del título (1,00 g) en forma de un aceite amarillo.

^{1}H-RMN (300 MHz, $CDCl_3$): δ = -0,23 (S, 6H), 0,62 (s, 9H), 1,22 (s, 2H), 1,82 (s, 3H), 2,56 (s, 2H), 3,78 (m, 2H), 4,02 (m, 2H), 6,85 (s, 1H), 6,96 (s, 1H), 7,06 (s, 1H).

LRMS (termonebulización): m/z [MH^+] 421.

PREPARACIÓN 32

1-Bromo-3-cloro-5-metoxibenceno



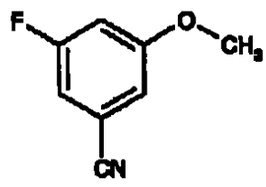
Se añadió gota a gota metóxido sódico (2,20 ml de una solución 4,5 M en metanol, 10,0 mmol) a una solución agitada de 1-fluoro-3-cloro-5-bromobenceno (1,00 g, 4,77 mmol) en metanol (28 ml) a temperatura ambiente en una atmósfera de nitrógeno. La reacción se calentó a reflujo durante 3 días y se enfrió a temperatura ambiente. La mezcla se concentró a presión reducida y el aceite amarillo resultante se disolvió en diclorometano (30 ml). La solución resultante se lavó con agua (2x20 ml) se secó sobre sulfato de magnesio se filtró y se concentró a presión reducida. El producto bruto se purificó por cromatografía en columna ultrarrápida sobre gel de sílice eluyendo con ciclohexano, proporcionando el

compuesto del título (302 mg) en forma de un aceite incoloro. ^{1}H-RMN (400 MHz, $CDCl_3$): δ = 3,77 (s, 3H), 6,82 (s, 1H), 6,94 (s, 1H), 7,09 (s, 1H).

Microanálisis: Encontrado: C, 37,94; H, 2,75. C_7H_6BrClO requiere C, 37,96; H, 2,73%.

PREPARACIÓN 33

3-Fluoro-5-metoxibenzonitrilo



Se añadió gota a gota metóxido sódico (1,50 ml de una solución 4,5 M en metanol, 7,10 mmol) a una solución agitada de 3,5-difluorobenzonitrilo (1,00 g, 7,10 mmol) en *N,N*-dimetilformamida (36 ml) a 0°C en una atmósfera de nitrógeno. La reacción se dejó calentar a temperatura ambiente y se agitó durante 14 horas. La reacción se diluyó con éter (40 ml), se lavó con agua (3x100 ml) y salmuera (100 ml), se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida. El producto bruto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con ciclohexano:acetato de etilo (95:5, en volumen), proporcionando el compuesto del título (418 mg) en forma de un aceite amarillo.

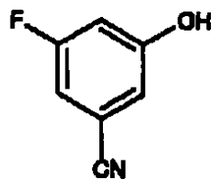
^{1}H-RMN (400 MHz, $CDCl_3$): δ = 3,84 (s, 3H), 6,82 (dd, 1H), 6,95 (dd, 1H), 6,96 (s, 1H).

LRMS (termonebulización): m/z [MNH_4^+] 169.

Microanálisis: Encontrado: C, 63,46; H, 3,95; N, 9,14.C_8H_6NOF requiere C, 63,58; H, 4,00; N, 9,27%.

PREPARACIÓN 34

3-Fluoro-5-hidroxibenzonitrilo



Se añadió gota a gota tricloruro de boro (1,65 ml de una solución 1,0 M en diclorometano, 1,65 mmol) a una solución agitada del nitrilo de la Preparación 33 (100 mg, 0,660 mmol) y yoduro de tetrabutilamonio (268 mg, 0,728 mmol) en diclorometano (3 ml) a -78°C. La reacción se dejó calentar a 0°C, se agitó durante 2 horas y después se dejó calentar a temperatura ambiente y se agitó durante 14 horas. La reacción se enfrió a 0°C, se inactivó cuidadosamente con hielo y después se concentró a presión reducida. El residuo se disolvió en éter (40 ml) y la solución resultante se lavó con agua (3x40 ml) y salmuera (40 ml), se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida. El producto bruto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con ciclohexano:acetato de etilo

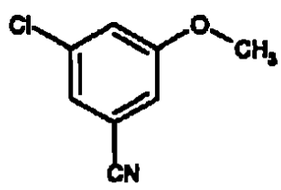
(90:10, en volumen), proporcionando el compuesto del título (50 mg) en forma de un sólido blanco, p.f. 138- 139°C.

^{1}H-RMN (300 MHz, $CDCl_3$): δ = 5,81 (s, 1H), 6,80 (dd, 1H), 6,94 (dd, 1H), 6,95 (s, 1H).

Microanálisis: Encontrado: C, 60,99; H, 3,01; N, 10,16. C_7H_4NOF requiere C, 61,32; H, 2,94; N, 10,22%.

PREPARACIÓN 35

3-Cloro-5-metoxibenzonitrilo



Se añadió en una porción tetraquis(trifenilfosfina) de paladio (174 mg, 0,150 mmol) a una solución agitada del bromuro de la Preparación 32 (500 mg, 2,26 mmol) y cianuro de cinc (146 mg, 1,24 mmol) en *N,N*-dimetilformamida (3 ml) a temperatura ambiente en una atmósfera de nitrógeno. La reacción se calentó a 100°C durante 14 horas y se enfrió a temperatura ambiente. La mezcla se concentró a presión reducida y el producto bruto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con ciclohexano:acetato de etilo (95:5, en volumen), proporcionando el compuesto del título (380 mg) en forma de un aceite amarillo.

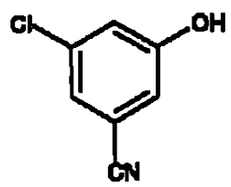
^{1}H-RMN (300 MHz, $CDCl_3$): δ = 3,82 (3H, s), 7,04 (s, 1H), 7,12

(s, 1H), 7,23 (s, 1H).

Microanálisis: Encontrado: C, 57,50; H, 3,63; N, 8,16. C_8H_6NOCl requiere C, 57,33; H, 3,61; N, 8,36%.

PREPARACIÓN 36

3-Cloro-5-hidroxibenzonitrilo



Se añadió gota a gota tricloruro de boro (26,0 ml de una solución 1,0 M en diclorometano, 26,0 mmol) a una solución agitada del nitrilo de la Preparación 35 (1,80 g, 10,0 mmol) y yoduro de tetrabutilamonio (4,36 g, 11,0 mmol) en diclorometano (50 ml) a -78°C. La reacción se dejó calentar a temperatura ambiente y se agitó durante 14 horas. La reacción se enfrió a 0°C, se inactivó cuidadosamente con hielo y se diluyó con diclorometano (100 ml). La fase orgánica se lavó con agua (3x40 ml) y salmuera (40 ml), se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida. El producto bruto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con con ciclohexano:acetato de etilo (80:20, en volumen), proporcionando el compuesto del título (900 mg) en forma de un sólido blanco.

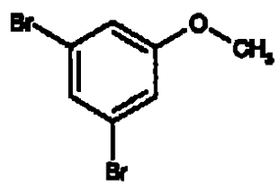
^{1}H-RMN (400 MHz, d_6DMSO): δ = 7,12 (m, 2H), 7,38 (s, 1H),

10,65 (s, 1H).

Microanálisis: Encontrado: C, 54,76; H, 2,81; N, 8,94. C_7H_4NOCl requiere C, 54,75; H, 2,63; N, 9,12%.

PREPARACIÓN 37

1,3-Dibromo-5-metoxibenceno



Se añadió gota a gota metóxido sódico (8,80 ml de una solución 4,5 M en metanol, 41,0 mmol) a una solución agitada de 3,5-dibromofluorobenceno (5,00 g, 19,0 mmol) en *N,N*-dimetilformamida (95 ml) a 0°C en una atmósfera de nitrógeno. La reacción se dejó calentar a temperatura ambiente, se agitó durante 1 hora y después se concentró a presión reducida. El residuo se disolvió en éter y la solución resultante se lavó con agua (3x300 ml) y salmuera (300 ml), se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida, proporcionando el compuesto del título (5,13 g) en forma de un sólido blanco.

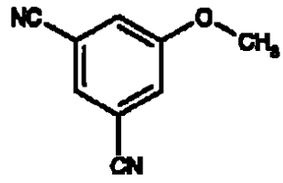
^{1}H-RMN (300 MHz, $CDCl_3$): δ = 3,79 (s, 3H), 7,00 (s, 2H), 7,26 (s, 1H).

LRMS (termonebulización): m/z [MH^+] 266.

Microanálisis: Encontrado: C, 31,56; H, 2,29. $C_7H_6OBr_2$ requiere C, 31,62; H, 2,27%.

PREPARACIÓN 38

3,5-Dicianometoxibenceno

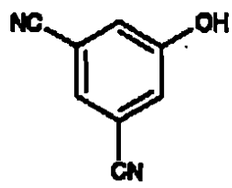


Se añadió en una porción tris(dibencilidenoacetona)-dipaladio (6,53 g, 7,15 mmol) a una solución agitada del bromuro de la Preparación 37 (38,0 g, 143 mmol) y cianuro de cinc (20,0 g, 172 mmol) en *N,N*-dimetilformamida (300 ml) a temperatura ambiente en una atmósfera de nitrógeno. La reacción se calentó a 100°C durante 14 horas y se enfrió a temperatura ambiente. Se añadió agua (1500 ml) y la mezcla se extrajo con acetato de etilo (3x500 ml). Los extractos orgánicos reunidos se filtraron y el filtrado se lavó con agua (500 ml), se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida. El sólido resultante se trituró con tolueno (1000 ml), proporcionando el compuesto del título (18,0 g) en forma de un sólido castaño.

^{1}H-RMN (300 MHz, $CDCl_3$): δ = 3,83 (3H, s), 7,31 (2H, s), 7,48 (1H, s).

PREPARACIÓN 39

3,5-Dicianohidroxibenceno

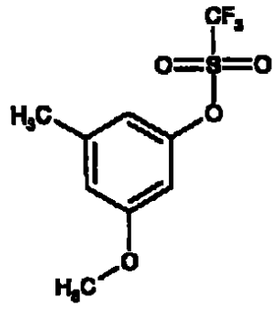


Se añadió en porciones el nitrilo de la Preparación 38 (9,60 g, 60,7 mmol) a una suspensión agitada de tricloruro de aluminio (32,4 g, 243 mmol) en diclorometano (250 ml) a 0°C en una atmósfera de nitrógeno. La suspensión se calentó a 45°C y se agitó durante 6 días. La reacción se enfrió a temperatura ambiente y se vertió cuidadosamente en hielo (450 ml). Se añadió gota a gota ácido clorhídrico concentrado (450 ml) y la suspensión resultante se agitó durante 10 minutos a temperatura ambiente. El sólido resultante se recogió por filtración, se lavó con agua y se secó sobre pentóxido de fósforo, proporcionando el compuesto del título (7,83 g) en forma de un sólido castaño que contenía aproximadamente un 11% de material de partida según mostraron la ^{1}H-RMN y el microanálisis.

^{1}H-RMN (400 MHz, $CDCl_3$): δ = 7,36 (m, 2H), 7,56 (m, 1H).

PREPARACIÓN 40

Trifluorometanosulfonato de 3-metoxi-5-metilfenilo

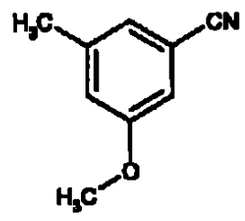


Se añadió gota a gota anhídrido trifluorometanosulfónico (2,02 ml, 12,0 mmol) a una solución agitada de 3-metoxi-5-metilfenol (1,50 g, 10,9 mmol) en piridina (20 ml) a -20°C en una atmósfera de nitrógeno. La reacción se calentó a 0°C, se agitó durante 90 minutos y se enfrió de nuevo a -20°C. Se añadió gota a gota más anhídrido trifluorometanosulfónico (1,01 ml, 6,00 mmol). La reacción se dejó calentar a temperatura ambiente, se agitó durante 14 horas y se vertió cuidadosamente en agua (100 ml). La fase acuosa se extrajo con éter (150 ml) y las fases orgánicas se lavaron con agua (3x75 ml), ácido clorhídrico 0,2 M (3x75 ml), una solución acuosa 1,0 M de carbonato sódico (2x75 ml), agua (75 ml) y salmuera (75 ml), se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida, proporcionando el compuesto del título (2,86 g) en forma de un aceite pardo pálido.

^{1}H-RMN (400 MHz, $CDCl_3$): δ = 2,35 (s, 3H), 3,80 (s, 3H), 6,60 (s, 1H), 6,68 (s, 1H), 6,73 (s, 1H).

PREPARACIÓN 41

3-Metoxi-5-metilbenzonitrilo



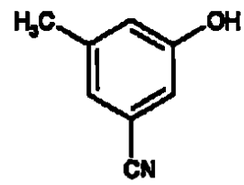
Se añadieron consecutivamente el triflato de la Preparación 40 (1,94 g, 7,10 mmol), dibromobis(trifenilfosfina)níquel (369 mg, 0,490 mmol), 1,1'bis(difenilfosfino)-ferroceno (331 mg, 0,590 mmol) y cianuro potásico (1,38 g, 21,3 mmol) a una suspensión agitada de cinc Rieke® (suministrado por la compañía química Aldrich, en forma de una suspensión, 5 g de cinc en 100 ml de tetrahidrofurano) (74 mg, 1,14 mmol) en acetonitrilo (4 ml) a temperatura ambiente. La reacción se calentó a 75°C durante 8 horas y después se enfrió a temperatura ambiente. La mezcla se repartió entre éter (200 ml) y agua (150 ml) y la fase orgánica se separó, se lavó con agua (2x100 ml) y salmuera (75 ml), se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida, dando un aceite pardo pálido. El producto bruto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con pentano:acetato de etilo (85:15, en volumen), proporcionando el compuesto del título (815 mg) en forma de un sólido blanco.

^{1}H-RMN (400 MHz, $CDCl_3$): δ = 2,34 (s, 3H), 3,80 (s, 3H), 6,93

(s, 1H), 6,94 (s, 1H), 7,04 (s, 1H).

PREPARACIÓN 42

3-Hidroxi-5-metilbenzonitrilo



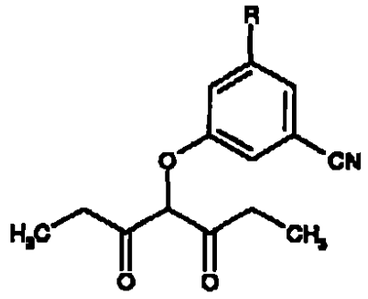
Se añadió gota a gota tricloruro de boro (17,6 ml de una solución 1,0 M en diclorometano, 17,6 mmol) a una solución agitada del nitrilo de la Preparación 41 (866 mg, 5,88 mmol) y yoduro de tetrabutilamonio (2,61 g, 7,05 mmol) en diclorometano (50 ml) a -78°C. La reacción se dejó calentar a temperatura ambiente y se agitó durante 20 minutos. La reacción se enfrió a 0°C, se inactivó cuidadosamente con hielo y se diluyó con diclorometano (100 ml). La fase orgánica se separó, se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida. El producto bruto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con pentano:acetato de etilo (50:50, en volumen), proporcionando el compuesto del título (677 mg) en forma de un sólido blanco.

^{1}H-RMN (400 MHz, $CDCl_3$): δ = 2,32 (s, 3H), 5,05 (s, 1H), 6,88 (s, 1H), 6,90 (s, 1H), 7,04 (s, 1H).

PREPARACIONES 43 A 46

Los compuestos de las siguientes Preparaciones indicados

en la tabla, de formula general:

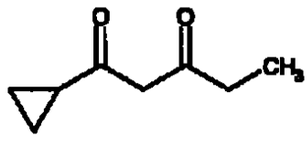


se prepararon por un procedimiento similar al de la Preparación 9 usando el apropiado material de partida de fenol y el cloruro de la Preparación 2.

Preparación No (Fenol No.)	R	LRMS	Datos Analíticos
43 (Preparación de Fenol 34)	F	m/z [MNH_4] 281 (termonebulización)	^{1}H-RMN (300 MHz, $CDCl_3$) δ = 1,05 (t 6H) 2,27 (q 4H) 6,89 (m 1H) 7,03 (s 1H) 7,04 (m 1H)
44 (Preparación de Fenol 42)	Me	m/z [M H] 258 (electronebulización)	^{1}H RMN (400 MHz $CDCl_3$) δ = 1,09 (t 6H) 2,32 (q 4H) 2 37 (s 3H) 6 96 (s 1H) 6,97 (s 1H) 7 15 (s 1H) 14,50 (s 1H)
45 (Preparación de Fenol 39)	CN	m/z [M-H] 269 (electronebulización)	^{1}H RMN (300 MHz $CDCl_3$) δ = 1,09 (m 6H) 2,30 (m 4H) 7 42 (s 2H) 7 61 (s 1H) 14,56 (s 1H)
46 (Preparación de Fenol 36)	Cl	m/z [M-H] 280 (termonebulización)	^{1}H RMN (400 MHz, $CDCl_3$) δ = 1,08 (m 6H) 2,31 (q 4H) 7 12 (s 1H) 7 19 (s 1H) 7,31 (s 1H)

PREPARACIÓN 47

1-Ciclopropil-1,3-pentanodiona



Una suspensión agitada de limaduras de magnesio (1,83 g, 75,0 mmol) en metanol (85 ml) se calentó a reflujo durante 90 minutos. La suspensión se enfrió a temperatura ambiente y se añadió una solución de ácido 3-cetopentanoico (17,4 g, 150,0 mmol) en metanol (15 ml). La suspensión blanca se disolvió, dando una solución amarilla pálida. La reacción se agitó a temperatura ambiente durante 1 hora y después se concentró a presión reducida, dando un sólido amarillo pálido que se disolvió en *N,N*-dimetilformamida (50 ml). En un matraz separado se añadió en porciones carbonildiimidazol (13,4 g, 83,0 mmol) a una solución agitada de ácido ciclopropanocarboxílico (6,46 g, 75,0 mmol) en *N,N*-dimetilformamida (150 ml) a temperatura ambiente en una atmósfera de nitrógeno. La reacción se agitó durante 90 minutos y después se añadió gota a gota la sal de magnesio preparada previamente. La reacción se agitó durante 3 días y después se vertió en ácido clorhídrico 1 M (150 ml). La fase acuosa se extrajo con éter (3x200 ml) y las fases orgánicas reunidas se secaron sobre sulfato de magnesio, se

filtraron y se concentraron a presión reducida. El producto bruto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con pentano:acetato de etilo (90:10, en volumen), proporcionando el compuesto del título (9,33 g) en forma de un aceite amarillo.

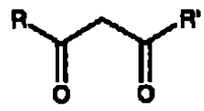
^{1}H-RMN (400 MHz, $CDCl_3$): estuvieron presentes formas ceto y enol, siendo el componente principal enol; señales enol δ = 1,00 (m, 7H), 1,60 (m, 1H), 2,25 (m, 2H), 5,59 (s, 1H), 15,62 (s, 1H); señales ceto δ = 1,00 (m, 7H), 2,01 (m, 1H), 2,52 (m, 2H), 3,68 (s, 2H).

LRMS (electronebulización): m/z [M-H$^+$] 139.

Microanálisis: Encontrado: C, 68,35; H, 8,72. $C_8H_{12}O_2$ requiere C, 68,55; H, 8,63%.

PREPARACIÓN 48

El compuesto de la siguiente Preparación indicado en la tabla, de formula general:

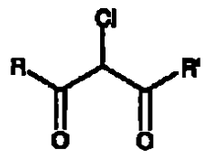


se preparó por un procedimiento similar al de la Preparación 47 usando el apropiado cetoácido y ácido carboxílico como materiales de partida.

Preparación No.	R	R	LRMS	Datos Analíticos
48	iPr	Et	m/z [M H] 141 (electronebulización)	^{1}H RMN (400 MHz, $CDCl_3$) estuvieron presentes formas ceto y enol siendo el componente principal enol δ = 1 12 (m 18H ceto y enol) 2 32 (m 4H ceto y enol) 2 49 (m 2H ceto y enol) 3,61 (s 2H ceto) 5 49 (s 1H enol) 15,52 (s 1H enol) Microanálisis Encontrado C 67 22 H 9 95 $C_9H_{14}O_2$ requiere C 67,57 H 9 92%

PREPARACIONES 49 A 51

El compuesto de la siguiente Preparación indicado en la tabla, de formula general:

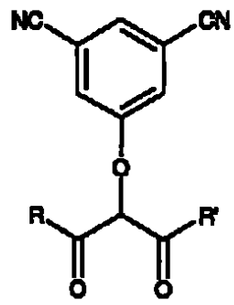


se preparó por un procedimiento similar al de la Preparación 42 usando el apropiado material de partida de dicetona.

Preparación No Diectona	R	R	LRMS	Datos Analíticos
49 (Preparación 47)	ciclopropilo	Et	m/z [M-H] 173 (electronebulización)	^{1}H RMN (400 MHz $CDCl_3$) δ = 1 10 (m 7H) 2,41 (m 1H) 2 61 (m 2H) 15 90 (s 1H)
50 (Diectona usada disponible en el mercado)	Me	Et	m/z [M-H] 166 (termonebulización)	^{1}H-RMN (300 MHz, $CDCl_3$) δ = 1 19 (m 3H) 2 27 (s 3H) 2 67 (q 2H) 15,40 (s 1H)
51 (Preparación 48)	iPr	Et	m/z [M-H] 175 (electronebulización)	^{1}H RMN (400 MHz, $CDCl_3$) δ = 1 18 (m 9H) 2 64 (q 2H) 3 20 (m 1H) 15,80 (s 1H)

PREPARACIONES 52 A 54

El compuesto de la siguiente Preparación indicado en la tabla, de formula general:

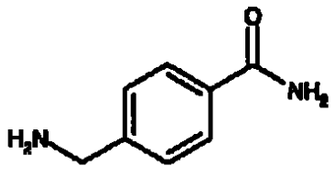


se preparó por un procedimiento similar al de la Preparación 9 usando el apropiado material de partida de dicetona y el fenol de la Preparación 39.

Preparación No Dicetona	R	R	LRMS	Datos Analíticos
52 (Preparación 49)	ciclopr	Et	m/z [M H] 282 (electronebulización)	^{1}H RMN (400 MHz, $CDCl_3$) δ = 0 93 (m 2H) 1 12 (t 3H) 1 21 (m 2H) 1 78 (m 1H) 2,29 (q 2H) 7,49 (s 2H) 7,61 (s 1H) 14 87 (s 1H)
53 (Preparación 19)	tBu	Me	m/z [MNH] 301 (termonebulización)	^{1}H RMN (400 MHz $CDCl_3$) δ = 1,08 (s 9H) 1,84 (s 3H) 7,30 (s 1H) 7,57 (s 2H) 15,42 (s 1H)
54 (Preparación 51)	iPr	Et	m/z [M H] 283 (electronebulización)	^{1}H-RMN (400 MHz $CDCl_3$) δ = 1 03 (m 9H) 2 23 (q 2H) 2,58 (m 1H) 7,41 (s 2H) 7,59 (s 1H) 14,63 (s 1H)

PREPARACIÓN 55

4-(Aminometil)benzamida



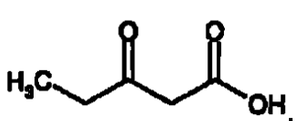
Se añadió en una porción hidróxido potásico en polvo (340 mg, 6 mmol) a una solución agitada de 4-(aminometil)benzonitrilo (200 mg, 1,5 mmol) en 2-metil-2-propanol (20 ml) a reflujo en una atmósfera de nitrógeno. La reacción se calentó a reflujo durante 30 minutos y se enfrió a temperatura ambiente. La mezcla se concentró a presión reducida y el producto bruto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco (95:5:0,5, en volumen), proporcionando el compuesto del título (150 mg) en forma de un sólido blanco.

^{1}H-RMN (300 MHz, CD_3OD): δ = 3,85 (s, 2H), 7,43 (d, 2H), 7,82 (d, 2H).

LRMS (termonebulización): m/z [MH^+] 151.

PREPARACIÓN 56

Ácido 3-oxopentanoico

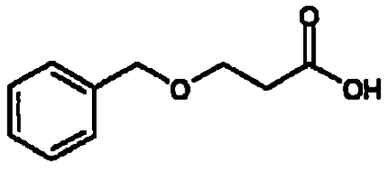


Se añadió por porciones hidróxido sódico (54 g, 1,35 mol) a una solución de metil éster del ácido 3-oxo-pentanoico (80 g, 0,62 mol) en tetrahidrofurano (300 ml) y agua (300 ml) a 0°C. La reacción se dejó calentar a temperatura ambiente y se agitó durante 18 horas. La mezcla de reacción se lavó con dietil éter (500 ml) y la fase acuosa se acidificó a pH 1 a 0°C con ácido clorhídrico concentrado (140 ml). La fase acuosa se extrajo con diclorometano (2x300 ml) y los extractos orgánicos reunidos se secaron sobre sulfato de magnesio y se concentraron a presión reducida, proporcionando el compuesto del título (44 g) en forma de un sólido blanco.

^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,12 (t, 3H), 2,59 (q, 2H), 3,49 (s, 2H).

PREPARACIÓN 57

Ácido 3-(benciloxi)propanoico



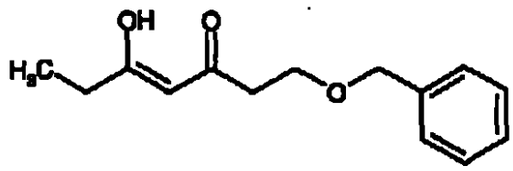
Se añadió sodio metálico (249 mg, 10,8 mmol) a alcohol bencílico (30 g, 278 mmol) a temperatura ambiente en una atmósfera de nitrógeno y la reacción se agitó durante 30 minutos. Después se añadió gota a gota acrilato de metilo (25,9 ml, 259 mmol) y la reacción se agitó a temperatura

ambiente durante 18h. Después de inactivar con una solución acuosa de cloruro amónico (200 ml), la mezcla se extrajo con acetato de etilo (2x300 ml) y los extractos orgánicos reunidos se lavaron con salmuera (100 ml), se secaron sobre sulfato de magnesio y se concentraron a presión reducida. El aceite residual se disolvió en etanol (300 ml) y se añadió gota a gota una solución acuosa 1 M de hidróxido sódico (300 ml). Después de 3 horas, el etanol se retiró a presión reducida y el residuo acuoso se lavó con diclorometano (200 ml). La fase acuosa después se acidificó con ácido clorhídrico acuoso 2N (150 ml), se extrajo con diclorometano (2x250 ml) y los extractos orgánicos reunidos se secaron sobre sulfato de magnesio y se concentraron a presión reducida. El aceite residual se disolvió en una solución acuosa al 10% de carbonato potásico (300 ml), se lavó con dietil éter (300 ml) y la fase acuosa se acidificó a pH 1 usando ácido clorhídrico concentrado. La mezcla después se extrajo con diclorometano (2x300 ml) y los extractos orgánicos reunidos se secaron sobre sulfato de magnesio y se concentraron a presión reducida, proporcionando el compuesto del título (44,4 g) en forma de un aceite incoloro.

^{1}H-RMN (300 MHz, $CDCl_3$): δ = 2,67 (t, 2H), 3,89 (t, 2H), 4,58 (s, 2H), 7,18 (m, 5H).

PREPARACIÓN 58

(4Z)-1-(Benciloxi)-5-hidroxi-4-hepten-3-ona



Una suspensión de limaduras de magnesio (1,74 g, 71,6 mmol) en metanol (85 ml) se calentó a reflujo en una atmósfera de nitrógeno durante 1,5 horas, se enfrió a temperatura ambiente y se añadió el β-ceto ácido de la Preparación 56 (16,6 g, 143 mmol). La reacción se agitó durante 1,5 horas y el disolvente se retiró a presión reducida, dando la sal de magnesio del ácido en forma de un sólido blanco. Mientras tanto, el ácido de la Preparación 57 (12,9 g, 71,6 mmol) se disolvió en dimetilformamida (150 ml) y se añadió en porciones carbonildiimidazol (12 g, 78,8 mmol) en una atmósfera de nitrógeno a temperatura ambiente. Ésto se agitó durante 1 hora y se añadió la sal de magnesio anterior como una solución en dimetilformamida (50 ml). Se apreció desprendimiento de gas y la reacción se dejó en agitación a temperatura ambiente durante 18 horas. La mezcla se concentró a presión reducida y el aceite naranja residual se disolvió en diclorometano (300 ml), se lavó con ácido clorhídrico acuoso 0,5 M (250 ml) que contenía metanol (10 ml) y la fase acuosa se separó y se extrajo con diclorometano (2x300 ml). Los extractos orgánicos reunidos se lavaron con salmuera (300 ml) que contenía metanol (20 ml), se secaron

sobre sulfato de magnesio y se concentraron a presión reducida. El aceite naranja residual se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con ciclohexano:acetato de etilo (80:20, en volumen), proporcionando el compuesto del título (12,0 g) en forma de un aceite naranja.

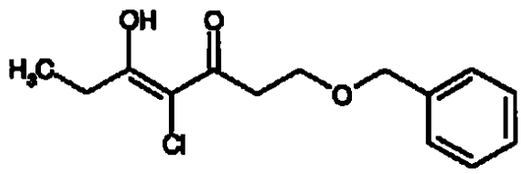
^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,17 (t, 3H), 2,33 (q, 2H), 2,58 (t, 2H), 3,76 (t, 2H), 4,53 (s, 2H), 5,57 (s, 1H), 7,13 (m, 5H).

LRMS (electronebulización) : m/z [MNa^+] 257.

Microanálisis: Encontrado C, 71,77; H, 7,74. $C_{14}H_{18}O_3$ requiere C, 71,76; H, 7,69%.

PREPARACIÓN 59

(4*E*)-1-(Benciloxi)-4-cloro-5-hidroxi-4-hepten-3-ona



Se añadió cloruro de trimetilsililo (10 ml, 51,3 mmol) a una solución del enol de la Preparación 58 (4,0 g, 17,1 mmol) en acetonitrilo (25 ml) en una atmósfera de nitrógeno a 0°C. Después se añadieron dimetilsulfóxido (3,6 ml, 51,3 mmol) seguido de bromuro de terc-butilamonio (275 mg, 0,85 mmol) y la reacción se agitó a 0°C durante 2 horas. La mezcla se diluyó con agua (100 ml), se extrajo con dietil éter (100

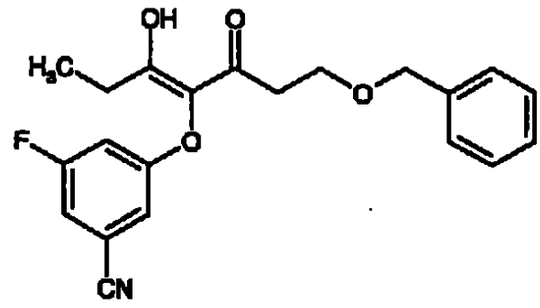
ml) y la fase orgánica se lavó con salmuera (50 ml), se secó sobre sulfato de magnesio y se concentró a presión reducida. El aceite rosa residual se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con ciclohexano:acetato de etilo (80:20, en volumen), proporcionando el compuesto del título (3,76 g) en forma de un aceite rosa.

^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,17 (t, 3H), 2,62 (q, 2H), 2,96 (t, 2H), 3,79 (t, 2H), 4,57 (s, 2H), 7,12 (m, 5H), 15,49 (s, 1H).

LRMS (electronebulización) : m/z [MNa^+] 291.

PREPARACIÓN 60

3-({(1*E*)-1-[3-(benciloxi)propanoil]-2-hidroxi-1-butenil}oxi)-5-fluorobenzonitrilo



Se añadió hidruro sódico (dispersión en aceite al 60%, 1,92 g, 48,0 mmol) a una solución agitada del fenol de la Preparación 34 (8,80 g, 48,0 mmol) en tetrahidrofurano (450 ml) en una atmósfera de nitrógeno a temperatura ambiente. Después de agitar durante 1 hora, se añadió el enol de la

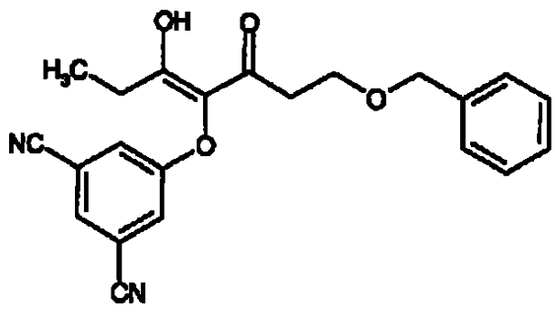
Preparación 59 (12,9 g, 48,0 mmol) y la reacción se agitó durante 64 horas. La mezcla se diluyó con agua (200 ml) y ácido clorhídrico acuoso 2 N (40 ml), se extrajo con acetato de etilo (2x150 ml) y los extractos orgánicos reunidos se lavaron con salmuera (100 ml), se secaron sobre sulfato de magnesio y se concentraron a presión reducida. El aceite naranja residual se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con ciclohexano:pentano (10:90, en volumen), proporcionando el compuesto del título (5,80 g) en forma de un aceite naranja.

^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,08 (t, 3H), 2,31 (q, 2H), 2,59 (t, 2H), 3,75 (t, 2H), 4,45 (s, 2H), 6,92 (m, 1H), 7,02 (m, 2H), 7,29 (m, 5H), 14,50 (s, 1H).

LRMS (electronebulización) : m/z [MNa^+] 392.

PREPARACIÓN 61

5-({(1*E*)-1-[3-(Benciloxi)propanol]-2-hidroxi-1-butenil}oxi)isoftalonitrilo



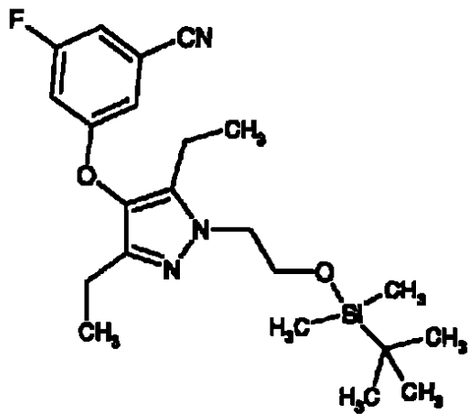
Se añadió hidruro sódico (dispersión en aceite al 60%,

412 mg, 12,3 mmol) a una solución agitada del fenol de la Preparación 39 (1,48 g, 10,3 mmol) en tetrahidrofurano (70 ml) en una atmósfera de nitrógeno a temperatura ambiente. Después de agitar durante 30 minutos, se añadió el enol de la Preparación 59 (2,76 g, 1,03 mmol) y la reacción se agitó durante 18 horas. Se añadieron cuidadosamente agua (100 ml) y ácido clorhídrico acuoso 2 N (10 ml) y la mezcla se extrajo con acetato de etilo (2x150 ml). Los extractos orgánicos se combinaron, se lavaron con salmuera (100 ml), se secaron sobre sulfato de magnesio y se concentraron a presión reducida. El residuo se purificó por cromatografía en columna ultrarrápida sobre gel de sílice eluyendo con (pentano:acetato de etilo 90:10, en volumen), proporcionando el compuesto del título (1,00 g) en forma de un aceite amarillo.

LRMS (termonebulización) : m/z [MH^+] 375.

PREPARACIÓN 62

3-{[1-(2-{[*terc*-Butil(dimetil)silil]oxi}etil)-3,5-dietil-1*H*-pirazol-4-il]oxi}-5-fluorobenzonitrilo



Se añadieron secuencialmente imidazol (477 mg, 7,02 mmol y cloruro de terc-butil-dimetil-sililo (977 mg, 6,48 mmol) a una solución del alcohol del Ejemplo 117 (1,65 g, 5,40 mmol) en dimetilformamida (11 ml) a temperatura ambiente en una atmósfera de nitrógeno. La reacción se agitó durante 18 horas y la mezcla se diluyó con agua (100 ml) y se extrajo con dietil éter (4x50 ml). Los extractos orgánicos reunidos se secaron sobre sulfato de magnesio, se concentraron a presión reducida y el residuo se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano: metanol (99:1, en volumen), proporcionando el compuesto del título (2,12 g) en forma de un aceite incoloro.

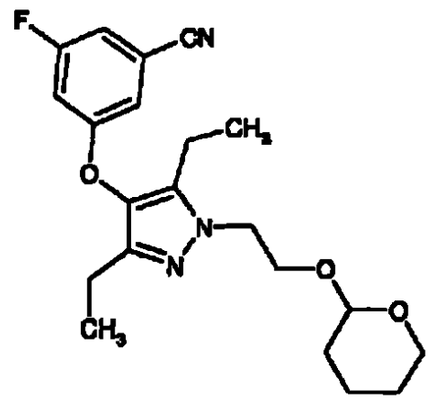
^{1}H-RMN (400 MHz, $CDCl_3$): δ = 0,03 (s, 6H), 0,84 (s, 9H), 1,10 (m, 6H), 2,42 (q, 2H), 2,56 (q, 2H), 4,00 (t, 2H), 4,09 (t, 2H), 6,86 (d, 1H), 6,99 (m, 2H).

LRMS (termonebulización) : m/z [MH^+] 419.

Microanálisis: Encontrado C, 62,73; H, 7,83; N, 9,75. $C_{22}H_{32}FN_3O_2Si.0,06CH_2Cl_2$ requiere C, 62,68; H, 7,66; N, 9,94%.

PREPARACIÓN 63

3-({3,5-Dietil-1-[2-(tetrahidro-2*H*-piran-2-iloxi)etil]-1*H*-pirazol-4-il}oxi)-5-fluorobenzonitrilo



Se añadió ácido p-tolueno-sulfónico (32 mg, 0,17 mmol) a una solución del alcohol del Ejemplo 117 (5,04 g, 16,6 mmol) y dihidropirano (7,57 ml, 83 mmol) en diclorometano (65 ml) a temperatura ambiente en una atmósfera de nitrógeno. La reacción se agitó durante 2 horas, pero quedaba material de partida, por lo que se añadió una alícuota más de ácido p-tolueno-sulfónico (284 mg, 1,49 mmol) y la reacción se agitó durante 1 hora. La mezcla se diluyó con dietil éter (90 ml) y se lavó con una solución acuosa mixta (agua (50 ml), salmuera (25 ml) y una solución acuosa saturada de bicarbonato sódico (25 ml)). La fase acuosa se extrajo con dietil éter (2x60 ml) y los extractos orgánicos reunidos se

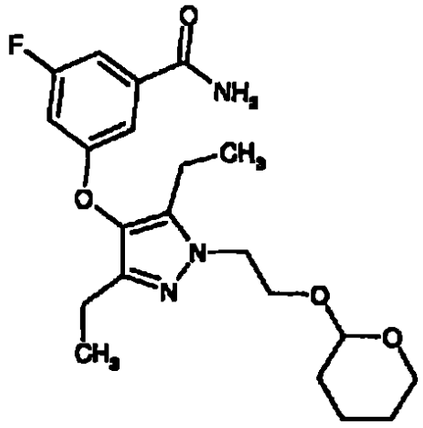
secaron sobre sulfato de magnesio, se concentraron a presión reducida y el residuo se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol (98:2, en volumen), proporcionando el compuesto del título (6,31 g) en forma de un aceite.

^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,08 (m, 6H), 1,52 (m, 6H), 2,39 (q, 2H), 2,54 (q, 2H), 3,45 (m, 1H), 3,64 (m, 1H), 3,75 (m, 1H), 4,06 (m, 1H), 4,17 (t, 2H), 4,51 (s, 1H), 6,82 (d, 1H), 7,22 (m, 2H).

LRMS (termonebulización) : m/z [MH^+] 388.

PREPARACIÓN 64

3-({3,5-Dietil-1-[2-(tetrahidro-2*H*-piran-2-iloxi)etil]-1*H*-pirazol-4-il}oxi)-5-fluorobenzamida



Se añadió carbonato de cesio (269 mg, 0,82 mmol) a una solución de 3-metil-3-pirazolin-5-ona (74 mg, 0,75 mmol) en dimetilsulfóxido (1 ml) en una atmósfera de nitrógeno a

temperatura ambiente y la reacción se agitó durante 15 minutos. Después se añadió el fluoruro de arilo de la Preparación 63 (291 mg, 0,75 mmol) disuelto en dimetilsulfóxido (1 ml) y la reacción se calentó a 100°C durante 18 horas. Después de enfriar a temperatura ambiente, la reacción se diluyó con agua (7 ml) y se extrajo con dietil éter (12 ml). La fase orgánica se lavó con salmuera (3,5 ml), se secó sobre sulfato de magnesio, se concentró a presión reducida y el residuo se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con un gradiente de disolventes de diclorometano:metanol (99:1 cambiando a 95:5, en volumen), proporcionando el compuesto del título no esperado (108 mg) en forma de un aceite.

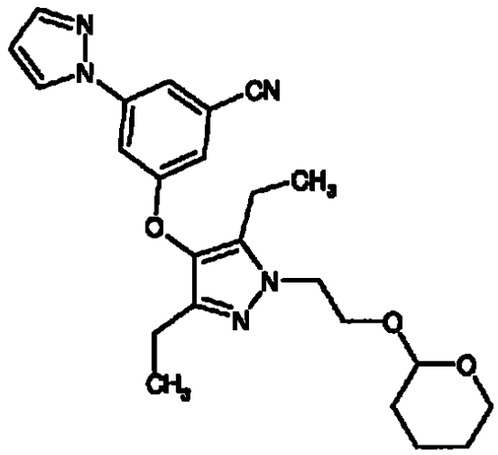
^{1}H-RMN (400 MHz, $CDCl_3$): δ = 1,12 (m, 6H), 1,56 (m, 6H), 2,44 (q, 2H), 2,59 (q, 2H), 3,48 (m, 1H), 3,69 (m, 1H), 3,79 (m, 1H), 4,08 (m, 1H), 4,20 (t, 2H), 4,54 (s, 1H), 6,72 (d, 1H), 7,15 (m, 2H).

LRMS (termonebulización) : m/z [MH^+] 406.

Microanálisis: Encontrado: C, 60,57; H, 6,97; N, 9,97. $C_{21}H_{28}FN_3O_4.0,08CH_2Cl_2.0,32H_2O$ requiere C, 60,57; H, 6,94; N, 10,05%.

PREPARACIÓN 65

3-({3,5-Dietil-1-[2-(tetrahidro-2*H*-piran-2-iloxi)etil]-1*H*-pirazol-4-il}oxi)-5-(1*H*-pirazol-1-il)benzonitrilo



Se añadió carbonato de cesio (269 mg, 0,82 mmol) a una solución de pirazol (51 mg, 0,75 mmol) en dimetilsulfóxido seco (1 ml) en una atmósfera de nitrógeno a temperatura ambiente y la reacción se agitó durante 15 minutos. Después se añadió el fluoruro de arilo de la Preparación 63 (291 mg, 0,75 mmol) disuelto en dimetilsulfóxido seco (1 ml) y la reacción se calentó a 100°C durante 18 horas. Después de la refrigeración a temperatura ambiente, la reacción se diluyó con agua (7 ml) y se extrajo con dietil éter (10 ml). La fase orgánica se lavó con salmuera (3 ml), se secó sobre sulfato de magnesio, se concentró a presión reducida y el residuo se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con un gradiente de disolventes de diclorometano:metanol (100:0 cambiando a 90:10, en volumen), proporcionando el compuesto del título (55 mg),

^{1}H-RMN (400MHz, $CDCl_3$): δ = 1,13 (m, 6H), 1,58 (m, 6H), 2,44

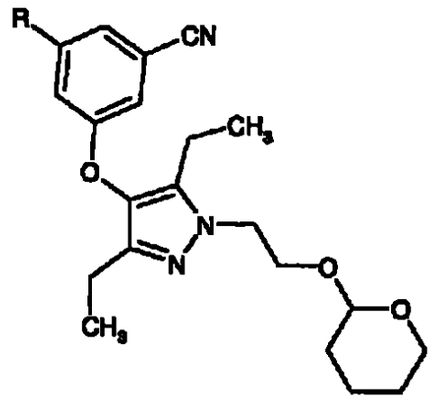
(q, 2H), 2,60 (q, 2H), 3,49 (m, 1H), 3,69 (m, 1H), 3,80 (m, 1H), 4,10 (m, 1H), 4,21 (t, 2H), 4,55 (s, 1H), 6,50 (s, 1H), 6,98 (s, 1H), 7,57 (s, 1H), 7,63 (s, 1H), 7,72 (s, 1H), 7,89 (s, 1H).

LRMS (termonebulización) : m/z [MH^+] 436, [MNa^+] 458.

HRMS: [MH^+] Encontrado 436,2352. $C_{24}H_{30}N_5O_3$ requiere 436,2343. [MNa^+] Encontrado 458,2168. $C_{24}H_{29}N_5O_3Na$ requiere 458,2162.

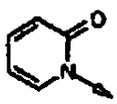
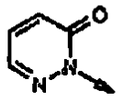
PREPARACIONES 66-68

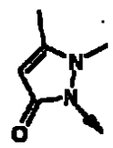
La preparación de las siguientes Preparaciones presentadas en la tabla, de fórmula general



se realizó por un procedimiento similar al de la Preparación 65, usando el heterociclo apropiado como material de partida.

Preparación No. (Material de partida, preparación no.)	R	Datos Analíticos

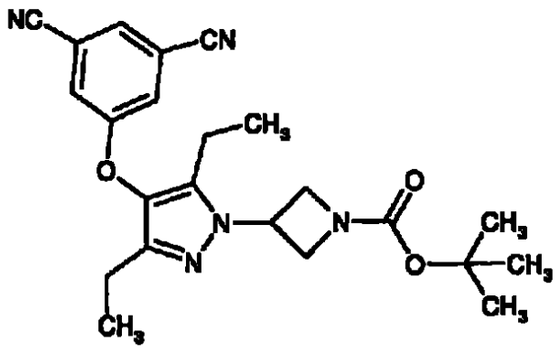
66 (63)		^{1}H RMN (400 MHz, $CDCl_3$): δ = 1,13 (m, 6H), 1,63 (m, 6H), 2,44 (q, 2H), 2,60 (q, 2H), 3,46 (m, 1H), 3,67 (m, 1H), 3,79 (m, 1H), 4,06 (m, 1H), 4,20 (t, 2H), 4,53 (s, 1H), 6,26 (t, 1H), 6,64 (d, 1H), 7,17 (s, 1H), 7,21 (s, 1H), 7,34 (s, 1H), 7,41 (t, 1H). LRMS (termoebulización) m/z [MH$^+$] 463, [MNa$^+$] 485. HRMS. [MH$^+$] Encontrado 463,2353. $C_{28}H_{31}N_2O_4$ requiere 463,2340 [MNa$^+$] Encontrado 485,2166. $C_{28}H_{30}N_2O_4Na$ requiere 485,2159.
67 (63)		^{1}H RMN (400 MHz, $CDCl_3$): δ = 1,10 (m, 6H), 1,56 (m, 6H), 2,41 (q, 2H), 2,56 (q, 2H), 3,44 (m, 1H), 3,64 (m, 1H), 3,75 (m, 1H), 4,05 (m, 1H), 4,27 (t, 2H), 4,50 (s, 1H), 7,00 (d, 1H), 7,06 (s, 1H), 7,20 (m, 1H), 7,31 (s, 1H), 7,64 (s, 1H), 7,86 (s, 1H). LRMS (termoebulización) . m/z [MH$^+$] 464, [MNa$^+$] 486. HRMS: [MH$^+$] Encontrado 464,2292. $C_{28}H_{30}N_3O_4$ requiere 464,2293 [MNa$^+$] Encontrado 486,2113. $C_{28}H_{29}N_3O_4Na$ requiere 486,2112

68[1] (63)		^{1}H RMN (400 MHz, $CDCl_3$): δ = 1.08 (m, 6H), 1.48 (m, 6H), 2.23 (s, 3H), 2.38 (q, 2H), 2.53 (q, 2H), 3.43 (m, 1H), 3.63 (m, 1H), 3.66 (s, 3H), 3.73 (m, 1H), 4.04 (m, 1H), 4.15 (t, 2H), 4.50 (s, 1H), 5.59 (s, 1H), 6.76 (s, 1H), 6.88 (s, 1H), 6.95 (s, 1H). LRMS (termonebulización) : m/z [MH$^+$] 480, [MNa$^+$] 502.

[1] El eluyente usado para la cromatografía en columna ultrarrápida de este compuesto fue diclorometano:metanol (99:1 cambiando a 95:5, en volumen).

PREPARACIÓN 69

3-[4-(3,5-Dicianofenoxi)-3,5-dietil-1*H*-pirazol-1-il]-1-azetidinocarboxilato de *terc*-butilo



Se añadió hidruro sódico (dispersión al 60% en aceite, 33 mg, 0,82 mmol) a una solución del pirazol del Ejemplo 122 (200 mg, 0,75 mmol) en dimetilformamida (3 ml) a 0°C en una atmósfera de nitrógeno y la reacción se agitó durante 10

minutos. Se añadió terc-butil éster del ácido 3-yodo-azetidina-1-carboxílico (234 mg, 0,82 mmol) y la reacción se agitó a temperatura ambiente durante 18 horas. La reacción se inactivó con agua (0,2 ml) y se concentró a presión reducida. El residuo se repartió entre diclorometano (5 ml) y agua (5 ml), la fase orgánica se aisló usando un cartucho vitrificado 5 µM Whatman PTFE, y después se concentró a presión reducida. El residuo se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con un gradiente de disolventes de acetato de etilo:pentano (20:80, después 25:75, después 34:66, después 50:50, después 75:25 y después 100:0, en volumen) cambiando a acetato de etilo:metanol (10:1, en volumen) y después a diclorometano:metanol:amoniaco 0,88 (90:10:1 y después 80:20:1, en volumen), proporcionando el compuesto del título (189 mg) en forma de un aceite amarillo pálido.

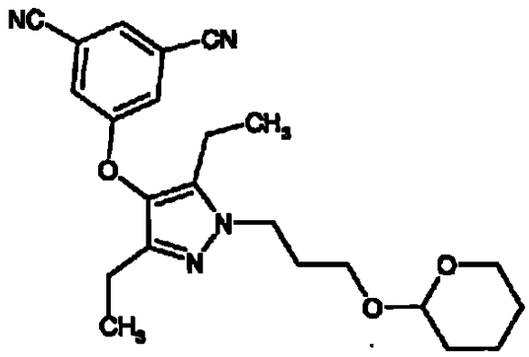
^{1}H RMN (400 MHz, $CDCl_3$): δ = 1,03-1,17 (m, 6H), 1,49 (s, 9H), 2,39-2,52 (m, 4H), 4,32 (m, 2H), 4,50 (m, 2H), 4,94 (m, 1H), 7,38 (s, 2H), 7,56 (s, 1H).

LRMS (termonebulización) : m/z [MH^+], 422, [MNa^+] 444.

Microanálisis: Encontrado C, 65,08; H, 6,49; N, 16,48. $C_{23}H_{27}N_5O_3.0,18.H_2O$ requiere C, 65,04; H, 6,49; N, 16,49%.

PREPARACIÓN 70

5-({3,5-Dietil-1-[3-(tetrahidro-2*H*-piran-2-iloxi)propil]-1*H*-pirazol-4-il}oxi)isoftalonitrilo



Se añadió hidruro sódico (dispersión al 60% en aceite, 33 mg, 0,82 mmol) a una solución del pirazol del Ejemplo 122 (200 mg, 0,75 mmol) en dimetilformamida (3 ml) a 0°C en una atmósfera de nitrógeno y la reacción se agitó durante 10 minutos. Se añadió 2-(3-bromo-propoxi)-tetrahidro-pirano (184 mg, 0,82 mmol) y la reacción se agitó a temperatura ambiente durante 18 horas. La reacción se inactivó con agua (0,2 ml) y se concentró a presión reducida. El residuo se repartió entre diclorometano (5 ml) y agua (5 ml), la fase orgánica se aisló usando un cartucho vitrificado 5 μM Whatman PTFE, y después se concentró a presión reducida. El residuo se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con un gradiente de disolventes de acetato de etilo:pentano (20:80, después 25:75, después 34:66, después 50:50, después 75:25 y después 100:0, en volumen) cambiando a acetato de etilo:metanol (10:1, en volumen) y después a diclorometano:metanol:amoniaco 0,88 (90:10:1 y después 80:20:1, en volumen), proporcionando el compuesto del título

(238 mg) en forma de un aceite amarillo pálido.

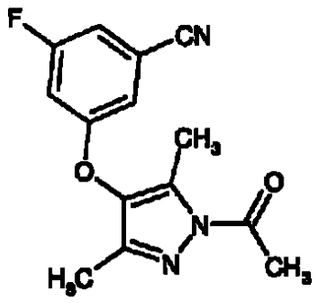
^{1}H RMN (400 MHz, $CDCl_3$): δ = 1,09 (m, 6H), 1,47-1,63 (m, 2H), 1,66-1,88 (m, 2H), 2,15 (dd, 2H), 2,38 (q, 2H), 2,53 (q, 2H), 3,37-3,55 (m, 2H), 3,75-3,90 (m, 2H), 4,11 (m, 2H), 4,56 (m, 1H), 7,37 (s, 2H), 7,55 (s, 1H).

LRMS (electro) : m/z [MH^+] 409, [MNa^+] 421.

Microanálisis: Encontrado C, 66,59; H, 6,91; N, 13,40, $C_{23}H_{28}N_4O_3.0,36H_2O$ requiere C, 66,57; H, 6,98; N, 13,50%.

PREPARACIÓN 71

3-[(1-Acetil-3,5-dimetil-1*H*-pirazol-4-il)oxi]-5-fluorobenzonitrilo



El fenol de la Preparación 34 (10,0 g, 72,7 mmol), 3-cloro-2,4-pentanodiona (7,10 g, 72,7 mmol) y carbonato de cesio (23,6 g, 72,9 mmol) se calentaron a reflujo en acetona (100 ml) en una atmósfera de nitrógeno durante 2 horas. La reacción se enfrió a temperatura ambiente, se añadió lentamente ácido clorhídrico acuoso 1 N (50 ml) y la mezcla se extrajo con acetato de etilo (3x100 ml). Los extractos orgánicos reunidos se secaron sobre sulfato de magnesio y se

concentraron a presión reducida. El aceite amarillo residual se disolvió en metanol (100 ml), se añadió hidrazina (5,3 ml, 109 mmol) y la reacción se agitó a temperatura ambiente en una atmósfera de nitrógeno durante 2 horas. El disolvente se retiró a presión reducida y el residuo se disolvió en dimetilformamida (50 ml) a 0°C. Se añadió lentamente cloruro de acetilo (5,1 ml, 72,0 mmol) seguido de hidruro sódico (dispersión al 60% en aceite, 2,8 g, 72,0 mmol) por porciones. La reacción se agitó durante 15 minutos, se añadió una solución saturada de cloruro amónico (50 ml), y la reacción se dejó calentar a temperatura ambiente. La mezcla se extrajo con acetato de etilo (3x100 ml) y los extractos orgánicos reunidos se secaron sobre sulfato de magnesio y se concentraron a presión reducida dando un aceite. Después de un período de reposo de 18 horas, se formó un sólido dentro del aceite, que se aisló por filtración, lavando con dietil éter (50 ml), proporcionando el compuesto del título (3,50 g) en forma de un sólido blanco, p.f. 109-111°C.

^{1}H RMN (400 MHz, $CDCl_3$): δ = 2,06 (s, 3H), 2,37 (s, 3H), 2,65 (s, 3H), 6,81 (d, 1H), 6,91 (s, 1H), 7,04 (d, 1H),

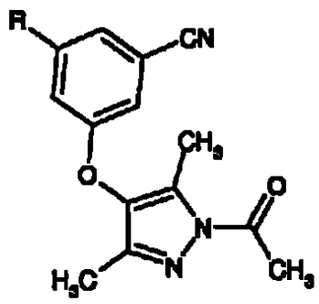
LRMS (termonebulización) : m/z [MH^+] 273.

Microanálisis: Encontrado C, 61,62; H, 4,44; N, 15,09, $C_{14}H_{12}N_3O_2F$ requiere C, 61,53; H, 4,43; N, 15,38%.

PREPARACIONES 72-74

Los compuestos presentados en la tabla, de fórmula

general



se realizaron por un procedimiento similar al de la Preparación 71, usando el fenol apropiado como material de partida.

Preparación No. (Material de partida, preparación no.)	R	Datos Analíticos
72 (39)	CN	p.f. 204-206°C ^{1}H RMN (400 MHz, $CDCl_3$): δ = 2.06 (s, 3H), 2.38 (s, 3H), 2.66 (s, 3H), 7.33 (s, 2H), 7.58 (s, 1H). LRMS (termonebulización) : m/z [MH$^+$] 281. Microanálisis: Encontrado C, 63.30; H, 4.25; N, 19.59. $C_{15}H_{12}N_4O_2.0.30H_2O$ requiere C, 63.06; H, 4.45; N, 19.61%.
73[1] (42)	Me	p.f. 152-154°C ^{1}H RMN (400 MHz, $CDCl_3$): δ = 2.05 (s, 3H), 2.33 (s, 3H), 2.38 (s, 3H), 2.66 (s, 3H), 6.88 (s, 1H), 6.91 (s, 1H), 7.12 (s,1H). LRMS (termonebulización) : m/z [MH$^+$] 270. Microanálisis: Encontrado C, 66.67; H, 5.71; N, 15.25. $C_{15}H_{15}N_3O_2$ requiere C, 66.9; H, 5.61; N, 15.60%.

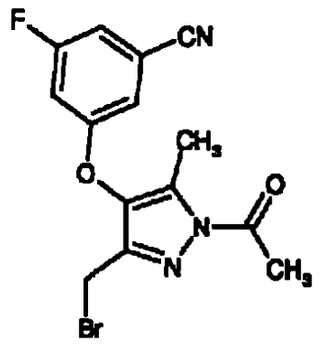
74[1] (comercial)	H	p.f. 131-133°C ^{1}H RMN (400 MHz, $CDCl_3$): δ = 2,13 (s, 3H), 2,40 (s, 3H), 2,70 (s, 3H), 7,15 (m, 2H), 7,35 (m, 1H), 7,40 (m, 1H). LRMS (termonebulización) : m/z [MH$^+$] 278. Microanálisis: Encontrado C, 65,87; H, 5,11; N, 16,33. $C_{14}H_{11}N_3O_2$ requiere C, 65,87; H, 5,13; N, 14,46%.

[1] El producto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con acetato de etilo:pentano (10:90, en volumen)

[2] El producto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con acetato de etilo:pentano (10:90 cambiando a 20:80, en volumen).

PREPARACIÓN 75

3-{[1-Acetil-3-(bromometil)-5-metil-1*H*-pirazol-4-il]oxi}-5-fluorobenzonitrilo



El pirazol de la Preparación 71 (1,00 g, 3,66 mmol) se disolvió en tetracloruro de carbono (20 ml) y la solución se

desgasificó burbujeando nitrógeno a su través durante 20 minutos a temperatura ambiente. Se añadieron *N*-bromosuccinimida (973 mg, 5,49 mmol) seguido de 2,2'-azobisisobutironitrilo (30 mg) y la reacción se calentó a 95°C durante 1 hora. La reacción se enfrió a temperatura ambiente, se concentró a presión reducida y se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con pentano:acetato de etilo (80:20, en volumen), proporcionando el compuesto del título (1,30 g) en forma de un aceite amarillo pálido.

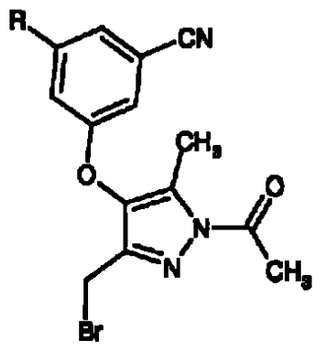
^{1}H RMN (400 MHz, $CDCl_3$): δ = 2,05 (s, 3H), 2,69 (s, 3H), 4,68 (s, 2H), 6,89 (d, 1H), 6,99 (s, 1H), 7,08 (d, 1H).

LRMS (termonebulización) : m/z [M-BrH$^+$] 272.

Microanálisis: Encontrado C, 45,08; H, 3,14; N, 11,44. $C_{14}H_{11}BrN_3O_2F.1,05H_2O$ requiere C, 45,31; H, 3,56; N, 11,32%.

PREPARACIONES 76-78

La preparación de las Preparaciones presentadas en la siguiente tabla, de fórmula general



se realizó por un procedimiento similar al de la Preparación 75, usando el pirazol apropiado como material de partida.

Preparación No. (Material de partida, preparación no.)	R	Datos Analíticos
76 (72)	CN	p.f. 132-134°C ^{1}H RMN (400 MHz, $CDCl_3$): δ = 2,06 (s, 3H), 2,66 (s, 3H), 4,67 (s, 2H), 7,40 (s, 2H), 7,63 (s, 1H). Microanálisis: Encontrado C, 47,65; H, 3,03; N, 14,79. $C_{13}H_{11}BrN_4O_2.0,93H_2O$ requiere C, 47,92; H, 3,45; N, 14,90%.
77[1,3] (73)	Me	p.f. 107-109°C ^{1}H RMN (400 MHz, $CDCl_3$): δ = 2,05 (s, 3H), 2,35 (s, 3H), 2,70 (s, 3H), 4,70 (s, 2H), 6,95 (s, 1H), 6,99 (s, 1H), 7,18 (s, 1H). Microanálisis: Encontrado C, 50,34; H, 3,89; N, 11,58. $C_{13}H_{13}BrN_2O_2.0,40H_2O$ requiere C, 50,69; H, 4,20; N, 11,82%.
78[1,3] (74)	H	p.f. 120-124°C ^{1}H RMN (400 MHz, $CDCl_3$): δ = 2,05 (s, 3H), 2,70 (s, 3H), 4,75 (s, 2H), 7,20 (m, 2H), 7,45 (m, 1H). Microanálisis: Encontrado C, 49,01; H, 3,47; N, 12,14. $C_{12}H_{11}BrN_2O_2.0,30H_2O$ requiere C, 49,00; H, 3,82; N, 12,24%.

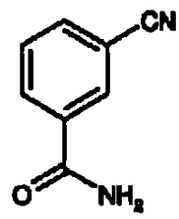
[1] A esta reacción se le añadió otra alícuota de 2,2'-azobisisobutironitrilo (30 mg) y se continuó el reflujo durante 2 horas más.

[2] El producto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con un gradiente de disolventes de acetato de etilo:pentano (0:100, después 2:98, después 5:95, después 10:90, después 15:85 y después 30:70, en volumen).

[2] El producto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con acetato de etilo:pentano (10:90 cambiando a 20:80, en volumen).

PREPARACIÓN 79

3-Cianobenzamida

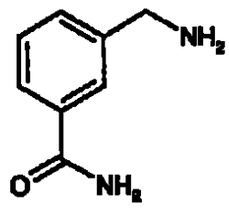


Se añadió lentamente solución de amoniaco 0,88 (30 ml) a una solución de cloruro de 3-cianobenzoílo (10 g, 60,3 mmol) en diclorometano (100 ml) a 0°C en una atmósfera de nitrógeno, y la reacción se agitó durante 20 minutos. La mezcla se filtró y el sólido se lavó con agua (50 ml) y después con dietil éter (50 ml), se destiló azeotrópicamente con tolueno y se secó al vacío, proporcionando el compuesto del título (9 g) en forma de un sólido blanco.

^{1}H RMN (400 MHz, CD_3OD): δ = 7,62 (m, 1H), 7,86 (m, 1H), 8,12 (m, 1H), 8,18 (s, 1H).

PREPARACIÓN 80

3-(Aminometil)benzamida

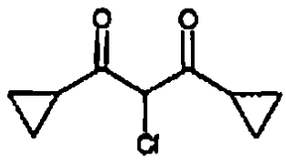


El nitrilo de la Preparación 79 (6,4 g, 43,8 mmol) se suspendió en ácido acético (60 ml) y se añadió paladio al 10% sobre carbono (100 mg). La reacción se sometió a una presión de 413,685 kPa a temperatura ambiente con hidrógeno y se agitó durante 18 horas. Quedaba material de partida, de forma que se añadió otra alícuota de paladio al 10% sobre carbono (500 mg) y se repitió el procedimiento. La mezcla de reacción se filtró a través de arbocel lavando con ácido acético y el filtrado se concentró a presión reducida. El residuo se destiló azeotrópicamente con tolueno y se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco 0,88 (100:0:0 cambiando a 90:10:1 y después 85:15:1,5, en volumen), proporcionando el compuesto del título (5,3 g) en forma de un aceite incoloro. ^{1}H RMN (400 MHz, CD_3OD): δ = 3,83 (s, 2H), 7,39 (dd, 1H), 7,49 (d, 1H), 7,73 (d, 1H), 7,81 (s, 1H).

PREPARACIÓN 81

2-Cloro-1,3-diciclopropil-1,3-propanodiona

524
527



Se añadió cloruro de trimetilsililo (16,6 ml, 130 mmol) a una solución de bromuro de terc-butilamonio (0,70 g, 2,17 mmol) en acetonitrilo (50 ml) en una atmósfera de nitrógeno a 0°C. Después se añadió 1,3-diciclopropil-propano-1,3-diona (ref: WO98155438) (6,62 g, 43,5 mmol) en acetonitrilo (15 ml) seguido de dimetilsulfóxido (9,25 ml, 130 mmol) gota a gota, y la reacción se dejó calentar a temperatura ambiente durante 4 horas. La mezcla se diluyó con agua (75 ml), se extrajo con dietil éter (3x35 ml) y los extractos orgánicos reunidos se secaron sobre sulfato de magnesio y se concentraron a presión reducida. El residuo se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con pentano:dietil éter (95:5, por volumen), proporcionando el compuesto del título (3,76 g) en forma de un aceite, que era una mezcla 80:20 de formas enol:ceto.

^{1}H RMN (400 MHz, $CDCl_3$): δ = 1,02 (m, 4H), 1,17 (m, 4H), 2,24 (m, 0,2H), 2,39 (m, 0,8H), 5,05 (s, 0,2H), 16,34 (s, 0,8H).

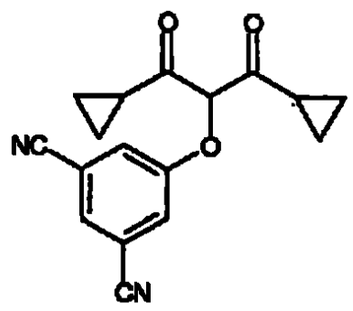
Microanálisis: Encontrado C, 57,59; H, 5,89. $C_9H_{11}ClO_2.0,02CH_2Cl_2$ requiere C, 57,92; H, 5,94.

PREPARACIÓN 82

5-[2-Ciclopropil-1-(ciclopropilcarbonil)-2-

525
528

oxoetillisoftalonitrilo



Se añadió carbonato de cesio (1,97 g, 6,06 mmol) a una solución agitada del fenol de la Preparación 39 (0,865 g, 6,00 mmol) en acetona (24 ml) en una atmósfera de nitrógeno a reflujo. Después de agitar durante 5 minutos, se añadió la dicetona de la Preparación 81 (1,12 g, 6,00 mmol) en acetona y la reacción se agitó durante 4 horas. Después de la refrigeración, la mezcla se diluyó con agua (25 ml) y la acetona se retiró a presión reducida. La fase acuosa se acidificó con ácido clorhídrico acuoso 2 N, se extrajo con diclorometano (50 ml) y la fase orgánica se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con un gradiente de disolventes de pentano:acetato de etilo (95:5 cambiando a 90:10 y después 80:20, en volumen), proporcionando el compuesto del título (1,03 g) en forma de un sólido blanco, que existía como el tautómero enol, p.f. 135-137°C.

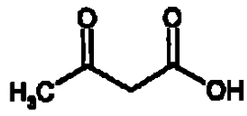
^{1}H RMN (400 MHz, $CDCl_3$): δ = 0,93 (m, 4H), 1,19 (m, 4H), 1,74 (m, 2H), 7,53 (s, 2H), 15,25 (s, 1H).

LRMS (electronebulización) : m/z [M-H$^+$] 293.

Microanálisis: Encontrado C, 69,18; H, 4,82; N, 9,35. $C_{17}H_{14}N_2O_3$ requiere C, 69,38; H, 4,79; N, 9,52%.

PREPARACIÓN 83

Ácido 3-oxobutanoico

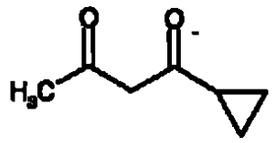


Se disolvió hidróxido sódico (37,9 g, 0,947 mol) en agua (770 ml) y se añadió a una solución de metil éster del ácido 3-oxo-butanoico (100 g, 0,861 mol) a temperatura ambiente durante 20 minutos. La reacción se agitó durante 18 horas, se inactivó con sulfato amónico (700 g) y se acidificó lentamente con una solución de ácido clorhídrico concentrado (21,5 ml) en agua (250 ml) con refrigeración en hielo. La mezcla de reacción se extrajo con dietil éter (6x200 ml) y los extractos orgánicos reunidos se secaron sobre sulfato de magnesio y se concentraron a presión reducida, proporcionando el compuesto del título (58,2 g) en forma de un aceite amarillo pálido que era una mezcla de los tautómeros ceto:enol.

^{1}H RMN (400 MHz, $CDCl_3$): δ = 2,00 (s, 3H-enol), 2,30 (s, 3H-ceto), 3,51 (s, 2H-ceto), 5,02 (s, 1 H-enol).

PREPARACIÓN 84

1-Ciclopropil-1,3-butanodiona



Se calentaron a reflujo limaduras de magnesio (3,04 g, 125 mmol) suspendidas en metanol (145 ml) en una atmósfera de nitrógeno durante 1 hora, se enfriaron a temperatura ambiente y se añadió gota a gota el β-cetoácido de la Preparación 83 (25,5 g, 250 mmol) disuelto en metanol (25 ml) con refrigeración en hielo. La reacción se agitó durante 1 hora a temperatura ambiente y el disolvente se retiró a presión reducida, dando la sal de magnesio del ácido. Mientras tanto, se disolvió ácido ciclopropano-carboxílico (9,91 ml, 125 mmol) en dimetilformamida (200 ml) y se añadió carbonildiimidazol (22,4 g, 138 mmol) por porciones en una atmósfera de nitrógeno a 0°C. Esta mezcla se agitó durante 1,5 horas y se añadió la sal de magnesio de antes como una solución en dimetilformamida (100 ml) a 0°C. La reacción se dejó en agitación a temperatura ambiente durante 92 horas y la mezcla se vertió en ácido clorhídrico acuoso 2 M (85 ml) y después se diluyó con agua (170 ml). La mezcla se extrajo con dietil éter (6x200 ml) y los extractos orgánicos reunidos se lavaron con salmuera (3x200 ml), se secaron sobre sulfato

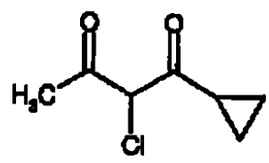
de magnesio y se concentraron a presión reducida. El aceite naranja residual se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con pentano:dietil éter (100:0 cambiando a 90:10 y después 80:20, en volumen), proporcionando el compuesto del título (7,39 g) en forma de un aceite amarillo.

^{1}H RMN (400 MHz, $CDCl_3$): δ = 0,83-0,95 (m, 2H), 1,06-1,10 (m, 2H), 1,54-1,63 (m, 1H), 2,00 (s, 3H).

LRMS (electronebulización) : m/z [MNa^+] 149.

PREPARACIÓN 85

2-Cloro-1-ciclopropil-1,3-butanodiona



Se añadió cloruro de trimetilsililo (18,9 ml, 174 mmol) a una solución de bromuro de terc-butilamonio (932 mg, 2,89 mmol) en acetonitrilo seco (50 ml) en una atmósfera de nitrógeno a temperatura ambiente, y la mezcla se enfrió a 0°C. Después se añadió la dicetona de la Preparación 84 (7,3 g, 57,9 mmol) en acetonitrilo (36 ml) seguida de la adición gota a gota de dimetilsulfóxido seco (12,3 ml, 174 mmol). La reacción se agitó a 0°C durante 1,5 horas y la mezcla se diluyó con agua (500 ml), se extrajo con dietil éter (2x200 ml y 100 ml) y los extractos orgánicos reunidos se secaron

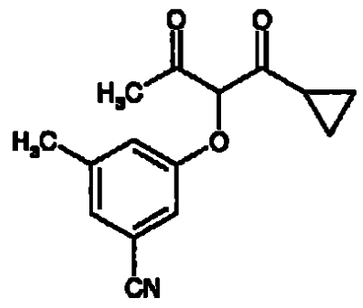
sobre sulfato sobre sulfato de magnesio y se concentraron a presión reducida. El aceite residual se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con pentano:dietil éter (100:0 cambiando a 95:5 y después 90:10, en volumen), proporcionando el compuesto del título (5,76 g) en forma de un aceite incoloro.

^{1}H RMN (400 MHz, $CDCl_3$): δ = 0,99-1,08 (m, 2H), 1,15-1,20 (m, 2H), 2,27 (s, 3H), 2,38-2,46 (m, 1H).

LRMS (electronebulización): m/z [M-H$^+$] 159.

PREPARACIÓN 86

3-[1-(Ciclopropilcarbonil)-2-oxopropoxi]-5-metilbenzonitrilo



Se añadieron carbonato de cesio (2,45 g, 8,30 mmol) y el fenol de la Preparación 42 (1 g, 7,50 mmol) a una solución agitada de la dicetona de la Preparación 85 (1,3 g, 8,30 mmol) en acetona (44 ml) en una atmósfera de nitrógeno a 60°C y la reacción se agitó durante 5 horas. Después de la refrigeración, la mezcla se inactivó con agua y la acetona se retiró a presión reducida. La fase acuosa se acidificó con ácido clorhídrico acuoso 1 N, se extrajo con acetato de etilo

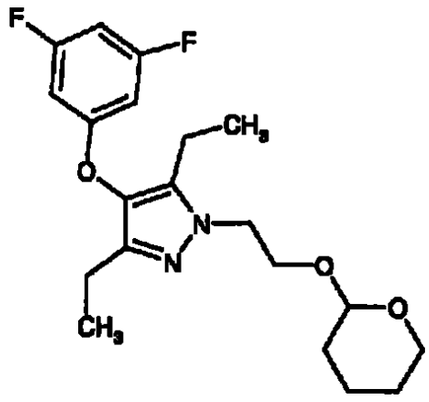
y la fase orgánica se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con pentano:acetato de etilo (85:15, en volumen), proporcionando el compuesto del título (1,03 g) en forma de un sólido rojo pálido.

^{1}H RMN (400 MHz, $CDCl_3$): δ = 0,85 (m, 2H), 1,12 (m, 2H), 1,86 (m, 1H), 1,94 (s, 3H), 2,35 (s, 3H), 6,99 (m, 2H), 7,10 (s, 1H).

LRMS (electronebulización) : m/z [M-H$^+$] 256.

PREPARACIÓN 87

4-(3,5-Difluorofenoxi)-3,5-dietil-1-[2-(tetrahidro-2*H*-piran-2-iloxi)etil]-1*H*-pirazol



Se añadió ácido p-tolueno sulfónico (360 mg, 1,89 mmol) a una solución del alcohol del Ejemplo 38 (5,6 g, 18,9 mmol) y dihidropirano (8,62 ml, 94,5 mmol) en diclorometano (75 ml) a temperatura ambiente en una atmósfera de nitrógeno. La

reacción se agitó durante 2 horas, se diluyó con dietil éter (100 ml) y se lavó con una solución acuosa mixta (agua (60 ml), salmuera (30 ml) y una solución acuosa saturada de bicarbonato sódico (30 ml)). La fase acuosa se extrajo con dietil éter (2x60 ml) y los extractos orgánicos reunidos se secaron sobre sulfato de magnesio, se concentraron a presión reducida y el residuo se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol (98:2, en volumen), proporcionando el compuesto del título (6,31 g) en forma de un aceite.

^{1}H RMN (400 MHz, $CDCl_3$): δ = 1,09 (m, 6H), 1,57 (m, 6H), 2,40 (q, 2H), 2,55 (q, 2H), 3,44 (m, 1H), 3,62 (m, 1H), 3,73 (m, 1H), 4,05 (m, 1H), 4,16 (t, 2H), 4,50 (s, 1H), 6,39 (m, 3H).

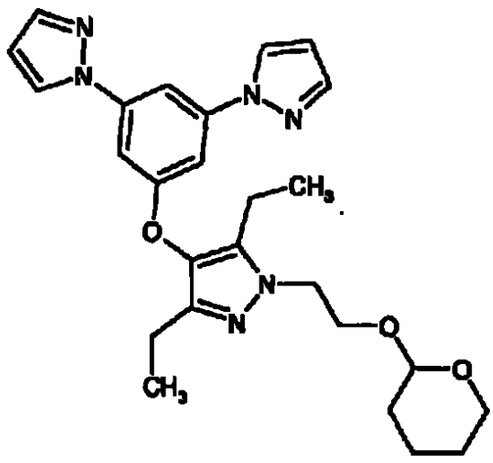
LRMS (termonebulización) : m/z [MH^+] 381.

Microanálisis: Encontrado C, 62,16; H, 6,92; N, 7,16. $C_{20}H_{26}N_2O_3.0,09CH_2Cl_2$ requiere C, 62,18; H, 6,80; N, 7,22%.

PREPARACIÓN 88

4-[3,5-Di(1*H*-pirazol-1-il)fenoxi]-3,5-dietil-1-[2-(tetrahidro-2*H*-piran-2-iloxi)etil]-1*H*-pirazol

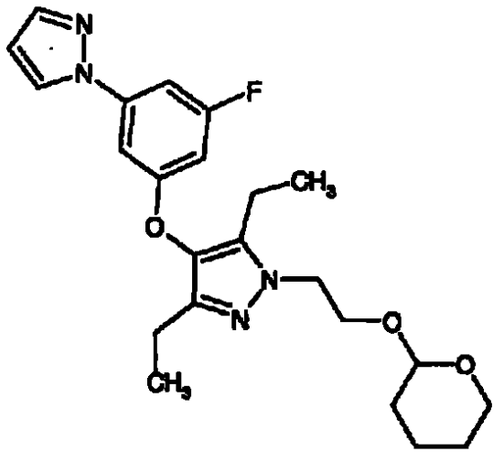
532
535



y

PREPARACIÓN 89

3,5-Dietil-4-[3-fluoro-5-(1*H*-pirazol-1-il)fenoxi]-1-[2-(tetrahidro-2*H*-piran-2-iloxi)etil]-1*H*-pirazol



Se añadió carbonato de cesio (538 mg, 1,65 mmol) a una solución de pirazol (102 mg, 1,50 mmol) en dimetilsulfóxido seco (2 ml) en una atmósfera de nitrógeno a temperatura

ambiente, y la reacción se agitó durante 15 minutos. Después se añadió el difluoruro de arilo de la Preparación 87 (570 mg, 1,50 mmol) disuelto en dimetilsulfóxido seco (2 ml) y la reacción se calentó a 100°C durante 18 horas. Después de la refrigeración a temperatura ambiente, la reacción se diluyó con agua (20 ml) y se extrajo con dietil éter (2x20 ml). La fase orgánica se lavó con salmuera (10 ml), se secó sobre sulfato de magnesio y se concentró a presión reducida. Quedaba algo de material de partida, de forma que el residuo se disolvió en dimetilsulfóxido (12 ml), se añadieron pirazol (510 mg, 7,50 mmol) seguido de carbonato de cesio (2,5 g, 7,66 mmol) y la reacción se calentó a 100°C durante 18 horas. Después de la refrigeración a temperatura ambiente, la reacción se diluyó con agua (6 ml), se extrajo con dietil éter (20 ml) y la fase orgánica se lavó con salmuera (10 ml), se secó sobre sulfato de magnesio, se concentró a presión reducida y el residuo se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con un gradiente de disolventes de diclorometano:metanol (100:0 cambiando a 96:4, en volumen). Esto dio dos fracciones, siendo la primera de ellas un solo producto (menos polar) y siendo la otra una mezcla de dos productos. La segunda fracción se purificó eluyendo con diclorometano:acetonitrilo (93:7 cambiando a 90:10, en volumen), proporcionando el producto más polar.

<u>Producto Menos Polar - Preparación 88 (254 mg)</u>

^{1}H RMN (400 MHz, $CDCl_3$): δ = 1,11 (m, 6H), 1,50 (m, 6H), 2,46 (q, 2H), 2,58 (q, 2H), 3,43 (m, 1H), 3,64 (m, 1H), 3,75 (m, 1H), 4,04 (m, 1H), 4,18 (t, 2H), 4,50 (s, 1H), 6,42 (s, 2H), 7,15 (s, 2H), 7,67 (s, 3H), 7,90 (s, 2H).

LRMS (electronebulización) : m/z [MH^+] 477, [MNa^+] 499.

HRMS: [MH^+] Encontrado 477,2612. $C_{26}H_{33}N_6O_3$ requiere 477,2609.

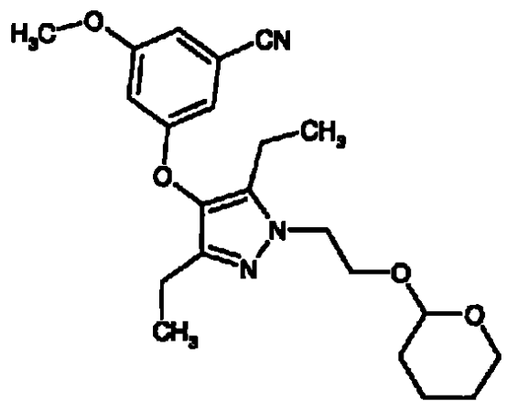
Producto Más Polar - Preparación 89 (37,7 mg)

^{1}H RMN (400 MHz, $CDCl_3$): δ = 1,11 (m, 6H), 1,46 (m, 6H), 2,43 (q, 2H), 2,57 (q, 2H), 3,43 (m, 1H), 3,64 (m, 1H), 3,75 (m, 1H), 4,05 (m, 1H), 4,17 (t, 2H), 4,51 (s, 1H), 6,42 (m, 2H), 7,07 (m, 2H), 7,66 (s, 1H), 7,82 (s, 1H).

LRMS (termonebulización) : m/z [MH^+] 429.

PREPARACIÓN 90

3-({3,5-Dietil-1-[2-(tetrahidro-2*H*-piran-2-iloxi)etil]-1*H*-pirazol-4-il}oxi)-5-metoxibenzonitrilo



Se añadió gota a gota metóxido sódico (25% p/v en metanol, 230 µl, 1,00 mmol) a una solución del fluoruro de

arilo de la Preparación 63 (387 mg, 1,00 mmol) en dimetilformamida (5 ml) a temperatura ambiente en una atmósfera de nitrógeno. La reacción se agitó durante 5 horas, se diluyó con agua (10 ml) y se extrajo con dietil éter (50 ml). La fase orgánica se secó sobre sulfato de magnesio, se concentró a presión reducida y el residuo se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol (97:3, en volumen), proporcionando el compuesto del título (400 mg) en forma de un aceite.

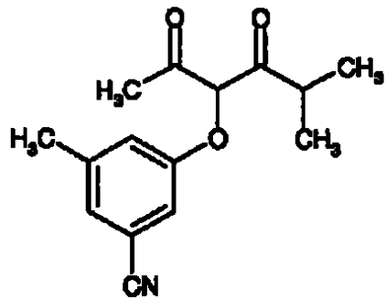
^{1}H RMN (400 MHz, $CDCl_3$): δ = 1,09 (m, 6H), 1,49 (m, 6H), 2,41 (q, 2H), 2,55 (q, 2H), 3,46 (m, 1H), 3,66 (m, 1H), 3,77 (m + s, 4H), 4,07 (m, 1H), 4,19 (t, 2H), 4,52 (m, 1H), 6,66 (s, 1H), 6,69 (s, 1H), 6,77 (s, 1H).

LRMS (termonebulización) : m/z [MH^+] 400.

Microanálisis: Encontrado C, 65,59; H, 7,32; N, 10,42. $C_{22}H_{29}N_3O_4.0,04CH_2Cl_2$ requiere C, 65,71; H, 7,28; N, 10,43%.

PREPARACIÓN 91

3-(1-Acetil-3-metil-2-oxobutoxi)-5-metilbenzonitrilo



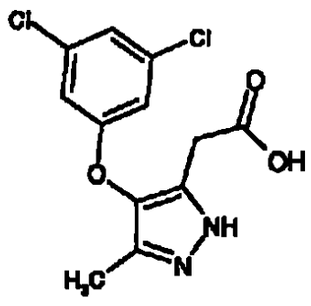
Se añadieron carbonato de cesio (1,50 g, 4,61 mmol) y el fenol de la Preparación 42 (609 mg, 4,61 mmol) a una solución agitada de la dicetona de la Preparación 23 (750 mg, 4,61 mmol) en acetona (23 ml) en una atmósfera de nitrógeno a 50°C, y la reacción se agitó durante 3 horas. Después de la refrigeración, la mezcla se inactivó con agua (10 ml) y la acetona se retiró a presión reducida. La fase acuosa se extrajo con diclorometano (4x25 ml) y los extractos orgánicos reunidos se secaron sobre sulfato de magnesio y se concentraron a presión reducida. El residuo se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con pentano:acetato de etilo (90:10, en volumen), proporcionando el compuesto del título (544 mg).

^{1}H RMN (400 MHz, $CDCl_3$): δ = 1,10 (m, 6H), 2,09 (s, 3H), 2,42 (s, 3H), 2,69 (m, 1H), 7,00 (s, 2H), 7,19 (s, 1H).

LRMS (termonebulización) : m/z [MNH_4^+] 277.

PREPARACIÓN 92

Ácido[4-(3,5-diclorofenoxi)-3-metil-1*H*-pirazol-5-il]acético



El pirazol del Ejemplo 208 (400 mg, 1,41 mmol) se agitó

a 100°C durante 14 horas en ácido clorhídrico concentrado (20 ml). La mezcla se enfrió a temperatura ambiente y el disolvente se retiró a presión reducida, dando un sólido amarillo. El sólido se disolvió en diclorometano (50 ml) y ácido clorhídrico acuoso 1 N (50 ml) y la capa orgánica se separó. Los extractos orgánicos se lavaron con ácido clorhídrico acuoso 1 N (50 ml), se secaron sobre sulfato de magnesio, se filtraron y el disolvente se retiró a presión reducida, proporcionando el compuesto del título (400 mg) en forma de un sólido amarillo, p.f. 156-158°C.

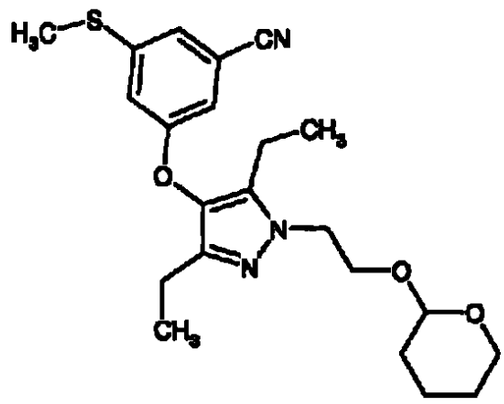
^{1}H RMN (400 MHz, CD_3OD): δ = 2,02 (s, 3H), 4,89 (s, 2H), 6,82 (s, 2H), 7,02 (s, 1H).

LRMS (termonebulización) : m/z [MH^+] 303.

Microanálisis: Encontrado C, 47,50; H, 3,50; N, 9,46. $C_{12}H_{10}Cl_2N_2O_3$ requiere C, 47,86; H, 3,35; N, 9,30%.

PREPARACIÓN 93

3-({3,5-Dietil-1-[2-(tetrahidro-2*H*-piran-2-iloxi)etil]-1*H*-pirazol-4-il}oxi)-5-(metilsulfanil)benzonitrilo



Se añadió tiometóxido sódico (180 mg, 2 mmol) a una solución agitada del fluoruro de arilo de la Preparación 63 (774 mg, 2,00 mmol) en dimetilformamida (10 ml) a temperatura ambiente en una atmósfera de nitrógeno. La mezcla de reacción se agitó durante 5 horas antes de calentarse a 100°C durante 18 horas. Se añadió una segunda porción de tiometóxido sódico (90 mg, 1 mmol) y la mezcla de reacción se calentó a 100°C durante 5 horas más. Después de la refrigeración a temperatura ambiente, la mezcla se diluyó con agua (10 ml) y se extrajo con dietil éter (2x50 ml). La fase orgánica se secó sobre sulfato de magnesio, se concentró a presión reducida y el residuo se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol (97:3, en volumen), proporcionando el compuesto del título (700 mg) en forma de un aceite.

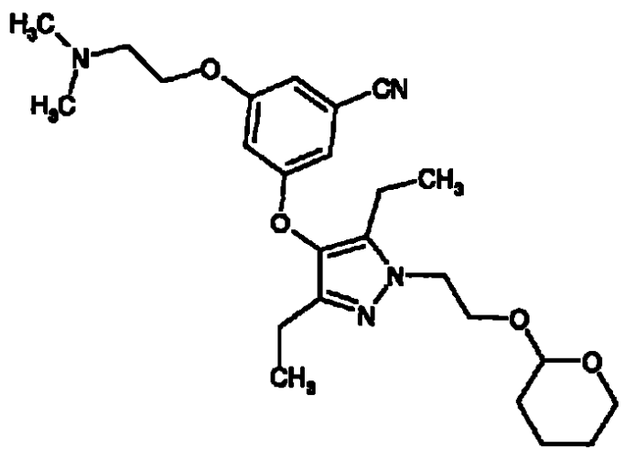
^{1}H RMN (400 MHz, $CDCl_3$): δ = 1,14 (m, 6H), 1,52 (m, 6H), 2,44 (q, 2H), 2,49 (s, 3H), 2,59 (q, 3H), 3,50 (m, 1H), 3,70 (m,

1H), 3,80 (m, 1H), 4,10 (m, 1H), 4,23 (m, 2H), 4,55 (m, 1H), 6,82 (s, 1H), 7,01 (s, 1H), 7,09 (s, 1H).

LRMS (APCI+): m/z [MH^+] 416.

PREPARACIÓN 94

3-({3,5-Dietil-1-[2-(tetrahidro-2*H*-piran-2-iloxi)etil]-1*H*-pirazol-4-il}oxi)-5-[2-(dimetilamino)etoxi]benzonitrilo



A una solución agitada de N,N-dimetiletanolamina (83 µl, 0,83 mmol) en dimetilformamida (2 ml) se añadió hidruro sódico (36 mg de una dispersión al 60% en peso en aceite, 0,90 mmol). Después de 10 minutos, se añadió una solución del fluoruro de arilo de la Preparación 63 (291 mg, 0,75 mmol) en dimetilformamida (2 ml) y la mezcla de reacción se agitó a temperatura ambiente durante 18 horas. La mezcla se diluyó con solución acuosa al 10% de carbonato potásico (12 ml) y se extrajo con dietil éter (2x7 ml). Los componentes orgánicos reunidos se secaron sobre sulfato de magnesio y se

concentraron a presión reducida. La mezcla de producto bruto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol (un gradiente de 99:1 a 90:10, en volumen), proporcionando el compuesto del título (180 mg) en forma de un aceite.

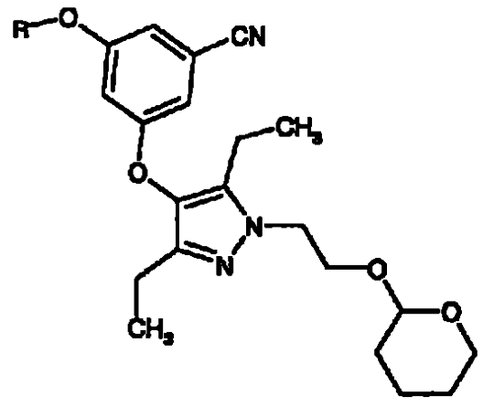
^{1}H RMN (400 MHz, $CDCl_3$): δ = 1,09 (m, 6H), 1,50 (m, 6H), 2,39 (q, 2H), 2,47 (s, 6H), 2,55 (q, 2H), 2,87 (m, 2H), 3,47 (m, 1H), 3,67 (m, 1H), 3,78 (m, 1H), 4,05 (m, 1H), 4,17 (m, 4H), 4,52 (m, 1H), 6,70 (s, 2H), 6,79 (s, 1H).

LRMS (electronebulización): m/z [MH^+] 457.

HRMS: [MH^+] 457,2810. $C_{25}H_{37}N_4O_4$ requiere 457,2810.

PREPARACIONES 95-97

La preparación de las siguientes Preparaciones presentadas en la tabla, de fórmula general



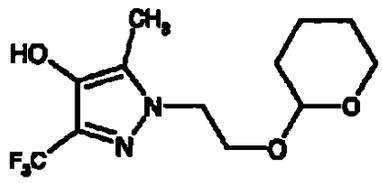
se realizó por un procedimiento similar al de la Preparación 94, usando el alcohol apropiado como material de partida.

Preparación No. (Material de partida, preparación no.)	R	Datos Analíticos
95 (63)	CH_2CH_2NHMe	^1H RMN (400 MHz, $CDCl_3$): δ = 1,09 (m, 6H), 1,50 (m, 6H), 2,39 (q, 2H), 2,54 (m, 5H), 3,04 (t, 2H), 3,46 (m, 1H), 3,66 (m, 1H), 3,78 (m, 1H), 4,05 (m, 1H), 4,11 (t, 2H), 4,17 (t, 2H), 4,52 (s, 1H), 6,70 (s, 2H), 6,81 (s, 1H) LRMS (electronebulización) : m/z 443 [MH$^+$] HRMS: [MH$^+$] 443,2654 $C_{24}H_{39}N_4O_4$ requiere 443,2653
96 (63)	CH_2CONH_2	^1H RMN (400 MHz, $CDCl_3$): δ = 1,11 (m, 6H), 1,48 (m, 6H), 2,43 (q, 2H), 2,58 (q, 2H), 3,46 (m, 1H), 3,67 (m, 1H), 3,80 (m, 1H), 4,08 (m, 1H), 4,25 (m, 2H), 4,45 (s, 2H), 4,52 (m, 1H), 5,54 (s ancho, 1H), 6,37 (s ancho, 1H), 6,72 (s, 1H), 6,85 (s, 2H). LRMS (electronebulización) : m/z 465 [MH$^+$] HRMS: [MH$^+$] 443,2282. $C_{25}H_{31}N_4O_3$ requiere 443,2289.
97 (63)	$CH_2CH_2OCH_3$	^1H RMN (400 MHz, $CDCl_3$): δ = 1,10 (m, 6H), 1,50 (m, 6H), 2,41 (q, 2H), 2,55 (q, 2H), 3,41 (s, 3H), 3,47 (m, 1H), 3,70 (m, 3H), 3,79 (m, 1H), 4,06 (m, 3H), 4,20 (m, 2H), 4,52 (s, 1H), 6,70 (s, 2H), 6,79 (s, 1H) LRMS (electronebulización) : m/z 466 [MH$^+$] HRMS: [MH$^+$] 443,2282. $C_{24}H_{34}N_4O_3$ requiere 443,2289.

PREPARACIÓN 98

5-Metil-1-[2-(tetrahidro-2*H*-piran-2-iloxi)etil]-3-

(trifluorometil)-1*H*-pirazol-4-ol



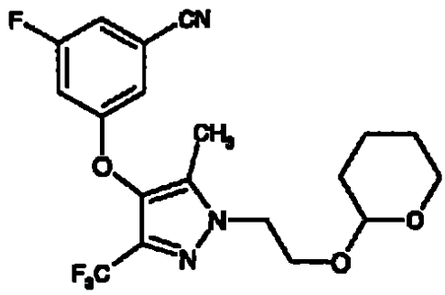
A una solución agitada de 1-(2-hidroxietil)-5-metil-3-(trifluorometil)-1*H*-pirazol-4-ol (600 mg, 2,86 mmol; Kenkyu Hokoku - Asahi Garasu Kogyo Gijutsu Shoreikai, 1988, 51, 139-49) en diclorometano (10 ml) y acetato de etilo (4 ml), se le añadió ácido para-toluenosulfónico (27 mg, 0,14 mmol) seguido de 3,4-dihidro-2H-piran (340 µl, 3,7 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 3 horas antes de concentrarse a presión reducida. La mezcla de producto bruto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con pentano:acetato de etilo (60:40, en volumen), proporcionando el compuesto del título (560 mg) en forma de un sólido blanco.

^{1}H RMN (400 MHz, $CDCl_3$): δ = 1,60 (m, 6H), 2,23 (s, 3H), 3,44 (m, 1H), 3,60 (m, 1H), 3,72 (m, 1H), 4,04 (m, 1H), 4,18 (m, 2H), 4,50 (s ancho, 1H).

LRMS (electronebulización): m/z [M-H$^+$] 293.

PREPARACIÓN 99

3-Fluoro-5-{[5-metil-1-[2-(tetrahidro-2*H*-piran-2-iloxi)etil]-3-(trifluorometil)-1*H*-pirazol-4-il]oxi}benzonitrilo



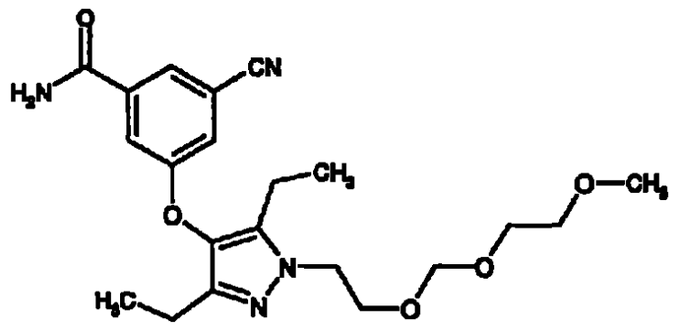
A una solución agitada del pirazol (214 mg, 0,73 mmol) de la Preparación 98 en dimetilformamida (0,7 ml) se le añadió 3,5-difluorobenzonitrilo (304 mg, 2,2 mmol) y carbonato potásico (304 mg, 2,2 mmol). La mezcla de reacción se calentó a 90°C durante 7 horas. Después de la refrigeración a temperatura ambiente, se añadió salmuera (20 ml) y la mezcla se extrajo con acetato de etilo (20 ml). El componente orgánico se separó, se lavó con salmuera (20 ml), se secó sobre sulfato de magnesio y se concentró a presión reducida. La mezcla de producto bruto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con pentano:acetato de etilo (80:20, en volumen), proporcionando el compuesto del título (267 mg) en forma de un aceite amarillo.

^{1}H RMN (400 MHz, $CDCl_3$): δ = 1,61 (m, 6H), 2,18 (s, 3H), 3,48 (m, 1H), 3,64 (m, 1H), 3,75 (m, 1H), 4,30 (t, 2H), 4,50 (s ancho, 1H), 6,85 (d, 1H), 6,94 (s, 1H), 7,05 (d, 1H).

LRMS (electronebulización): m/z [M-H$^+$] 412.

PREPARACIÓN 100

3-Ciano-5-[(3,5-dietil-1-{2-[(2-metoxietoxi)metoxi]etil}-1*H*-pirazol-4-il)oxi]benzamida



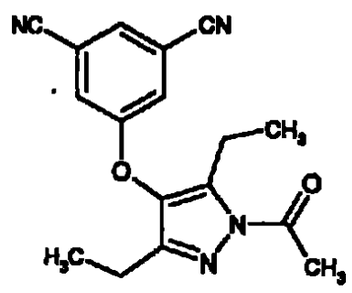
A una solución agitada del pirazol del Ejemplo 261 (193 mg, 0,49 mmol) en tetrahidrofurano (2 ml) se le añadió una solución acuosa de hidróxido sódico 2 M (8,7 µl, 0,49 mmol) y la mezcla de reacción se calentó a 65°C durante 24 horas. Después de la refrigeración a temperatura ambiente, se añadió una segunda porción de solución de hidróxido sódico 2M (8,7 µl, 0,49 mmol) y la mezcla se calentó a 65°C durante 24 horas. Se añadió solución acuosa de hidróxido sódico 6 M (100 µl) y la mezcla se calentó a 65°C durante 24 horas. La mezcla de reacción se concentró a presión reducida, se diluyó con agua (75 ml), se neutralizó a pH 7 usando solución acuosa de ácido clorhídrico 2 M y se extrajo con diclorometano (2x25 ml). Los componentes orgánicos reunidos se secaron sobre sulfato de magnesio y se concentraron a presión reducida, dando una mezcla de producto bruto que se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con

diclorometano:metanol (100:0, 98:2, 96,5:3,5 y después 95:5, en volumen), proporcionando el compuesto del título (60 mg) en forma de un aceite incoloro.

^{1}H RMN (400 MHz, $CDCl_3$): δ = 1,10 (m, 6H), 2,40 (q, 2H), 2,55 (q, 2H), 3,36 (s, 3H), 3,50 (q, 2H), 3,59 (q, 2H), 3,94 (q, 2H), 4,20 (q, 2H), 4,64 (s, 2H), 7,30 (s, 1H), 7,59 (s, 1H), 7,70 (s, 1H).

PREPARACIÓN 101

5-[(1-Acetil-3,5-dietil-1*H*-pirazol-4-il)oxi]isoftalonitrilo



A una solución agitada del pirazol del Ejemplo 122 (3,0 g, 11,3 mmol) en dimetilformamida (45 ml) a 0°C se le añadió cloruro de acetilo (1,2 ml, 17,0 mmol), seguido de hidruro sódico por porciones (678 mg de una dispersión al 60% en peso en aceite, 17,0 mmol). El baño de refrigeración se retiró y la mezcla de reacción se agitó a temperatura ambiente durante 40 minutos. La reacción se inactivó por adición de solución acuosa saturada de cloruro amónico (4 ml) y se concentró a presión reducida, dando un residuo naranja. Este material se repartió entre acetato de etilo (200 ml) y agua (200 ml). El

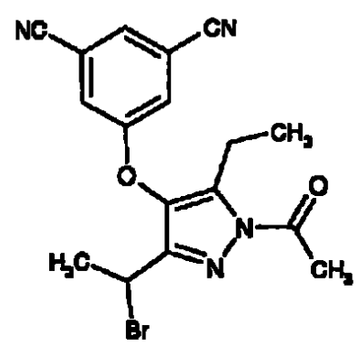
componente orgánico se lavó con agua (100 ml) y con salmuera (75 ml) y después se secó sobre sulfato de magnesio antes de concentrarse a presión reducida. La mezcla de producto bruto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol (100:0, 99:1, y después 98:2, en volumen), proporcionando el compuesto del título (2,67 g) en forma de un sólido blanco.

^{1}H RMN (400 MHz, $CDCl_3$): δ = 1,15 (t, 3H), 1,19 (t, 3H), 2,43 (q, 2H), 2,72 (s, 3H), 3,85 (q, 2H), 7,38 (s, 2H), 7,61 (s, 1H).

LRMS (electronebulización): m/z 331 [$M+Na^+$].

PREPARACIÓN 102

5-{[1-Acetil-3-(1-bromoetil)-5-etil-1*H*-pirazol-4-il]oxi}isoftalonitrilo



Una solución del pirazol de la Preparación 101 (881 mg, 2,86 mmol) en tetracloruro de carbono (12 ml) se desgasificó haciendo pasar una corriente de nitrógeno a través de la solución durante 20 minutos. Se añadió N-bromosuccinimida

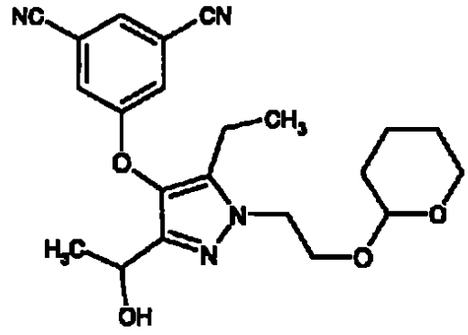
(763 mg, 4,28 mmol) seguida de AIBN (30 mg) y la mezcla de reacción se calentó a 85°C durante 4 horas. Después de la refrigeración a temperatura ambiente, la mezcla se concentró a presión reducida y el residuo se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con pentano:acetato de etilo (un gradiente de 100:0 a 67:33, en volumen), proporcionando el compuesto del título (348 mg) en forma de un aceite incoloro.

^{1}H RMN (400 MHz, $CDCl_3$): δ = 1,10 (t, 3H), 2,00 (d, 3H), 2,70 (s, 3H), 2,80 (m, 2H), 4,95 (q, 1H), 7,42 (s, 2H), 7,60 (s, 1H).

LRMS (electronebulización): m/z 283 [MH^+].

PREPARACIÓN 103

5-({5-Etil-3-(1-hidroxietil)-1-[2-(tetrahidro-2*H*-piran-2-iloxi)etil]-1*H*-pirazol-4-il}oxi)isoftalonitrilo



A una solución agitada del pirazol del Ejemplo 263 (197 mg, 0,70 mmol) en dimetilformamida (3 ml) a 0°C se le añadió 2-(2-bromoetoxi)tetrahidro-2*H*-pirano (105 µl, 0,70 mmol)

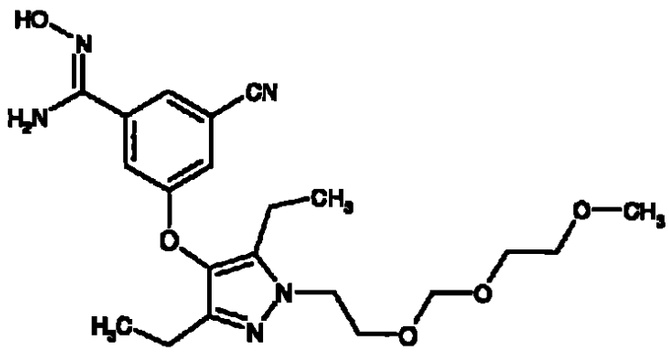
seguido de hidruro sódico (31 mg, 0,77 mmol). Después de 15 minutos, el baño se refrigeración se retiró y la mezcla se agitó a temperatura ambiente durante 60 horas. La mezcla de reacción se inactivó por la adición de solución acuosa saturada de cloruro amónico (0,5 ml) y después se concentró a presión reducida. La mezcla de producto bruto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol (un gradiente de 100:0 a 95:5, en volumen), proporcionando el compuesto del título (84 mg) en forma de una espuma blanca que revierte a un aceite tras reposo.

^{1}H RMN (400 MHz, $CDCl_3$): δ = 1,11 (t, 3H), 1,45 (d, 3H), 1,65 (m, 6H), 2,59 (q, 2H), 3,50 (m, 1H), 3,70 (m, 1H), 3,81 (m, 1H), 4,11 (m, 1H), 4,25 (t, 2H), 4,56 (m, 1H), 4,76 (m, 1H), 7,40 (s, 2H), 7,55 (s, 1H).

LRMS (electronebulización): m/z 411 [MH^+].

PREPARACIÓN 104

3-Ciano-5-[(3,5-dietil-1-{2-[(2-metoxietoxi)metoxi]etil}-1*H*-pirazol-4-il)oxi]-*N*-hidroxibencenocarboximidamida



A una solución agitada del pirazol del Ejemplo 261 (1,5 g, 3,76 mmol) en etanol (7,5 ml), se le añadió una solución de carbonato sódico (200 mg, 1,88 mmol) y clorhidrato de hidroxilamina (262 mg, 3,76 mmol) en agua (7,5 ml). Después de agitar durante 5 horas a temperatura ambiente, la mezcla de reacción se concentró a presión reducida y el residuo se repartió entre diclorometano (50 ml) y agua (40 ml). La fase acuosa se separó y se extrajo con diclorometano (30 ml). Los componentes orgánicos se combinaron, se secaron sobre sulfato de magnesio y se concentraron a presión reducida. La mezcla de producto bruto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol (un gradiente de 100:0 a 96:4, en volumen), proporcionando el compuesto del título (1,13 mg) en forma de un aceite incoloro.

^{1}H RMN (400 MHz, $CDCl_3$): δ = 1,11 (m, 6H), 2,42 (q, 2H), 2,58 (q, 2H), 3,41 (s, 3H), 3,59 (m, 4H), 3,95 (t, 2H), 4,17 (t, 2H), 4,61 (s, 2H), 4,77 (s ancho, 2H), 7,38 (m, 1H), 7,49 (m,

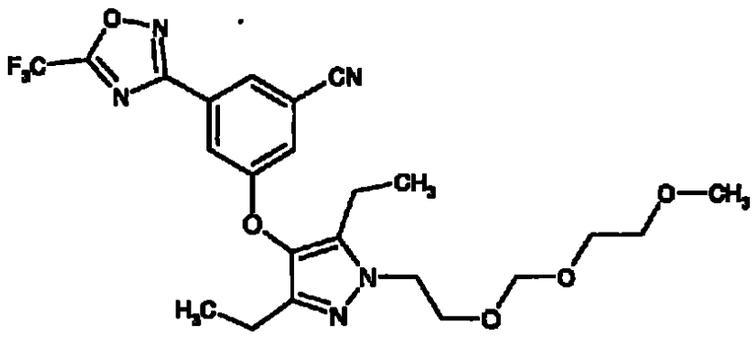
2H).

LRMS (electronebulización): m/z 432 [MH^+].

Microanálisis: Encontrado C, 57,50; H, 6,71; N, 16,01. $C_{21}H_{26}N_4O_4$+0,4H_2O requiere C, 57,50; H, 6,85; N, 15,96%.

PREPARACIÓN 105

3-[(3,5-Dietil-1-{2-[(2-metoxietoxi)metoxi]etil}-1*H*-pirazol-4-il)oxi]-5-[5-(trifluorometil)-1,2,4-oxadiazol-3-il]benzonitrilo



A una solución agitada de la amidoxima de la Preparación 104 (300 mg, 0,70 mmol) en piridina (3 ml), se le añadió anhídrido trifluoroacético (118 µl, 0,83 mmol). Después de agitar a temperatura ambiente durante 2 horas, la mezcla de reacción se calentó a 110°C durante 18 horas. Después de la refrigeración a temperatura ambiente, la mezcla se concentró a presión reducida y el residuo se repartió entre solución acuosa de HCl 2 M (6 ml) y diclorometano (6 ml). La fase orgánica se separó y se concentró a presión reducida. El residuo se purificó por cromatografía ultrarrápida sobre gel

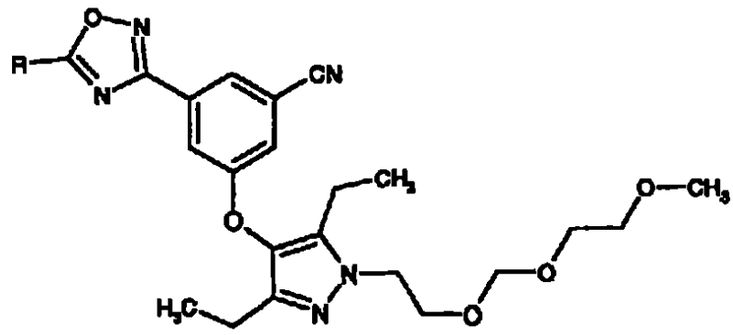
de sílice eluyendo con diclorometano:metanol (un gradiente de 100:0 a 90:10, en volumen), proporcionando el compuesto del título (259 mg) en forma de un aceite incoloro.

^{1}H RMN (400 MHz, $CDCl_3$): δ = 1,14 (m, 6H), 2,46 (q, 2H), 2,59 (q, 2H), 3,39 (s, 3H), 3,53 (q, 2H), 3,59 (q, 2H), 3,95 (q, 2H), 4,29 (q, 2H), 4,68 (s, 2H), 7,34 (s, 1H), 7,87 (s, 1H), 8,04 (s, 1H).

LRMS (APCI): m/z 532 (MH+)

PREPARACIONES 106-108

La preparación de las siguientes Preparaciones presentadas en la tabla, de fórmula general

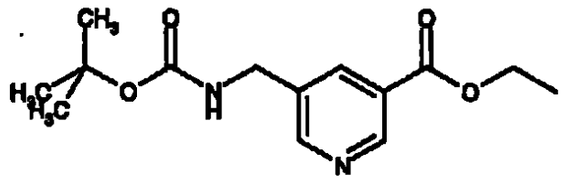


se realizó por un procedimiento similar al de la Preparación 105, usando el cloruro de ácido apropiado como agente de acilación en lugar de anhídrido trifluoroacético.

Preparación No.	R	Datos Analíticos
106	Me	^{1}H RMN (400 MHz, $CDCl_3$): δ = 1.14 (m, 6H), 2.46 (q, 2H), 2.59 (q, 2H), 2.67 (s, 3H), 3.39 (s, 3H), 3.55 (q, 2H), 3.59 (q, 2H), 3.95 (q, 2H), 4.22 (q, 2H), 4.68 (s, 2H), 7.27 (s, 1H), 7.82 (s, 1H), 8.00 (s, 1H). LRMS (electronebulización): m/z 478 [M+Na$^+$] Microanálisis: Encontrado C, 59.91; H, 6.27; N, 15.38. $C_{23}H_{29}N_5O_5$+0.3H_2O requiere C, 59.94; H, 6.475; N, 15.19%.
107	Et	^{1}H RMN (400 MHz, $CDCl_3$): δ = 1.14 (m, 6H), 1.44 (t, 3H), 2.42 (q, 2H), 2.48 (q, 2H), 2.98 (q, 2H), 3.39 (s, 3H), 3.53 (q, 2H), 3.59 (q, 2H), 3.95 (q, 2H), 4.20 (q, 2H), 4.48 (s, 2H), 7.30 (s, 1H), 7.84 (s, 1H), 8.01 (s, 1H). LRMS (electronebulización): m/z 492 (M+Na$^+$)
108	^{i}Pr	^{1}H RMN (400 MHz, $CDCl_3$): δ = 1.11 (m, 6H), 1.49 (d, 6H), 2.44 (q, 2H), 2.49 (q, 2H), 3.30 (sept. 1H), 3.39 (s, 3H), 3.54 (m, 2H), 3.59 (m, 2H), 3.95 (t, 2H), 4.23 (t, 2H), 4.91 (s, 2H), 7.22 (m, 1H), 7.83 (m, 1H), 8.02 (m, 1H). LRMS (electronebulización): m/z 506 (M+Na$^+$). Microanálisis: Encontrado C, 61.87; H, 6.76; N, 14.62. $C_{25}H_{33}N_5O_5$ requiere C, 62.10; H, 6.88; N, 14.48%.

PREPARACIÓN 109

5-{[(*terc*-Butoxicarbonil)amino]metil}nicotinato de etilo



A una solución agitada de 5-cianonicotinato de etilo (3,0 g, 17,0 mmol; Annalen Der Chemie, 1959, 621, 106-136) en etanol (200 ml), se le añadió ácido clorhídrico concentrado (3,4 ml) seguido de paladio al 5% sobre carbono (300 mg). La mezcla de reacción se agitó a temperatura ambiente en una atmósfera de hidrógeno (344,737 kPa) durante 18 horas. La mezcla de reacción se filtró a través de Arbocel® y se concentró a presión reducida. La mezcla de producto bruto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco 0,880 (un gradiente de 95:5:0,5 a 85:5:1,5, en volumen), proporcionando la amina intermedia (2,1 g) en forma de un sólido aceitoso amarillo. Este material (2,1 g, 11,7 mmol) se suspendió en diclorometano (22 ml), a lo que se añadió trietilamina (1,8 ml, 13,0 mmol) seguido de dicarbonato de di-terc-butilo (2,84 g, 13 mmol). Después de 48 horas, la mezcla de reacción se diluyó con diclorometano (50 ml) y se lavó con agua (50 ml). El componente orgánico se secó sobre sulfato de magnesio y se concentró a presión reducida antes de purificarse por cromatografía ultrarrápida sobre gel de sílice eluyendo con

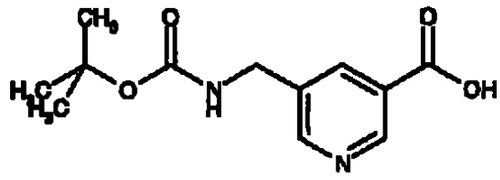
diclorometano:metanol:amoniaco 0,88 (un gradiente de 100:0:0 a 95:5:0,5, en volumen), proporcionando el compuesto del título (2,0 g) en forma de un aceite amarillo.

^{1}H RMN (400 MHz, $CDCl_3$): δ = 1,40 (m, 12H), 4,42 (m, 4H), 8,22 (s, 1H), 8,71 (s, 1H), 9,12 (s, 1H).

LRMS (APCI): m/z 279 ($M-H^+$)

PREPARACIÓN 110

Ácido 5-{[(*terc*-butoxicarbonil)amino]metil}nicotínico



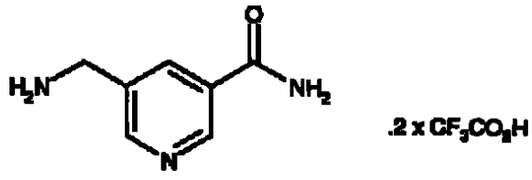
A una solución agitada del éster de la Preparación 109 (2,00 g, 7,10 mmol) en una solución acuosa de hidróxido sódico 1M (15 ml, 15 mmol) se le añadió metanol (15 ml). La mezcla de reacción se agitó a temperatura ambiente durante 18 horas, después de lo cual el metanol se retiró a presión reducida. La solución acuosa se lavó con dietil éter (2x25 ml), se enfrió a 0°C y se neutralizó a pH 7 por la adición de solución acuosa de ácido clorhídrico 2 M (7,5 ml). La mezcla se concentró a presión reducida, dando un aceite amarillo (1,5 g).

^{1}H RMN (400 MHz, $CDCl_3$): δ = 1,37 (s, 9H), 4,16 (d, 2H), 7,51 (m, 1H), 8,07 (s, 1H), 8,50 (s, 1H), 8,88 (s, 1H).

LRMS (APCI): m/z 251 ($M-H^+$).

PREPARACIÓN 111

5-(Aminometil)nicotinamida



.2 x CF_3CO_2H

A una solución agitada del ácido de la Preparación 110 (770 mg, 3,10 mmol) en dimetilformamida (15 ml) se le añadió carbonildiimidazol (600 mg, 3,70 mmol). Después de 10 minutos, se añadió amoniaco 0,88 (1 ml). Después de una hora más, la mezcla de reacción se concentró a presión reducida y el residuo se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco 0,88 (un gradiente de 95:5:0,5 a 80:20:1, en volumen), proporcionando el intermedio boc-protegido. A una solución agitada de este material en diclorometano (20 ml), se le añadió ácido trifluoroacético (6 ml). Después de 18 horas, se añadió una segunda porción de ácido trifluoroacético (6 ml) y la mezcla de reacción se agitó a temperatura ambiente durante 24 horas. La solución se concentró a presión reducida, dando un residuo aceitoso que se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco 0,88 (100:0:0, después 90:10:1 y después 80:20:1, en volumen), proporcionando el compuesto del título (650 mg) en forma de un aceite amarillo.

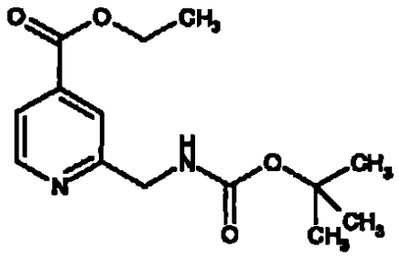
^{1}H RMN (400 MHz, $(CD_3)_2SO$: δ = 4,11 (s, 2H), 7,5 (s ancho), 7,59 (s ancho), 8,14 (s ancho), 8,31 (m, 1H), 8,72 (m, 1H), 8,90 (m, 1H).

LRMS (electronebulización): m/z 152 (MH^+)

HRMS: [MH^+] 152,0819. $C_7H_{10}N_3O$ requiere 152,0818.

PREPARACIÓN 112

2-{[(*terc*-butilcarbonil)amino]metil}isonicotinato de etilo



A una solución agitada de 2-cianoisonicotinato de etilo (2,00 g, 11,0 mmol, J. Med. Chem., 1976, 19, 483) en etanol (20 ml) se le añadió solución acuosa de ácido clorhídrico 2 M (7,5 ml) seguida de paladio al 5% sobre carbono (200 mg). La mezcla de reacción se agitó a temperatura ambiente en una atmósfera de hidrógeno (413,685 kPa) durante 48 horas. La mezcla se filtró a través de arbocel y el filtrado se concentró a presión reducida. El residuo se secó por medio de destilación azeotrópica usando tolueno a presión reducida. A una solución agitada del residuo (3,00 g) en diclorometano (22 ml), se le añadió trietilamina (4,6 ml, 33 mmol) seguida de dicarbonato de di-terc-butilo (2,62 g, 12,0 mmol). Después

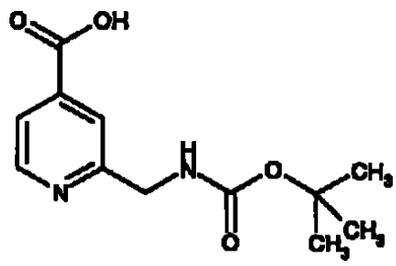
de agitar durante 1 hora a temperatura ambiente, la mezcla de reacción se diluyó con diclorometano (100 ml) y se lavó con agua (50 ml). El componente orgánico se lavó con salmuera (50 ml), se secó sobre sulfato de magnesio y se concentró a presión reducida, dando a sólido aceitoso pardo. La mezcla de producto bruto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:-amoniaco 0,88 (98:2:0,2 y después 97:3:0,3, en volumen), proporcionando el compuesto del título (2,20 g) en forma de un aceite amarillo.

^{1}H RMN (400 MHz, $CDCl_3$): δ = 1,38 (t, 3H), 1,45 (s, 9H), 4,38 (q, 2H), 4,50 (m, 2H), 5,50 (s ancho, 1H), 7,73 (d, 1H), 7,81 (s, 1H), 8,65 (d, 1H).

LRMS (electronebulización): m/z 281 (MH^+).

PREPARACIÓN 113

Ácido 2-{[(*terc*-Butoxicarbonil)amino]metil}isonicotínico



A una solución agitada del éster de la Preparación 112 (1,50 g, 5,35 mmol) en metanol (10 ml), se le añadió una solución acuosa de hidróxido sódico 1 M (10 ml). Después de

1 hora, la mezcla de reacción se enfrió a 0°C y se neutralizó por la adición de solución acuosa de ácido clorhídrico 2 M (5 ml). La mezcla de reacción se concentró a presión reducida y el residuo se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco 0,88 (80:20:1, en volumen), proporcionando el compuesto del título (1,30 g) en forma de una espuma amarilla.

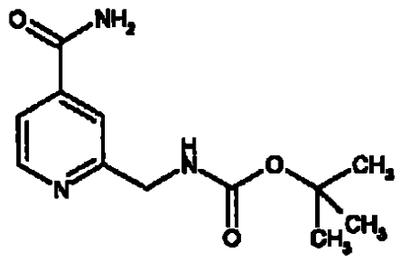
^{1}H RMN (400 MHz, CD_3OD): δ = 1,43 (s, 9H), 4,36, (s, 2H), 7,68 (m, 1H), 7,81 (s, 1H), 8,47 (m, 1H).

LRMS (electronebulización): m/z 251 ($M-H^+$)

HRMS: [MH^+] 253,1179. $C_{12}H_{17}N_2O_4$ requiere 253,1183.

PREPARACIÓN 114

[4-(Aminocarbonil)-2-piridinil]metilcarbamato de *terc*-butilo



A una solución agitada del ácido de la Preparación 113 (1,3 g, 5,20 mmol) en dimetilformamida (10 ml), se le añadió 1-hidroxibenzotriazol (950 mg, 6,20 mmol) seguido de sal clorhidrato de 1-(3-dimetilaminopropil)-3-etilcarbodiimida (1,20 g, 6,20 mmol). Después de 1 hora, se añadió amoniaco 0,88 (5 ml) y la mezcla de reacción se agitó a temperatura

ambiente durante 1,5 horas. La mezcla se concentró a presión reducida y se secó por destilación azeotrópica usando tolueno a presión reducida, dando un semisólido amarillo. La mezcla de producto bruto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco 0,88 (95:5:0,5, en volumen), proporcionando el compuesto del título (1,1 g) en forma de un aceite transparente que cristalizó tras reposo. Este material se purificó adicionalmente por trituración con dietil éter (10 ml), dando una muestra del producto deseado (1,0 g) en forma de polvo blanco.

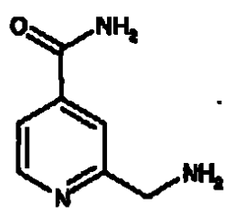
^{1}H RMN (400 MHz, D6-DMSO): δ = 1,39 (s, 9H), 4,25 (m, 2H), 7,44 (m, 1H), 7,61 (m, 1H), 7,66 (s ancho, 2H), 8,21 (s ancho, 1H), 8,59 (d, 1H).

LRMS (electronebulización): m/z 250 ($M-H^+$)

Microanálisis: Encontrado C, 57,26; H, 6,86; N, 16,65. $C_{12}H_{17}N_3O_3$ requiere C, 57,36; H, 6,82; N, 16,72%.

PREPARACIÓN 115

2-(Aminometil)isonicotinamida



A una solución agitada de la piridina de la Preparación

114 (1,00 g, 3,98 mmol) en diclorometano (50 ml), se le añadió ácido trifluoroacético (15 ml). Después de agitar a temperatura ambiente durante 18 horas, la mezcla de reacción se concentró a presión reducida y se purificó por cromatografía de intercambio iónico en Dowex 50-X8-200 eluyendo con agua seguida de amoniaco 0,88:metanol:agua (5:5:90, en volumen), proporcionando el compuesto del título (265 mg) en forma de un sólido blanco.

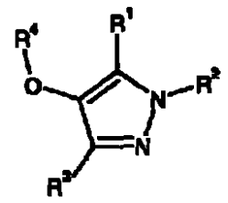
^{1}H RMN (400 MHz, D6-DMSO): δ = 2,1 (s ancho, 1H), 3,4 (s ancho, 1H), 3,85 (2H, s), 7,57 (m, 1H), 7,60 (s ancho, 1H), 7,80 (m, 1H), 8,16 (s ancho, 1H), 8,59 (m, 1H).

LRMS (APCI): m/z 152 (MH^+).

Habiendo descrito la invención como antecede se declara como propiedad lo contenido en las siguientes:

REIVINDICACIONES

1. Un compuesto de fórmula (I)



(I)

o una sal, solvato o derivado farmacéuticamente aceptable del mismo, en la que:

R^1 es H, alquilo C_1-C_6, cicloalquilo C_3-C_7, fenilo, bencilo, halo, -CN, $-OR^7$, $-CO_2R^{10}$, $-CONR^5R^{10}$, R^8 o R^9, estando dichos alquilo C_1-C_6, cicloalquilo C_3-C_7, fenilo y bencilo opcionalmente sustituidos con halo, -CN, $-OR^{10}$, $S(O)_xR^{10}$, $-CO_2R^{10}$, $-CONR^5R^{10}$, $-OCONR^5R^{10}$, $-NR^5CO_2R^{10}$, $-NR^{10}R^{11}$, $-NR^5COR^{10}$, $-SO_2NR^5R^{10}$, $-NR^5CONR^5R^{10}$, $-NR^5SO_2R^{10}$ o R^{10}; y

R^2 es H, alquilo C_1-C_6, alquenilo C_3-C_6, alquinilo C_3-C_6, cicloalquilo C_3-C_7, cicloalquenilo C_3-C_7, fenilo, bencilo, R^8 o R^9, estando dichos alquilo C_1-C_6, cicloalquilo C_3-C_7, fenilo y bencilo opcionalmente sustituidos con halo, $-OR^5$, OR^{12}, -CN, $-CO_2R^7$, $-OCONR^5R^5$, $-CONR^5R^5$, $-C(=NR^5)NR^5OR^5$, $-CONR^5NR^5R^5$, $-NR^6R^6$, $-NR^5R^{12}$, $-NR^5COR^5$, $-NR^5COR^8$, $-NR^5COR^{12}$, $-NR^5CO_2R^5$, $-NR^5CONR^5R^5$, $-SO_2NR^5R^5$, $-NR^5SO_2R^5$, $-NR^5SO_2NR^5R^5$, R^8 o R^9;

o, R^1 y R^2, cuando se toman conjuntamente, representan alquileno C_3-C_4 lineal, opcionalmente sustituido con oxo, estando un grupo metileno de dicho alquileno C_3-C_4 opcionalmente reemplazado por un átomo de oxígeno o un átomo de nitrógeno, estando opcionalmente sustituido dicho átomo de nitrógeno por R^{10};

R^3 es H, alquilo C_1-C_6, cicloalquilo C_3-C_7, fenilo, bencilo, halo, -CN, $-OR^7$, $-CO_2R^5$, $-CONR^5R^5$, R^8 o R^9, estando dichos alquilo C_1-C_6, cicloalquilo C_3-C_7, fenilo y bencilo opcionalmente sustituidos con halo, -CN, $-OR^5$, $-CO_2R^5$, $-CONR^5R^5$, $-OCONR^5R^5$, $-NR^5CO_2R^5$, $-NR^6R^6$, $-NR^5COR^5$, $-SO_2NR^5R^5$, $-NR^5CONR^5R^5$, $-NR^5SO_2R^5$, R^8 o R^9;

R^4 es fenilo, naftilo o piridilo, estando cada uno opcionalmente sustituido con R^8, halo, -CN, alquilo C_1-C_6, haloalquilo C_1-C_6, cicloalquilo C_3-C_7, alcoxi C_1-C_6, $-CONR^5R^5$, OR^{13}, SO_xR^6, O-(alquileno C_1-C_6)-$CONR^5R^5$, O-(alquileno C_1-C_6)-NR^5R^5 o O-(alquileno C_1-C_6)-OR^6;

cada R^5 es independientemente H, alquilo C_1-C_6 o cicloalquilo C_3-C_7 o, cuando dos grupos R^5 están unidos al mismo átomo de nitrógeno, estos dos grupos, tomados conjuntamente con el átomo de nitrógeno al que están unidos, representan azetidinilo, pirrolidinilo, piperidinilo, homopiperidinilo, piperazinilo, homopiperazinilo o morfolinilo, estando dichos azetidinilo, pirrolidinilo, piperidinilo, homopiperidinilo, piperazinilo, homopiperazinilo y morfolinilo opcionalmente

sustituidos con alquilo C_1-C_6 o cicloalquilo C_3-C_7;

cada R^6 es independientemente H, alquilo C_1-C_6 o cicloalquilo C_3-C_7;

R^7 es alquilo C_1-C_6 o cicloalquilo C_3-C_7;

R^8 es un grupo heterocíclico aromático de cinco o seis miembros que contiene (i) de 1 a 4 heteroátomos de nitrógeno o (ii) 1 ó 2 heteroátomos de nitrógeno y 1 heteroátomo de oxígeno o azufre o (iii) 1 ó 2 heteroátomos de oxígeno o azufre, estando dicho grupo heterocíclico opcionalmente sustituido con halo, oxo, -CN, $-COR^5$, $-CONR^5R^5$, $-SO_2NR^5R^5$, $-NR^5SO_2R^5$, $-OR^5$, $-NR^5R^5$, -(alquileno C_1-C_6)-NR^5R^5, alquilo C_1-C_6, fluoroalquilo (C_1-C_6) o cicloalquilo C_3-C_7;

R^9 es un grupo heterocíclico de cuatro a siete miembros, saturado o parcialmente insaturado, que contiene (i) 1 ó 2 heteroátomos de nitrógeno o (ii) 1 heteroátomo de nitrógeno y 1 heteroátomo de oxígeno o 1 heteroátomo de azufre o (iii) 1 heteroátomo de oxígeno o azufre, estando dicho grupo heterocíclico opcionalmente sustituido con oxo, alquilo C_1-C_6, cicloalquilo C_3-C_7, $-SO_2R^5$, $-CONR^5R^5$, $-COOR^5$, -CO-(alquileno C_1-C_6)-OR^5 o $-COR^5$ y opcionalmente sustituido en un átomo de carbono que no es adyacente a un heteroátomo con halo, $-OR^5$, $-NR^5R^5$, $-NR^5COR^5$, $-NR^5COOR^5$, $-NR^5CONR^5R^5$, $-NR^5SO_2R^5$ o -CN;

R^{10} es H, R^8, R^9, R^{13}, alquilo C_1-C_6, cicloalquilo C_3-C_7 o -(alquil C_1-C_6)-(cicloalquilo C_3-C_7), estando dichos alquilo C_1-C_6 y cicloalquilo C_3-C_7 opcionalmente sustituidos con $-OR^5$,

$-OR^{13}$, R^8, R^9, R^{13} o $-COR^{13}$;

R^{11} es H, alquilo C_1-C_6 o cicloalquilo C_3-C_7, estando dichos alquilo C_1-C_6 y cicloalquilo C_3-C_7 opcionalmente sustituidos con $-OR^5$, $-NR^5R^5$, $-NR^5COR^5$, $-CONR^5R^5$, R^8 o R^9;

R^{12} es alquilo C_1-C_6 sustituido con R^8, R^9, $-OR^5$, $-CONR^5R^5$, $-NR^5COR^5$ o $-NR^5R^5$;

R^{13} es fenilo opcionalmente sustituido con halo, -CN, $-COR^5$, $-CONR^5R^5$, $-SO_2NR^5R^5$, $-NR^5SO_2R^5$, $-OR^5$, $-NR^5R^5$, -(alquileno C_1-C_6)-NR^5R^5, alquilo C_1-C_6, haloalquilo (C_1-C_6) o cicloalquilo C_3-C_7; y

x es 0, 1 ó 2;

con la condición de que (a) cuando tanto R^1 como R^3 son fenilo, R^2 no es metilo; y (b) cuando R^1 es etoxi y R^3 es etoxicarbonilo, R^2 no es fenilo.

2. Un compuesto de acuerdo con la reivindicación 1, en el que R^1, cuando se toma por separado, es H, alquilo C_1-C_6, cicloalquilo C_3-C_7 o $-OR^7$, estando dichos alquilo C_1-C_6 y cicloalquilo C_3-C_7 opcionalmente sustituidos con halo, -CN, $-OR^{10}$, $S(O)_xR^{10}$, $-CO_2R^{10}$, $-CONR^5R^{10}$, $-OCONR^5R^{10}$, $-NR^5CO_2R^{10}$, $-NR^{10}R^{11}$, $-NR^5COR^{10}$, $-SO_2NR^5R^{10}$, $-NR^5CONR^5R^{10}$, $-NR^5SO_2R^{10}$ o R^{10}.

3. Un compuesto de acuerdo con la reivindicación 1 ó 2, en el que R^1, cuando se toma por separado, es H, alquilo C_1-C_6, cicloalquilo C_3-C_7 o $-OR^7$, estando dicho alquilo C_1-C_6

opcionalmente sustituido con halo, $-OR^{10}$, $-NR^{10}R^{11}$, $-NR^5COR^{10}$ o R^{10}.

4. Un compuesto de acuerdo con cualquier reivindicación precedente, en el que R^2, cuando se toma por separado, es H, alquilo C_1-C_6, alquenilo C_3-C_6 o R^9, estando dicho alquilo C_1-C_6 opcionalmente sustituido con halo, $-OR^5$, OR^{12}, $-CN$, $-CO_2R^7$, $-OCONR^5R^5$, $-CONR^5R^5$, $-C(=NR^5)NR^5OR^5$, $-CONR^5NR^5R^5$, $-NR^6R^6$, $-NR^5R^{12}$, $-NR^5COR^5$, $-NR^5COR^8$, $-NR^5COR^{12}$, $-NR^5CO_2R^5$, $-NR^5CONR^5R^5$, $-SO_2NR^5R^5$, $-NR^5SO_2R^5$, R^8 o R^9.

5. Un compuesto de acuerdo con cualquier reivindicación precedente, en el que R^2, cuando se toma por separado, es H, alquilo C_1-C_6, alquenilo C_3-C_6 o R^9, estando dicho alquilo C_1-C_6 opcionalmente sustituido con $-OR^5$, OR^{12}, $-CN$, $-CO_2R^7$, $-CONR^5R^5$, $-C(=NR^5)NR^5OR^5$, $-CONR^5NR^5R^5$, $-NR^6R^6$, $-NR^5R^{12}$, $-NR^5COR^8$, $-NR^5COR^{12}$, $-NR^5CO_2R^5$, R^8 o R^9.

6. Un compuesto de acuerdo con la reivindicación 1, en el que R^1 y R^2, cuando se toman conjuntamente, representan alquileno C_3-C_4 lineal, opcionalmente sustituido con oxo, reemplazándose un grupo metileno de dicho alquileno C_3-C_4 por un átomo de oxígeno o un átomo de nitrógeno, estando dicho átomo de nitrógeno opcionalmente sustituido con R^{10}.

7. Un compuesto de acuerdo con las reivindicaciones 1 ó 6, en el que R^1 y R^2, cuando se toman conjuntamente, representan propileno lineal, reemplazándose un grupo metileno por un átomo de oxígeno, o butileno lineal, reemplazándose un grupo metileno por un átomo de nitrógeno, estando dichos propileno y butileno opcionalmente sustituidos con oxo y estando dicho átomo de nitrógeno opcionalmente sustituido con R^{10}.

8. Un compuesto de acuerdo con cualquier reivindicación precedente, en el que R^3 es H o alquilo C_1-C_6, estando dicho alquilo C_1-C_6 opcionalmente sustituido con halo, -CN, -OR^5, -CO_2R^5, -$CONR^5R^5$, -$OCONR^5R^5$, -$NR^5CO_2R^5$, -NR^6R^6, -NR^5COR^5, -$SO_2NR^5R^5$, -$NR^5CONR^5R^5$, -$NR^5SO_2R^5$, R^8 o R^9.

9. Un compuesto de acuerdo con cualquier reivindicación precedente, en el que R^3 es H o alquilo C_1-C_6.

10. Un compuesto de acuerdo con cualquier reivindicación precedente, en el que R^4 es fenilo opcionalmente sustituido con R^8, halo, -CN, alquilo C_1-C_6, haloalquilo C_1-C_6, cicloalquilo C_3-C_7, alcoxi C_1-C_6, -$CONR^5R^5$, OR^{13}, SO_xR^6, O-(alquileno C_1-C_6)-$CONR^5R^5$, O-(alquileno C_1-C_6)-NR^5R^5 o O-(alquileno C_1-C_6)-OR^6; o naftilo.

11. Un compuesto de acuerdo con cualquier reivindicación

precedente, en el que R^4 es fenilo sustituido con R^8, halo, -CN, alquilo C_1-C_6, haloalquilo C_1-C_6, cicloalquilo C_3-C_7, alcoxi C_1-C_6, $-CONR^5R^5$, OR^{13}, SO_xR^6, O-(alquileno C_1-C_6)-$CONR^5R^5$, O-(alquileno C_1-C_6)-NR^5R^5 o O-(alquileno C_1-C_6)-OR^6.

12. Un compuesto de acuerdo con cualquier reivindicación precedente, en el que R^4 es fenilo sustituido con R^8, halo, -CN, alquilo C_1-C_6, haloalquilo C_1-C_6, cicloalquilo C_3-C_7 o alcoxi C_1-C_6.

13. Un compuesto de acuerdo con cualquier reivindicación precedente, en el que R^4 es fenilo sustituido con halo, -CN o alquilo C_1-C_6.

14. Un compuesto de acuerdo con cualquier reivindicación precedente, en el que R^8 es pirrolilo, imidazolilo, pirazolilo, 1,2,3-triazolilo, 1,2,4-triazolilo, tetrazolilo, oxazolilo, isoxazolilo, tiazolilo, isotiazolilo, 1,2,4-oxadiazolilo, 1,3,4-oxadiazolilo, furanilo, tienilo, piridinilo, piridazinilo, pirimidinilo o pirazinilo, estando cada uno opcionalmente sustituido con halo, -CN, $-COR^5$, $-CONR^5R^5$, $-SO_2NR^5R^5$, $-NR^5SO_2R^5$, $-OR^5$, $-NR^5R^5$, -(alquileno C_1-C_6)-NR^5R^5, alquilo C_1-C_6, fluoro(alquilo C_1-C_6) o cicloalquilo C_3-C_7.

15. Un compuesto de acuerdo con cualquier reivindicación

precedente, en el que R^8 es imidazolilo, pirazolilo, 1,2,4-triazolilo, 1,2,4-oxadiazolilo, 1,3,4-oxadiazolilo, piridinilo, pirazinilo o pirimidinilo, estando cada uno opcionalmente sustituido con halo, -CN, $-COR^5$, $-CONR^5R^5$, $-SO_2NR^5R^5$, $-NR^5SO_2R^5$, $-OR^5$, $-NR^5R^5$, -(alquileno C_1-C_6)-NR^5R^5, alquilo C_1-C_6, fluoroalquilo (C_1-C_6) o cicloalquilo C_3-C_7.

16. Un compuesto de acuerdo con cualquier reivindicación precedente, en el que R^8 es imidazolilo, pirazolilo, 1,2,4-triazolilo, 1,2,4-oxadiazolilo, 1,3,4-oxadiazolilo, piridinilo, pirazinilo o pirimidinilo, estando cada uno opcionalmente sustituido con $-OR^5$, $-NR^5R^5$ o alquilo C_1-C_6.

17. Un compuesto de acuerdo con cualquier reivindicación precedente, en el que R^9 es azetidinilo, tetrahidropirrolilo, piperidinilo, azepinilo, oxetanilo, tetrahidrofuranilo, tetrahidropiranilo, oxepinilo, morfolinilo, piperazinilo o diazepinilo, estando cada uno opcionalmente sustituido con oxo, alquilo C_1-C_6, cicloalquilo C_3-C_7, $-SO_2R^5$, $-CONR^5R^5$, $-COOR^5$, -CO-(alquileno C_1-C_6)-OR^5 o $-COR^5$ y opcionalmente sustituido en un átomo de carbono que no es adyacente a un heteroátomo con halo, $-OR^5$, $-NR^5R^5$, $-NR^5COR^5$, $-NR^5COOR^5$, $-NR^5CONR^5R^5$, $-NR^5SO_2R^5$ o -CN.

18. Un compuesto de acuerdo con cualquier reivindicación

precedente, en el que R^9 es azetidinilo, piperidinilo, tetrahidrofuranilo, piperazinilo o morfolinilo, estando cada uno opcionalmente sustituido con oxo, alquilo C_1-C_6, cicloalquilo C_3-C_7, $-SO_2R^5$, $-CONR^5R^5$, $-COOR^5$, -CO-(alquileno C_1-C_6)-OR^5 o $-COR^5$ y opcionalmente sustituido en un átomo de carbono que no es adyacente a un heteroátomo con halo, $-OR^5$, $-NR^5R^5$, $-NR^5COR^5$, $-NR^5COOR^5$, $-NR^5CONR^5R^5$, $-NR^5SO_2R^5$ o -CN.

19. Un compuesto de acuerdo con cualquier reivindicación precedente, en el que R^9 es azetidinilo, piperidinilo, tetrahidrofuranilo, piperazinilo o morfolinilo, estando cada uno opcionalmente sustituido con alquilo C_1-C_6, $-SO_2R^5$, $-CONR^5R^5$, $-COOR^5$, -CO-(alquileno C_1-C_6)-OR^5 o $-COR^5$ y opcionalmente sustituido en un átomo de carbono que no es adyacente a un heteroátomo con $-OR^5$ o $-NR^5COR^5$.

20. Un compuesto de acuerdo con cualquier reivindicación precedente, en el que R^{10} es H, R^8, R^9, R^{13}, alquilo C_1-C_6 o -(alquil C_1-C_6)-(cicloalquilo C_3-C_7), estando dicho alquilo C_1-C_6 opcionalmente sustituido con $-OR^5$, $-OR^{13}$, R^8, R^9, R^{13} o $-COR^{13}$.

21. Un compuesto de acuerdo con cualquier reivindicación precedente, en el que R^{10} es H, R^8, R^9, R^{13}, alquilo C_1-C_6 o -(alquil C_1-C_6)-(cicloalquilo C_3-C_7), estando dicho alquilo C_1-C_6 opcionalmente sustituido con $-OR^5$ o R^{13}.

22. Un compuesto de acuerdo con cualquier reivindicación precedente, en el que R^{11} es H o alquilo C_1-C_6, estando dicho alquilo C_1-C_6 opcionalmente sustituido con $-OR^5$, $-NR^5R^5$, $-NR^5COR^5$, $-CONR^5R^5$, R^8 o R^9.

23. Un compuesto de acuerdo con cualquier reivindicación precedente, en el que R^{11} es H o alquilo C_1-C_6, estando dicho alquilo C_1-C_6 opcionalmente sustituido con $-OR^5$ o $-NR^5COR^5$.

24. Un compuesto de acuerdo con cualquier reivindicación precedente, en el que R^{12} es alquilo C_1-C_4 sustituido con R^8, R^9, $-OR^5$, $-CONR^5R^5$, $-NR^5COR^5$ o $-NR^5R^5$.

25. Un compuesto de acuerdo con cualquier reivindicación precedente, en el que R^{12} es alquilo C_1-C_4 sustituido con R^9, $-OR^5$, $-NR^5COR^5$ o $-NR^5R^5$.

26. Un compuesto de acuerdo con cualquier reivindicación precedente, en el que R^{13} es fenilo sustituido con halo, -CN, $-COR^5$, $-CONR^5R^5$, $-SO_2NR^5R^5$, $-NR^5SO_2R^5$, $-OR^5$, $-NR^5R^5$, -(alquileno C_1-C_6)-NR^5R^5, alquilo C_1-C_6, haloalquilo(C_1-C_6) o cicloalquilo C_3-C_7.

27. Un compuesto de acuerdo con cualquier reivindicación

precedente, en el que R^{13} es fenilo sustituido con halo, -CN, $-CONR^5R^5$, $-SO_2NR^5R^5$ o $-OR^5$.

28. 2-[4-(3,5-Diclorofenoxi)-3,5-dimetil-1*H*-pirazol-1-il]etanol;

2-[4-(3,5-Diclorofenoxi)-3,5-dietil-1*H*-pirazol-1-il]etanol;

4-(3,5-Diclorofenoxi)-3,5-dietil-1*H*-pirazol;

[4-(3,5-Diclorofenoxi)-3,5-dietil-1*H*-pirazol-1-il]acetonitrilo;

5-{[4-(3,5-Diclorofenoxi)-3,5-dietil-1*H*-pirazol-1-il]metil}-1*H*-pirazol-3-ol;

6-{[4-(3,5-Diclorofenoxi)-3,5-dietil-1*H*-pirazol-1-il]metil}-2-metil-4(3*H*)-pirimidinona;

2-Amino-6-{[4-(3,5-diclorofenoxi)-3,5-dietil-1*H*-pirazol-1-il]metil}-4-(3*H*)-pirimidinona;

2-[4-(3,5-Diclorofenoxi)-3,5-dietil-1*H*-pirazol-1-il]-*N*-hidroxietanimidamida;

[4-(3,5-Diclorofenoxi)-3,5-dietil-1*H*-pirazol-1-il]acetatode metilo;

2-[4-(3,5-Diclorofenoxi)-3,5-dietil-1*H*-pirazol-1-il]acetamida;

2-[4-(3,5-Diclorofenoxi)-3,5-dietil-1*H*-pirazol-1-il]acetohidrazida;

5-{[4-(3,5-Diclorofenoxi)-3,5-dietil-1*H*-pirazol-1-il]metil}-1,3,4-oxadiazol-2(3*H*)-ona;

2-[4-(3,5-Diclorofenoxi)-3,5-dietil-1*H*-pirazol-1-il]etilamina;

3-{[4-(3,5-Diclorofenoxi)-3,5-dietil-1*H*-pirazol-1-il]metil}-1,2,4-oxadiazol-5-ol;

5-{[4-(3,5-Diclorofenoxi)-3,5-dietil-1*H*-pirazol-1-il]metil}-1,3,4-oxadiazol-2-amina;

N-{2-[4-(3,5-Diclorofenoxi)-3,5-dietil-1*H*-pirazol-1-il]etil}-2-metoxiacetamida;

N-{2-[4-(3,5-Diclorofenoxi)-3,5-dietil-1*H*-pirazol-1-il]etil}-2-piridinocarboxamida;

N-{2-[4-(3,5-Diclorofenoxi)-3,5-dietil-1*H*-pirazol-1-il]etil}-2-pirazinocarboxamida;

3-{[3,5-Dietil-1-(2-hidroxietil)-1*H*-pirazol-4-il]oxi}benzonitrilo;

4{[3,5-Dietil-1-(2-hidroxietil)-1*H*-pirazol-4-il]oxi}-3,5-dimetilbenzonitrilo;

3-Cloro-4-{[3,5-dietil-1-(2-hidroxietil)-1*H*-pirazol-4-il]oxi}benzonitrilo;

5-{[3,5-Dietil-1-(2-hidroxietil)-1*H*-pirazol-4-il]oxi}-2-fluorobenzonitrilo;

2-[4-(4-Clorofenoxi)-3,5-dietil-1*H*-pirazol-1-il]etanol;

2-[4-(3-Clorofenoxi)-3,5-dietil-1*H*-pirazol-1-il]etanol;

2-[4-(2-Clorofenoxi)-3,5-dietil-1*H*-pirazol-1-il]etanol;

2-[4-(2,6-Diclorofenoxi)-3,5-dietil-1*H*-pirazol-1-il]etanol;

2-[4-(2,3-Diclorofenoxi)-3,5-dietil-1*H*-pirazol-1-il]etanol;

2-[4-(2,4-Diclorofenoxi)-3,5-dietil-1*H*-pirazol-1-il]etanol;

2-[3,5-Dietil-4-(2-fluorofenoxi)-1*H*-pirazol-1-il]etanol;

2-[3,5-Dietil-4-(3-fluorofenoxi)-1*H*-pirazol-1-il]etanol;

2-[4-(3,5-Dimetilfenoxi)-3,5-dietil-1*H*-pirazol-1-il]etanol;

2-[3,5-Dietil-4-(4-fluoro-3-metilfenoxi)-1*H*-pirazol-1-il]etanol;

2-[4-(2,5-Diclorofenoxi)-3,5-dietil-1*H*-pirazol-1-il]etanol;

2-[4-(3,4-Diclorofenoxi)-3,5-dietil-1*H*-pirazol-1-il]etanol;

2-[4-(2,6-Difluorofenoxi)-3,5-dietil-1*H*-pirazol-1-il]etanol;

2-[4-(2,5-Difluorofenoxi)-3,5-dietil-1*H*-pirazol-1-il]etanol;

2-[4-(3,5-Difluorofenoxi)-3,5-dietil-1*H*-pirazol-1-il]etanol;

4-(3,5-Diclorofenoxi)-3,5-dietil-1-(2-metoxietil)-1*H*-pirazol;

4-(3,5-Diclorofenoxi)-3,5-dietil-1-(metoximetil)-1*H*-pirazol;

4-(3,5-Diclorofenoxi)-3,5-dietil-1-metil-1*H*-pirazol;

4-(3,5-Diclorofenoxi)-3-etil-1*H*-pirazol;

4-{2-[4-(3,5-Diclorofenoxi)-3,5-dietil-1*H*-pirazol-1-il]etil}morfolina;

N-{2-[4-(3,5-Diclorofenoxi)-3,5-dietil-1*H*-pirazol-1-il]etil}-*N*-(2-metoxietil)amina;

1-(1-{2-[4-(3,5-Diclorofenoxi)-3,5-dietil-1*H*-pirazol-1-il]etil}-4-piperidinil)etanona;

N-{2-[4-(3,5-Diclorofenoxi)-3,5-dietil-1*H*-pirazol-1-il]etil}-*N*,*N*-dimetilamina;

N-[2-({2-[4-(3,5-Diclorofenoxi)-3,5-dietil-1*H*-pirazol-1-il]etil}amino)etil]acetamida;

N-{2-[4-(3,5-Diclorofenoxi)-3,5-dietil-1*H*-pirazol-1-il]etil}-*N*-metilamina;

N-{2-[4-(3,5-Diclorofenoxi)-3,5-dietil-1*H*-pirazol-1-il]etil}-*N*-(tetrahidro-2-furanilmetil)amina;

3-{[4-(3,5-Diclorofenoxi)-3,5-dietil-1*H*-pirazol-1-il]metil}morfolina;

1-(3-Azetidinil)-4-(3,5-diclorofenoxi)-3,5-dietil-1*H*-pirazol;

7-(3,5-diclorofenoxi)-6-etil-2,3-dihidropirazolo[5,1-*b*][1,3]oxazol;

4-(3,5-Diclorofenoxi)-3,5-dimetil-1*H*-pirazol;

1-[4-(3,5-Diclorofenoxi)-3,5-dietil-1*H*-pirazol-1-il]-2-propanol;

2-{2-[4-(3,5-Diclorofenoxi)-3,5-dietil-1*H*-pirazol-1-il)etoxi]etanamina;

4-{[4-(3,5-Diclorofenoxi)-3-metil-1*H*-pirazol-5-il]metil}morfolina;

4-(3,5-Diclorofenoxi)-3-metil-5-[(2-metil-1*H*-imidazol-1-il)metil]-1*H*-pirazol;

2-[4-(3,5-Diclorofenoxi)-3-etil-5-metoxi-1*H*-pirazol-1-il]etanol;

1-{[4-(3,5-Diclorofenoxi)-3-metil-1*H*-pirazol-5-il]metil}-1*H*-1,2,4-triazol;

3-[(3,5-Dietil-1*H*-pirazol-4-il)oxi]benzonitrilo;

3-{[1-(2-Aminoetil)-3,5-dietil-1*H*-pirazol-4-il]oxi}benzonitrilo;

2-[4-(3-Cianofenoxi)-3,5-dietil-1*H*-pirazol-1-il]acetamida;

[4-(3-Cianofenoxi)-3,5-dietil-1*H*-pirazol-1-il]acetato de etilo;

1-Alil-4-(3,5-diclorofenoxi)-3,5-dietil-1*H*-pirazol;

N-{[4-(3,5-Diclorofenoxi)-3-metil-1*H*-pirazol-5-il]metil}-*N*-(4-metoxibencil)amina;

N-(Ciclopropilmetil)[4-(3,5-diclorofenoxi)-3-metil-1*H*-pirazol-5-il]metanamina;

[4-(3,5-Diclorofenoxi)-3-metil-1*H*-pirazol-5-il]-*N*,*N*-dimetilmetanamina;

[4-(3,5-Diclorofenoxi)-3-metil-1*H*-pirazol-5-il]-*N*-metilmetanamina;

1-{[4-(3,5-Diclorofenoxi)-3-metil-1*H*-pirazol-5-il]metil}-4-metilpiperazina;

1-{[4-(3,5-Diclorofenoxi)-3-metil-1*H*-pirazol-5-il]metil}-4-piperidinocarboxamida;

N-{[4-(3,5-Diclorofenoxi)-3-metil-1*H*-pirazol-5-il]metil}-2-metoxietanamina;

1-Acetil-5-{[4-(3,5-diclorofenoxi)-3-metil-1*H*-pirazol-5-il]metil}piperazina;

N-[2-({[4-(3,5-diclorofenoxi)-3-metil-1*H*-pirazol-5-il]metil}amino)etil]acetamida;

N-(1{[4-(3,5-Diclorofenoxi)-3-metil-1*H*-pirazol-5-il]metil}-4-piperidinil)acetamida;

1-{[4-(3,5-Diclorofenoxi)-3-metil-1*H*-pirazol-5-il]metil}-4-

metoxipiperidina;

3-Cloro-5-[(3,5-dimetil-1*H*-pirazol-4-il)oxi]benzonitrilo;

3-{[5-(Aminometil)-3-metil-1*H*-pirazol-4-il]oxi}-5-clorobenzonitrilo;

3-Cloro-5-{[3-metil-5-(1-piperazinilmetil)-1*H*-pirazol-4-il]oxi}benzonitrilo;

3-Cloro-5-[(5-{[(4-cianobencil)amino]metil}-3-metil-1*H*-pirazol-4-il)oxi]benzonitrilo;

3-Cloro-5-[(3-metil-5-{[4-(metilsulfonil)-1-piperazinil]metil}-1*H*-pirazol-4-il)oxi]benzonitrilo;

3-Cloro-5-[(5-{[4-(metoxiacetil)-1-piperazinil]metil}-3-metil-1*H*-pirazol-4-il)oxi]benzonitrilo;

4-{[4-(3-Cloro-5-cianofenoxi)-3-metil-1*H*-pirazol-5-il]metil}-1-piperazinocarboxilato de metilo;

4-[({[4-(3-Cloro-5-cianofenoxi)-3-metil-1*H*-pirazol-5-il]metil}amino)metil]bencenosulfonamida;

4-(3,5-Diclorofenoxi)-5-(metoximetil)-3-metil-1*H*-pirazol;

3-*terc*-Butil-4-(3,5-diclorofenoxi)-5-metil-1*H*-pirazol;

4-(3,5-Diclorofenoxi)-3-etil-5-metil-1*H*-pirazol;

4-Ciano-*N*-{[4-(3,5-diclorofenoxi)-3-metil-1*H*-pirazol-5-il]metil}benzamida;

3-Ciano-*N*-{[4-(3,5-diclorofenoxi)-3-metil-1*H*-pirazol-5-il]metil}benzamida;

N-{[4-(3,5-Diclorofenoxi)-3-metil-1*H*-pirazol-5-il]metil}-*N*-(3-piridinilmetil)amina;

3-({5-[(4-Acetil-1-piperazinil)metil]-3-metil-1*H*-pirazol-4-il}oxi)-5-clorobenzonitrilo;

3-Cloro-5-[(5-{[(4-cianobencil)(metil)amino]metil}-3-metil-1*H*-pirazol-4-il)oxi]benzonitrilo;

3-Cloro-5-[(5-{[(4-cianobencil)(2-hidroxietil)amino]metil}-3-metil-1*H*-pirazol-4-il)oxi]benzonitrilo;

3-Cloro-5-({3-metil-5-[(2-metil-1*H*-imidazol-1-il)metil]-1*H*-pirazol-4-il}oxi)benzonitrilo;

2-(4-(3,5-Diclorofenoxi)-3-metil-5-{[(3-piridinilmetil)-amino]metil}-1*H*-pirazol-1-il)etanol;

5-[(3-Isopropil-5-metil-1*H*-pirazol-4-il)oxi]isoftalonitrilo;

5-{[1-(2-Hidroxietil)-3-isopropil-5-metil-1*H*-pirazol-4-il]oxi}isoftalonitrilo;

3-(3,5-Diclorofenoxi)-2-etil-6,7-dihidropirazolo[1,5-a]pirazin-4(5*H*)-ona;

3-(3,5-Diclorofenoxi)-2-etil-4,5,6,7-tetrahidropirazolo[1,5-a]pirazina;

3-(3,5-Diclorofenoxi)-2-etil-5-metil-4,5,6,7-tetrahidropirazolo[1,5-a]pirazina;

4-[(3-(3,5-Diclorofenoxi)-2-etil-6,7-dihidropirazolo[1,5-a]pirazin-5-(4*H*)-il]metil]benzonitrilo;

3-(3,5-Diclorofenoxi)-2-etil-5-(4-metoxibencil)-4,5,6,7-tetrahidropirazolo[1,5-a]pirazina;

[1-(2-Aminoetil)-4-(3,5-diclorofenoxi)-3-etil-1*H*-pirazol-5-il]metanol;

2-[4-(3,5-Diclorofenoxi)-5-(etoximetil)-3-etil-1*H*-pirazol-1-il]etilamina;

2-[4-(3,5-Diclorofenoxi)-3-etil-5-(1*H*-pirazol-1-ilmetil)-1*H*-pirazol-1-il]etilamina;

N-{[1-(2-Aminoetil)-4-(3,5-diclorofenoxi)-3-etil-1*H*-pirazol-5-il]metil}-*N*-(4-metoxibencil)amina;

4-[({[1-(2-Aminoetil)-4-(3,5-diclorofenoxi)-3-etil-1*H*-pirazol-5-il]metil}amino)metil]benzonitrilo;

2-[5-[(4-Acetil-1-piperazinil)metil]-4-(3,5-diclorofenoxi)-3-etil-1*H*-pirazol-1-il]etilamina;

N-[2-({[1-(2-Aminoetil)-4-(3,5-diclorofenoxi)-3-etil-1*H*-pirazol-5-il]metil}amino)etil]acetamida;

Bromhidrato de [4-(3,5-diclorofenoxi)-3-metil-1*H*-pirazol-5-il]metanamina;

N-{[4-(3,5-Diclorofenoxi)-3-metil-1*H*-pirazol-5-il]metil}-*N*-(4-fluorobencil)amina;

4-[({[4-(3,5-Diclorofenoxi)-3-metil-1*H*-pirazol-5-il]metil}amino)metil]benzonitrilo;

3-Cloro-5-[(1,3,5-trimetil-1*H*-pirazol-4-il)oxi]benzonitrilo;

3-Cloro-5-[(5-{[(4-cianobencil)amino]metil}-1,3-dimetil-1*H*-pirazol-4-il)oxi]benzonitrilo;

3-Cloro-5-{[1-(2-hidroxietil)-3,5-dimetil-1*H*-pirazol-4-il]oxi}benzonitrilo;

3-Cloro-5{[5-{[(4-cianobencil)amino]metil}-1-(2-hidroxietil)-3-metil-1*H*-pirazol-4-il]oxi}benzonitrilo;

4-[({[4-(3-Cloro-5-cianofenoxi)-3-metil-1*H*-pirazol-5-il]metil}amino)metil]benzamida;

3-{[3,5-Dietil-1-(2-hidroxietil)-1*H*-pirazol-4-il]oxi}-5-fluorobenzonitrilo;

3-{[3,5-Dietil-1-(2-hidroxietil)-1*H*-pirazol-4-il]oxi}-5-metilbenzonitrilo;

5-{[3,5-Dietil-1-(2-hidroxietil)-1*H*-pirazol-4-il]oxi}isoftalonitrilo;

3-Cloro-5-{[3,5-dietil-1-(2-hidroxietil)-1*H*-pirazol-4-il]oxi}benzonitrilo;

3-[(3,5-Dietil-1*H*-pirazol-4-il)oxi]5-fluorobenzonitrilo;

5-[3,5-Dietil-1*H*-pirazol-4-il)oxi]isoftalonitrilo;

3-[(3,5-Dietil-1*H*-pirazol-4-il)oxi]-5-metilbenzonitrilo;

3-Cloro-5-[(3,5-dietil-1*H*-pirazol-4-il)oxi]benzonitrilo;

3-{[1-(2-Aminoetil)-3,5-dietil-1*H*-pirazol-4-il)oxi}-5-metilbenzonitrilo;

3-{[1-(2-Aminoetil)-3,5-dietil-1*H*-pirazol-4-il]oxi}-5-clorobenzonitrilo;

5-{[1-(2-Aminoetil)-3,5-dietil-1*H*-pirazol-4-il]oxi}isoftalonitrilo;

3-{[1-(2-Aminoetil)-3,5-dietil-1*H*-pirazol-4-il]oxi}-5-fluorobenzonitrilo;

5-[(3-Ciclopropil-5-etil-1*H*-pirazol-4-il)oxi]isoftalonitrilo;

5-[(3-*terc*-Butil-5-metil-1*H*-pirazol-4-il)oxi]isoftalonitrilo;

5-[(5-Etil-3-isopropil-1*H*-pirazol-4-il)oxi]isoftalonitrilo;

4-(3,5-Diclorofenoxi)-3,5-dietil-1-(1-metil-3-azetidinil)-1*H*-pirazol;

2-[4-(3,5-Diclorofenoxi)-3-etil-1*H*-pirazol-1-il]etilamina;

2-[4-(3,5-Diclorofenoxi)-5-etil-1*H*-pirazol-1-il]etilamina;

2-[4-(3,5-Diclorofenoxi)-3-etil-5-(hidroximetil)-1*H*-pirazol-1-il]etilcarbamato de *terc*-butilo;

2-[4-(3,5-Diclorofenoxi)-5-(etoximetil)-3-etil-1*H*-pirazol-1-il]etilcarbamato de *terc*-butilo;

2-[5-(Bromometil)-4-(3,5-diclorofenoxi)-3-etil-1*H*-pirazol-1-il]etilcarbamato de *terc*-butilo;

2-[5-(Aminometil)-4-(3,5-diclorofenoxi)-3-etil-1*H*-pirazol-1-il]etilcarbamato de *terc*-butilo;

2-[5-[(4-Acetil-1-piperazinil)metil]-4-(3,5-diclorofenoxi)-3-etil-1*H*-pirazol-1-il]etilcarbamato de *terc*-butilo;

2-[4-(3,5-Diclorofenoxi)-3-etil-5-(1*H*-pirazol-1-ilmetil)-1*H*-pirazol-1-il]etilcarbamato de *terc*-butilo;

2-[5-({[2-(Acetilamino)etil]amino}metil)-4-(3,5-diclorofenoxi)-3-etil-1*H*-pirazol-1-il]etilcarbamato de *terc*-butilo;

2-(4-(3,5-Diclorofenoxi)-3-etil-5-{[(4-metoxibencil)amino]-metil}-1*H*-pirazol-1-il)etilcarbamato de *terc*-butilo;

2-[5-{[(4-Cianobencil)amino]metil}-4-(3,5-diclorofenoxi)-3-etil-1*H*-pirazol-1-il]etilcarbamato de *terc*-butilo;

3-{[5-(Bromometil)-1,3-dimetil-1*H*-pirazol-4-il]oxi}5-clorobenzonitrilo;

3-[(3,5-Dietil-1-metil-1*H*-pirazol-4-il)oxi]benzonitrilo;

3-{[3,5-Dietil-1-(2-metoxietil)-1*H*-pirazol-4-il]oxi}benzonitrilo;

3-({5-[2-(Benciloxi)etil]-3-etil-1*H*-pirazol-4-il}oxi)-5-fluorobenzonitrilo;

3-{[3-Etil-5-(2-hidroxietil)-1*H*-pirazol-4-il]oxi}-5-fluorobenzonitrilo;

3-({5-[2-(4-Cianofenoxi)etil]-3-etil-1*H*-pirazol-4-il}oxi)-5-fluorobenzonitrilo;

3-[(3-Etil-5-{2-[(2-metil-3-piridinil)oxi]etil}-1*H*-pirazol-4-il)oxi]-5-fluorobenzonitrilo;

3-({3-Etil-5-[2-(3-piridiniloxi)etil]-1*H*-pirazol-4-il}oxi)-5-fluorobenzonitrilo;

3-[(5-{2-[(2-Amino-3-piridinil)oxi]etil}-3-etil-1*H*-pirazol-4-il)oxi]-5-fluorobenzonitrilo;

5-({5-[2-(Benciloxi)etil]-3-etil-1*H*-pirazol-4-il}oxi)isoftalonitrilo;

5-{[3-Etil-5-(2-hidroxietil)-1*H*-pirazol-4-il}oxi)isoftalonitrilo;

3-{[5-(Aminometil)-1-(2-hidroxietil)-3-metil-1*H*-pirazol-4-il]oxi}-5-clorobenzonitrilo;

5-[(1-Alil-3-*terc*-butil-5-metil-1*H*-pirazol-4-il)oxi]isoftalonitrilo;

5-{[3-*terc*-Butil-1-(2-hidroxietil)-5-metil-1*H*-pirazol-4-il]oxi}isoftalonitrilo;

5-{[1-(2-Aminoetil)-3-*terc*-butil-5-metil-1*H*-pirazol-4-il]oxi}isoftalonitrilo;

3-{[3,5-Dietil-1-(2-hidroxietil)-1*H*-pirazol-4-il]oxi}-5-(1*H*-1,2,4-triazol-1-il)benzonitrilo;

3-{[3,5-Dietil-1-(2-hidroxietil)-1*H*-pirazol-4-il]oxi}-5-(4-oxo-1(4*H*)-piridinil)benzonitrilo;

3-{[3,5-Dietil-1-(2-hidroxietil)-1*H*-pirazol-4-il]oxi}-5-(1*H*-1,2,3-triazol-1-il)benzonitrilo;

3-{[3,5-Dietil-1-(2-hidroxietil)-1*H*-pirazol-4-il]oxi}-5-(2*H*-1,2,3-triazol-2-il)benzonitrilo;

3-{[3,5-Dietil-1-(2-hidroxietil)-1*H*-pirazol-4-il]oxi}-5-fluorobenzamida;

3-{[3,5-Dietil-1-(2-hidroxietil)-1*H*-pirazol-4-il]oxi}-5-(1*H*-pirazol-1-il)benzamida;

3-{[3,5-Dietil-1-(2-hidroxietil)-1*H*-pirazol-4-il]oxi}-5-(2-oxo-1(2*H*)-piridinil)benzamida;

3-{[3,5-Dietil-1-(2-hidroxietil)-1*H*-pirazol-4-il]oxi}-5-(6-oxo-1(6*H*)-piridazinil)benzamida;

3-{[3,5-Dietil-1-(2-hidroxietil)-1*H*-pirazol-4-il]oxi}-5-(2,3-dimetil-5-oxo-2,5-dihidro-1*H*-pirazol-1-il)benzamida;

5-{[3-Ciclopropil-5-etil-1-(2-hidroxietil)-1*H*-pirazol-4-il]oxi}isoftalonitrilo;

5-{[5-Ciclopropil-3-etil-1-(2-hidroxietil)-1*H*-pirazol-4-il]oxi}isoftalonitrilo;

5-{[5-Etil-1-(2-hidroxietil)-3-isopropil-1*H*-pirazol-4-

il]oxi}isoftalonitrilo;

5-{[3-Etil-1-(2-hidroxietil)-5-isopropil-1*H*-pirazol-4-il]oxi}isoftalonitrilo;

Carbamato de 2-[4-(3,5-dicianofenoxi)-3,5-dietil-1*H*-pirazol-1-il]etilo;

N-{2-[4-(3,5-Dicianofenoxi)-3,5-dietil-1*H*-pirazol-1-il]etil}sulfamida;

N-{2-[4-(3,5-Dicianofenoxi)-3,5-dietil-1*H*-pirazol-1-il]etil}-2-metoxiacetamida;

5-{[1-(3-Azetidinil)-3,5-dietil-1*H*-pirazol-4-il]oxi}isoftalonitrilo;

5-{[3,5-Dietil-1-(3-hidroxipropil)-1*H*-pirazol-4-il]oxi}isoftalonitrilo;

5-[(3,5-Dietil-1-metil-1*H*-pirazol-4-il)oxi]isoftalonitrilo;

5-{[3,5-Dietil-1-(2-metoxietil)-1*H*-pirazol-4-il]oxi}isoftalonitrilo;

5-{[1-(3-Aminopropil)-3,5-dietil-1*H*-pirazol-4-il]oxi}isoftalonitrilo;

[4-(3,5-Dicianofenoxi)-3,5-dietil-1*H*-pirazol-1-il]acetatode metilo;

2-[4-(3,5-Dicianofenoxi)-3,5-dietil-1*H*-pirazol-1-il]acetamida;

5-{[3,5-Dietil-1-(hidroximetil)-1*H*-pirazol-4-il]oxi}isoftalonitrilo;

3-[({[4-(3-Ciano-5-fluorofenoxi)-3-metil-1*H*-pirazol-5-

il]metil}amino)metil]benzamida;

4-[({[4-(3-Ciano-5-fluorofenoxi)-3-metil-1*H*-pirazol-5-il]metil}amino)metil]benzamida;

4-[({[4-(3,5-Dicianofenoxi)-3-metil-1*H*-pirazol-5-il]metil}amino)metil]benzamida;

3-[({[4-(3-Cloro-5-cianofenoxi)-3-metil-1*H*-pirazol-5-il]metil}amino)metil]benzamida;

4-[({[4-(3-Ciano-5-metilfenoxi)-3-metil-1*H*-pirazol-5-il]metil}amino)metil]benzamida;

4-[({[4-(3-Cianofenoxi)-3-metil-1*H*-pirazol-5-il]metil}amino)metil]benzamida;

5-[(3,5-Diciclopropil-1*H*-pirazol-4-il)oxi]isoftalonitrilo;

5-{[3,5-Diciclopropil-1-(2-hidroxietil)-1*H*-pirazol-4-il]oxi}isoftalonitrilo;

5-{[1-(2-Aminoetil)-3,5-diciclopropil-1*H*-pirazol-4-il]oxi}isoftalonitrilo;

3-{[3-Ciclopropil-1-(2-hidroxietil)-5-metil-1*H*-pirazol-4-il]oxi}-5-metilbenzonitrilo;

3-{[5-Ciclopropil-1-(2-hidroxietil)-3-metil-1*H*-pirazol-4-il]oxi}-5-metilbenzonitrilo;

3-[3-Ciclopropil-1-(2-aminoetil)-5-metil-1*H*-pirazol-4-iloxi]-5-metil-benzonitrilo;

3-[(3-Ciclopropil-5-metil-1*H*-pirazol-4-il)oxi]-5-metilbenzonitrilo;

3-{[1-(3-Aminopropil)-3,5-dietil-1*H*-pirazol-4-il]oxi}-5-

metilbenzonitrilo;

3-{[3,5-Dietil-1-(2-hidroxietil)-1*H*-pirazol-4-il]oxi}-4-metoxibenzonitrilo;

2-[3,5-Dietil-4-(1-naftiloxi)-1*H*-pirazol-1-il]etanol;

2-[3,5-Dietil-4-(2-naftiloxi)-1*H*-pirazol-1-il]etanol;

2-{4-[3,5-Di(1*H*-pirazol-1-il)fenoxi]-3,5-dietil-1*H*-pirazol-1-il}etanol;

2-{3,5-Dietil-4-[3-fluoro-5-(1*H*-pirazol-1-il)fenoxi]-1*H*-pirazol-1-il}etanol;

3-{[3,5-Dietil-1-(2-hidroxietil)-1*H*-pirazol-4-il]oxi}-5-metoxibenzonitrilo;

2-[4-(3,5-Difluorofenoxi)-3,5-dietil-1*H*-pirazol-1-il]etilamina;

3-{[1-(2-Aminoetil)-3,5-dietil-1*H*-pirazol-4-il]oxi}-5-fluorobenzamida;

3-[(3-Isopropil-5-metil-1*H*-pirazol-4-il)oxi]-5-metilbenzonitrilo;

3-{[1-(2-Aminoetil)-3-isopropil-5-metil-1*H*-pirazol-4-il]oxi}-5-metilbenzonitrilo;

2-[4-(3,5-Diclorofenoxi)-3,5-dietil-1*H*-pirazol-1-il]-*N*-(2-piridinilmetil)acetamida;

[4-(3,5-Diclorofenoxi)-3-metil-1*H*-pirazol-5-il]acetonitrilo;

1-{[4-(3,5-Diclorofenoxi)-3-metil-1*H*-pirazol-5-il]acetil}piperidina;

(3*R*)-1-{[4-(3,5-Diclorofenoxi)-3-metil-1*H*-pirazol-5-

il]acetil}-3-piperidinol;

N-(2,4-Diclorobencil)-2-[4-(3,5-diclorofenoxi)-3-metil-1*H*-pirazol-5-il]acetamida;

2-[4-(3,5-Diclorofenoxi)-3-metil-1*H*-pirazol-5-il]-*N*-(6-metil-2-piridinil)acetamida;

2-[4-(3,5-Diclorofenoxi)-3-metil-1*H*-pirazol-5-il]-*N*-[4-(trifluorometil)bencil]acetamida;

N-(3-Clorobencil)-2-[4-(3,5-diclorofenoxi)-3-metil-1*H*-pirazol-5-il]acetamida;

2-[4-(3,5-Diclorofenoxi)-3-metil-1*H*-pirazol-5-il]-*N*-[2-(trifluorometil)bencil]acetamida;

2-[4-(3,5-Diclorofenoxi)-3-metil-1*H*-pirazol-5-il]-*N*-(4-fluorobencil)acetamida;

N-Bencil-2-[4-(3,5-diclorofenoxi)-3-metil-1*H*-pirazol-5-il]-*N*-metilacetamida;

3-Cloro-5-[(5-{[(2-clorobencil)amino]metil}-3-metil-1*H*-pirazol-4-il)oxi]benzonitrilo;

3-({5-[(Bencilamino)metil]-3-metil-1*H*-pirazol-4-il}oxi)-5-clorobenzonitrilo;

3-[(5-{[Bencil(metil)amino]metil}-3-metil-1*H*-pirazol-4-il)oxi]-5-clorobenzonitrilo;

3-Cloro-5-{[5-({[(5-cloro-2-piridinil)metil]amino}metil)-3-metil-1*H*-pirazol-4-il]oxi}benzonitrilo;

3-Cloro-5-[(3-metil-5-{[(4-piridinilmetil)amino]metil}-1*H*-pirazol-4-il)oxi]benzonitrilo;

3-Cloro-5-[(3-metil-5-{[(4-metilbencil)amino]metil}-1*H*-pirazol-4-il)oxi]benzonitrilo;

3-Cloro-5-[(5-{[(3-metoxipropil)amino]metil}-3-metil-1*H*-pirazol-4-il)oxi]benzonitrilo;

4-[2-({[4-(3-Cloro-5-cianofenoxi)-3-metil-1*H*-pirazol-5-il]metil}amino)etil]bencenosulfonamida;

3-Cloro-5-{[3-metil-5-({[(1*S*)-1-feniletil]amino}metil)-1*H*-pirazol-4-il]oxi}benzonitrilo;

3-Cloro-5-[(5-{[(4-clorobencil)amino]metil}-3-metil-1*H*-pirazol-4-il)oxi]benzonitrilo;

3-Cloro-5-[(3-metil-5-{[metil(2-feniletil)amino]metil}-1*H*-pirazol-4-il)oxi]benzonitrilo;

3-Cloro-5-({3-metil-5-[(1*H*-pirazol-3-ilamino)metil]-1*H*-pirazol-4-il}oxi)benzonitrilo;

N-[2-({[4-(3-Cloro-5-cianofenoxi)-3-metil-1*H*-pirazol-5-il]metil}amino)etil]acetamida;

3-Cloro-5-[(5-{[(3-clorobencil)amino}metil}-3-metil-1*H*-pirazol-4-il)oxi}benzonitrilo;

3-Cloro-5-{[5-({[3-fluoro-5-(trifluorometil)bencil]amino}-metil)-3-metil-1*H*-pirazol-4-il]oxi}benzonitrilo;

3-Cloro-5-[(3-metil-5-{[(6-metil-2-piridinil)amino]metil}-1*H*-pirazol-4-il)oxi]benzonitrilo;

3-Cloro-5-[(5-{[(4-hidroxi-6-metil-2-pirimidinil)amino]-metil}-3-metil-1*H*-pirazol-4-il)oxi]benzonitrilo;

3-Cloro-5-[(5-{[(4-fluorobencil)amino]metil}-3-metil-1*H*-

pirazol-4-il)oxi]benzonitrilo;

3-Cloro-5-{[5-({[(1*R*)-2-hidroxi-1-feniletil]amino}metil)-3-metil-1*H*-pirazol-4-il]oxi}benzonitrilo;

3-({5-[(Bencilamino)metil]-3-metil-1*H*-pirazol-4-il}oxi)-5-clorobenzonitrilo;

3-Cloro-5-[(5-{[(3-metoxibencil)amino]metil}-3-metil-1*H*-pirazol-4-il)oxi]benzonitrilo;

3-Cloro-5-{[3-metil-5-({[4-(trifluorometil)bencil]amino}-metil)-1*H*-pirazol-4-il]oxi}benzonitrilo;

3-Cloro-5-{[5-({[(1*R*)-1-(hidroximetil)-2-metilpropil]amino}-metil)-3-metil-1*H*-pirazol-4-il]oxi}benzonitrilo;

3-Cloro-5-[(5-{[(2-metoxibencil)amino]metil}-3-metil-1*H*-pirazol-4-il)oxi]benzonitrilo;

3-Cloro-5-{[3-metil-5-({[2-(2-tienil)etil]amino}metil)-1*H*-pirazol-4-il]oxi}benzonitrilo;

3-Cloro-5-[(3-metil-5-{[(3-piridinilmetil)amino]metil}-1*H*-pirazol-4-il)oxi]benzonitrilo;

3-Cloro-5-{[3-metil-5-({[2-(trifluorometil)bencil]amino}-metil)-1*H*-pirazol-4-il]oxi}benzonitrilo;

3-Cloro-5-[(5-{[(2,4-diclorobencil)amino]metil}-3-metil-1*H*-pirazol-4-il)oxi]benzonitrilo;

3-Cloro-5-[(3-metil-5-{[(2-piridinilmetil)amino]metil}-1*H*-pirazol-4-il)oxi]benzonitrilo;

3-Cloro-5-[(5-{[(3,4-diclorobencil)amino]metil}-3-metil-1*H*-pirazol-4-il)oxi]benzonitrilo;

3-Cloro-5-[(3-metil-5-{[(3-fenilpropil)amino]metil}-1*H*-pirazol-4-il)oxi}benzonitrilo;

3-Cloro-5-[(5-{[(4-metoxibencil)amino]metil}-3-metil-1*H*-pirazol-4-il)oxi]benzonitrilo;

3-{[3,5-Dietil-1-(2-hidroxietil)-1*H*-pirazol-4-il]oxi}-5-(metilsulfanil)benzonitrilo;

3-{[3,5-Dietil-1-(2-hidroxietil)-1*H*-pirazol-4-il]oxi}-5-(metilsulfinil)benzonitrilo;

3-{[3,5-Dietil-1-(2-hidroxietil)-1*H*-pirazol-4-il]oxi}-5-(metilsulfonil)benzonitrilo;

3-{[3,5-Dietil-1-(2-hidroxietil)-1*H*-pirazol-4-il]oxi}-5-[2-(dimetilamino)etoxi]benzonitrilo;

3-{[3,5-Dietil-1-(2-hidroxietil)-1*H*-pirazol-4-il]oxi}-5-[2-(metilamino)etoxi]benzonitrilo;

2-(3-Ciano-5-{[3,5-dietil-1-(2-hidroxietil)-1*H*-pirazol-4-il]oxi}fenoxi)acetamida;

3-{[3,5-Dietil-1-(2-hidroxietil)-1*H*-pirazol-4-il]oxi}-5-(2-metoxietoxi)benzonitrilo;

3-{[1-(2-Aminoetil)-3,5-dietil-1*H*-pirazol-4-il]oxi}-5-metoxibenzonitrilo;

3-{[1-(2-Aminoetil)-3,5-dietil-1*H*-pirazol-4-il]oxi}-5-(1*H*-pirazol-1-il)benzonitrilo;

3,5-Diclorofenil-3-metil-5-[(3-metil-1,2,4-oxadiazol-5-il)metil]-1*H*-pirazol-4-il éter;

3-Fluoro-5-{[1-(2-hidroxietil)-5-metil-3-(trifluorometil)-1*H*-

pirazol-4-il]oxi}benzonitrilo;

5-[(3,5-Dietil-1-{2-[(2-metoxietoxi)metoxi]etil}-1*H*-pirazol-4-il)oxi]isoftalonitrilo;

3-Ciano-5-{[3,5-dietil-1-(2-hidroxietil)-1*H*-pirazol-4-il]oxi}benzamida;

5-{[5-Etil-3-(1-hidroxietil)-1*H*-pirazol-4-il]oxi}-isoftalonitrilo;

5-{[5-Etil-3-(1-hidroxietil)-1-(2-hidroxietil)-1*H*-pirazol-4-il]oxi}isoftalonitrilo;

3-{[3,5-Dietil-1-(2-hidroxietil)-1*H*-pirazol-4-il]oxi}-5-(5-trifluorometil-1,2,4-oxadiazol-3-il)benzonitrilo;

3-{[3,5-Dietil-1-(2-hidroxietil)-1*H*-pirazol-4-il]oxi}-5-(5-metil-1,2,4-oxadiazol-3-il)benzonitrilo;

3-{[3,5-Dietil-1-(2-hidroxietil)-1*H*-pirazol-4-il]oxi}-5-(5-etil-1,2,4-oxadiazol-3-il)benzonitrilo;

3-{[3,5-Dietil-1-(2-hidroxietil)-1*H*-pirazol-4-il]oxi}-5-(5-isopropil-1,2,4-oxadiazol-3-il)benzonitrilo;

5-[({[4-(3-Cloro-5-cianofenoxi)-3-metil-1*H*-pirazol-5-il]metil}amino)metil]nicotinamida;

2-[({[4-(3-Cloro-5-cianofenoxi)-3-metil-1*H*-pirazol-5-il]metil}amino)metil]isonicotinamida;

2-[4-(3,5-Dicianofenoxi)-3,5-dietil-1*H*-pirazol-1-il]etil fosfato de di(*terc*-butilo);

Fosfato diácido de 2-[4-(3,5-dicianofenoxi)-3,5-dietil-1*H*-pirazol-1-il]etilo;

Sal sulfato de 5-{[3,5-dietil-1-(2-hidroxietil)-1*H*-pirazol-4-il]oxi}isoftalonitrilo;

5-{[3,5-Dietil-1-(2-hidroxietil)-1*H*-pirazol-4-il]oxi}isoftalonitrilo;

Sal tosilato de 5-{[3,5-dietil-1-(2-hidroxietil)-1*H*-pirazol-4-il]oxi}isoftalonitrilo;

Sal mesilato de 5-{[3,5-dietil-1-(2-hidroxietil)-1*H*-pirazol-4-il]oxi}isoftalonitrilo;

Sal bis-mesilato de 3-{[1-(2-aminoetil)-3,5-dietil-1*H*-pirazol-4-il]oxi}-5-metilbenzonitrilo;

Sal fosfato de 3-{[1-(2-aminoetil)-3,5-dietil-1*H*-pirazol-4-il]oxi}-5-metilbenzonitrilo;

Sal tartrato de 3-{[1-(2-aminoetil)-3,5-dietil-1*H*-pirazol-4-il]oxi}-5-metilbenzonitrilo (L);

Sal succinato de 3-{[1-(2-aminoetil)-3,5-dietil-1*H*-pirazol-4-il]oxi}-5-metilbenzonitrilo;

Sal citrato 3-{[1-(2-aminoetil)-3,5-dietil-1*H*-pirazol-4-il]oxi}-5-metilbenzonitrilo (L);

o una sal, solvato o derivado farmacéuticamente aceptable de los mismos.

29. 3-{[3,5-Dietil-1-(2-hidroxietil)-1*H*-pirazol-4-il]oxi}-5-fluorobenzonitrilo;

3-{[3,5-Dietil-1-(2-hidroxietil)-1*H*-pirazol-4-il]oxi}-5-metilbenzonitrilo;

5-{[3,5-Dietil-1-(2-hidroxietil)-1*H*-pirazol-4-il]oxi}isoftalonitrilo;

3-Cloro-5-{[3,5-dietil-1-(2-hidroxietil)-1*H*-pirazol-4-il]oxi}benzonitrilo;

5-[(3,5-Dietil-1*H*-pirazol-4-il)oxi]isoftalonitrilo;

3-[(3,5-Dietil-1*H*-pirazol-4-il)oxi]-5-metilbenzonitrilo;

3-Cloro-5-[(3,5-dietil-1*H*-pirazol-4-il)oxi]benzonitrilo;

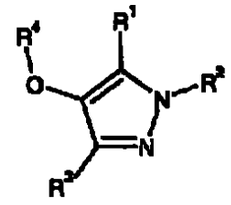
3-{[1-(2-Aminoetil)-3,5-dietil-1*H*-pirazol-4-il]oxi}-5-metilbenzonitrilo;

3-{[1-(2-Aminoetil)-3,5-dietil-1*H*-pirazol-4-il]oxi}-5-clorobenzonitrilo;

5-{[1-(2-Aminoetil)-3,5-dietil-1*H*-pirazol-4-il]oxi}isoftalonitrilo;

o una sal, solvato o derivado farmacéuticamente aceptable de los mismos.

30. Un compuesto de fórmula (I)



(I)

o una sal o solvato farmacéuticamente aceptable del mismo, en la que:

R^1 es H, alquilo C_1-C_6, -Oalquilo C_1-C_6, -Ocicloalquilo C_3-C_7,

estando dicho alquilo C_1-C_6 opcionalmente sustituido con R^{15};

R^2 es H, alquilo C_1-C_3, propenilo o R^{15} unido a C, estando dicho alquilo C_1-C_3 opcionalmente sustituido con -OH, $-OCH_3$, $-OCH_2CH_2NH_2$, -CN, $-CO_2CH_3$, $-CONH_2$, $-C(=NH)NH_2$, $-CONHNH_2$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-NHCH_2CH_2NHCOCH_3$, $-NHCH_2CH_2OCH_3$, $-NHCH_2R^{15}$, $-NHCOR^{15}$, $-NHCOCH_2OCH_3$ o R^{15};

R^3 es alquilo C_1-C_6;

R^4 es fenilo opcionalmente sustituido con halo, -CN, alquilo C_1-C_6, haloalquilo C_1-C_6, cicloalquilo C_3-C_7 o alcoxi C_1-C_6; y

R^{15} es azetidinilo, tetrahidrofuranilo, morfolinilo, piperazinilo, pirazolilo, oxadiazolilo, piridinilo o pirimidinilo, estando cada uno opcionalmente sustituido con -OH, $-NH_2$, oxo o alquilo C_1-C_6 o -CO(alquilo C_1-C_6).

31. Una composición farmacéutica que incluye un compuesto de fórmula (I) o una sal, solvato o derivado farmacéuticamente aceptable del mismo, de acuerdo con cualquier reivindicación precedente, junto con uno o más excipientes, diluyentes o vehículos farmacéuticamente aceptables.

32. Una composición farmacéutica de acuerdo con la reivindicación 31, que incluye uno o más agentes terapéuticos adicionales.

33. Un compuesto de fórmula (I) o una sal, solvato o

derivado farmacéuticamente aceptable del mismo de acuerdo con cualquiera de las reivindicaciones 1 a 30, o una composición farmacéutica de acuerdo con la reivindicación 31 ó 32, para uso como un medicamento.

34. Un compuesto de fórmula (I) o una sal, solvato o derivado farmacéuticamente aceptable del mismo de acuerdo con cualquiera de las reivindicaciones 1 a 30, o una composición farmacéutica de acuerdo con la reivindicación 31 ó 32, para uso como un inhibidor o modulador de la transcriptasa inversa.

35. Un compuesto de fórmula (I) o una sal, solvato o derivado farmacéuticamente aceptable del mismo de acuerdo con cualquiera de las reivindicaciones 1 a 30, o una composición farmacéutica de acuerdo con la reivindicación 31 ó 32, para uso en el tratamiento de una infección por VIH o por un retrovirus relacionado genéticamente, o del síndrome de inmunodeficiencia adquirida resultante (SIDA).

36. El uso de un compuesto de fórmula (I) o de una sal, solvato o derivado farmacéuticamente aceptable del mismo de acuerdo con cualquiera de las reivindicaciones 1 a 30, o de una composición farmacéutica de acuerdo con la reivindicación 31 ó 32, para la fabricación de un medicamento que tiene

actividad inhibidora o moduladora de la transcriptasa inversa.

37. El uso de un compuesto de fórmula (I) o de una sal, solvato o derivado farmacéuticamente aceptable del mismo de acuerdo con cualquiera de las reivindicaciones 1 a 30, o de una composición farmacéutica de acuerdo con la reivindicación 31 ó 32, para la fabricación de un medicamento para el tratamiento de una infección por VIH o por un retrovirus relacionado genéticamente, o del síndrome de inmunodeficiencia adquirida resultante (SIDA).

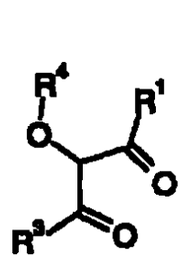
38. Un procedimiento de tratamiento de un mamífero, incluyendo un ser humano, con un inhibidor o modulador de la transcriptasa inversa, que incluye tratar a dicho mamífero con una cantidad eficaz de un compuesto de fórmula (I), o con una sal, solvato o derivado farmacéuticamente aceptable del mismo de acuerdo con cualquiera de las reivindicaciones 1 a 30, o con una composición farmacéutica de acuerdo con la reivindicación 31 ó 32.

39. Un procedimiento de tratamiento de un mamífero, incluyendo un ser humano, con una infección por VIH o por un retrovirus relacionado genéticamente, o con el síndrome de inmunodeficiencia adquirida resultante (SIDA), que incluye

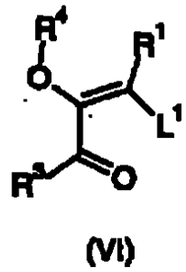
tratar a dicho mamífero con una cantidad eficaz de un compuesto de fórmula (I), o con una sal, solvato o derivado farmacéuticamente aceptable del mismo de acuerdo con cualquiera de las reivindicaciones 1 a 30, o con una composición farmacéutica de acuerdo con la reivindicación 31 ó 32.

40. Un procedimiento para preparar un compuesto de fórmula (I) o una sal, solvato o derivado farmacéuticamente aceptable del mismo de acuerdo con cualquiera de las reivindicaciones 1 a 30, que comprende:

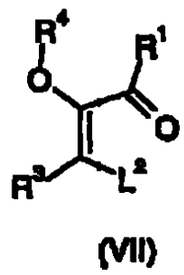
(A) excepto cuando R^1 o R^3 es halo, $-OR^8$ o -CN, la condensación de un compuesto de fórmula (II), (VI) o (VII)



(II),



(VI) o



(VII)

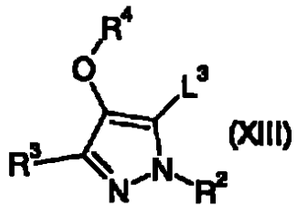
con un compuesto de fórmula

$$H_2NNHR^2 \quad (V)$$

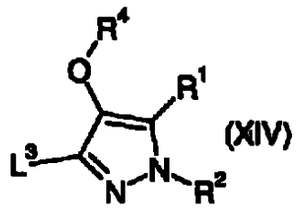
o una sal o hidrato del mismo;

(B) para la preparación de un compuesto de fórmula (I) en la que R^1 o R^3 es $-OR^8$, la reacción de, respectivamente, un

compuesto de fórmula (XIII) o (XIV)


(XIII)

o

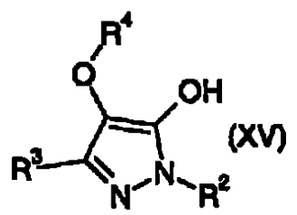

(XIV)

con un alcohol de fórmula (XXI)

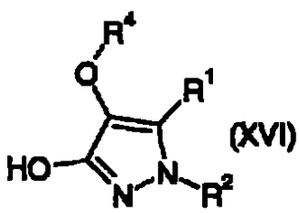
R^5OH (XXI)

en presencia de un catalizador de paladio adecuado y monóxido de carbono;

(C) para la preparación de un compuesto de fórmula (I) en la que R^1 o R^3 es $-OR^8$, la reacción de, respectivamente, un compuesto de fórmula (XV) o (XVI),


(XV)

o

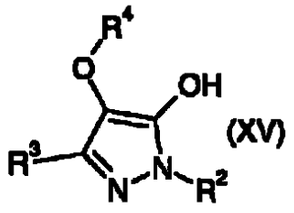

(XVI)

con un compuesto de fórmula (XXI)

R^5OH (XXI)

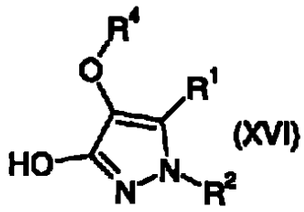
en condiciones de deshidratación; o

(D) para la preparación de un compuesto de fórmula (I) en la que R^1 o R^3 es halo, la reacción de, respectivamente, un compuesto de fórmula (XV) o (XVI)



(XV)

o



(XVI)

con un agente de halogenación; o

(E) la interconversión de un compuesto de fórmula (I) en otro compuesto de fórmula (I); o

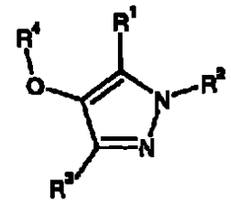
(F) la desprotección de un derivado protegido de un compuesto de fórmula (I); y

opcionalmente la conversión de un compuesto de fórmula (I) preparado por uno cualquiera de los procedimientos (A) a (F) en una sal, solvato o derivado farmacéuticamente aceptable del mismo.

41. Un compuesto de fórmula (II), (VI), (VII), (XIII) o (XIV).

RESUMEN

Esta invención se refiere a derivados de pirazol de fórmula (I)



(I)

o a sales, solvatos o derivados farmacéuticamente aceptables de los mismos, en la que R^1 a R^4 se definen en la descripción, y a procedimientos para la preparación de los mismos, a intermedios usados en su preparación, a composiciones que los contienen y a los usos de tales derivados.

Los compuestos de la presente invención se unen a la enzima transcriptasa inversa y son moduladores, especialmente inhibidores, de la misma. Como tales, los compuestos de la presente invención son útiles en el tratamiento de una diversidad de trastornos, incluyendo aquellos en los que está implicada la inhibición de la transcriptasa inversa. Los trastornos de interés incluyen los causados por el Virus de la Inmunodeficiencia Humana (VIH) y por retrovirus relacionados genéticamente, tales como el Síndrome de Inmunodeficiencia Adquirida (SIDA).

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB 02/01234

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D231/18 C07D231/20 A61K31/415 A61K31/4162 A61K31/4155
A61P31/18 C07D403/06 C07D413/06 C07D401/12 C07D403/12
C07D405/12 C07D403/04 C07D498/04 C07D401/06 C07D471/04

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 3 963 742 A (CROSS BARRINGTON ET AL) 15 June 1976 (1976-06-15) example 25	1,10-13
A	GENIN M J ET AL: "NOVEL 1,5-DIPHENYLPYRAZOLE NONNUCLEOSIDE HIV-1 REVERSE TRANSCRIPTASE INHIBITORS WITH ENHANCED ACTIVITY VERSUS THE DELAVIRDINE-RESISTANT P236L MUTANT: LEAD IDENTIFICATION AND SAR OF 3- AND 4-SUBSTITUTED DERIVATIVES" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 43, 2000, pages 1034-1040, XP002178918 ISSN: 0022-2623 cited in the application the whole document	1,39

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[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
24 June 2002	17/07/2002

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	De Jong, B

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	SMODIS J ET AL: "The Synthesis and Transformations of Substituted 2-Hydroxy-3-dimethylaminopropenoates. The Preparation of Condensed 3-Hydroxypyran-2-ones" TETRAHEDRON, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 54, no. 33, 13 August 1998 (1998-08-13), pages 9799-9810, XP004127445 ISSN: 0040-4020 page 9801	41
X	LIPINSKI ET AL: "Bronchodilator and antiulcer Phenoxypyrimidinones" JOURNAL OF MEDICINAL CHEMISTRY., vol. 23, 1980, pages 1026-1031, XP002201971 AMERICAN CHEMICAL SOCIETY. WASHINGTON., US ISSN: 0022-2623 table II	41
X	REGITZ; SCHÄFER: "Stabile enole von alpha-'Aryl(alkyl)oxy!dibenzoylmethanen" LIEBIGS ANNALEN DER CHEMIE., vol. 7, 1981, pages 1172-1185, XP002201972 VERLAG CHEMIE GMBH. WEINHEIM., DE ISSN: 0170-2041 page 1174	41
X	MUNCH; HAUSER: "Acylations of certain alpha-alkoxy and alpha-aryloxy ketones and esters" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY., vol. 71, 1949, pages 770-773, XP002201973 AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC., US ISSN: 0002-7863 page 770, right-hand column	41
X	ORAZIO ET AL: "Reaction of some 1,2-diaza-1,3-butadienes with activated methine compounds" JOURNAL OF ORGANIC CHEMISTRY., vol. 63, 1998, pages 9880-9887, XP002201974 AMERICAN CHEMICAL SOCIETY. EASTON., US ISSN: 0022-3263 compound 2s	41

-/—

INTERNATIONAL SEARCH REPORT

Interna[illegible]al Application No
PCT/IB 02/01234

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	OLSEN ET AL: "Synthesis of functionalized aryloxy" JOURNAL OF ORGANIC CHEMISTRY., vol. 60, no. 19, 1995, pages 6025-6031, XP002201975 AMERICAN CHEMICAL SOCIETY. EASTON., US ISSN: 0022-3263 compound 16	41

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Int[illegible]ional application No.
PCT/IB 02/01234

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

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

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 38,39 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compounds.

2. [X] Claims Nos.: 1-12,14-27,30-35,40,41
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

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

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

605 602

INTERNATI NAL SEARCH REPORT

International Application No. PCT/IB 02 01234

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-12,14-27,30-35,40,41

Present claims 1-12,14-27,30-35,40,41 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search was only comprehensive for compounds according to claim 13 and their corresponding intermediates of formula XIII and XIV. It should however be noted that the search report can be considered as complete, for all claimed compounds insofar the prior art documents mention their reverse transcriptase inhibiting activity or their anti HIV activity.

The initial phase of the search for compounds of formula (II), (VI) and (VII) according to claim 41, revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claim(s) may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, a meaningful search over the whole breadth of claim 41 is impossible. Consequently, the search for compounds of formula (II), (VI) and (VII) was only comprehensive for compounds according to the examples.

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

Ination on patent family members

Intern Application No
PCT/1B 02/01234

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 3963742 A	15-06-1976	US 4041046 A	09-08-1977
		US 4058391 A	15-11-1977
		AR 216425 A1	28-12-1979
		AU 498491 B2	15-03-1979
		AU 8236375 A	06-01-1977
		BE 831272 A4	12-01-1976
		CA 1066294 A1	13-11-1979
		DK 317975 A	13-01-1976
		FI 752005 A	13-01-1976
		FR 2295027 A2	16-07-1976
		GB 1519494 A	26-07-1978
		IT 1050692 B	20-03-1981
		NZ 177874 A	28-04-1978
		RO 68992 A1	30-07-1981
		SE 7508002 A	11-02-1976
		ZA 7503894 A	26-05-1976

603 604 606

SUPERINDUSTRIA Y COMERCIO
Radicacion 03079617 00000000 Folios: 600
Fecha (AMD): 2003-09-10 17:14:01
Tramite 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia 2020 DIVISION DE NUEVAS CREACIONES

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

	USUARIO	RADICADOR
PATENTE DE INVENCIÓN X 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. ✓	( )	( )
- Descripcion de la invención ✓	NA	( )
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 grafica y fotografica 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	( )	( )
Representacion grafica del esquema de trazado	( )	( )
Comprobante de pago de las tasas establecidas	( )	( )
COMPLETA ( )	INCOMPLETA ( )	( )

Firma Responsable Andrea Rossi

Fecha

Industria y Comercio
SUPERINTENDENCIA

607
604

Folio 602

2020
Bogotá DC

Doctor(a)
CARLOS R OLARTE
Apoderado(a)
PFIZER INC

REFERENCIA.	Radicación No	03-079617
	Solicitud Internacional	PCT/IB2002/01234
	Fecha inicio fase nacional	10/11/2003
	Trámite	011
	Evento	379
	Actuación	416
	Oficio No	1302
	Folios	001

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

Cúmplase
Dado en Bogotá DC, 04 NOV 2011

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

202055