08 - 13173

SUPERINTENDENCIA
INVE



Organización y Digitalización CSA Ltda

Industria y Comercio

SUPERINTENDENCIA

PCT

DELEGATURA DE PROPIEDAD INDUSTRIAL

DIVISIÓN DE NUEVAS CREACIONES

08 - 13173

SOLICITUD DE PATENTE DE INVENCIÓN

TITULO DERIVADOS DE XANTINA COMO AGONISTAS DE HM74A SELECTIVOS

SOLICITANTE: SMITHKLINE BEECHAM CORPORATION

DIRECCIÓN: One Franklin Plaza, P.O Box 7929, Philadelphia, PA 19101 E.U.A.

AGK 34/49T

APODERADO: CARLOS R. OLARTE

BOGOTÁ 8 de Febrero de 2008

P2008/000030

OLARTERAISBECK

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 08-013173- -00000-0000
Fecha: 2008-02-11 12:31:27 Dep: 2020 NUECREACIONI
Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 703

PETITORIO - FORMULARIO UNICO DE SOLICITUD
PATENTE PCT
ENTRADA EN FASE NACIONAL **P2008/000030**

SOLICITUD DE:

(1) [X] Patente de Invención. [ ] Patente de Modelo de Utilidad.

[X] Capítulo I. [ ] Capítulo II.

(2) **SOLICITANTE (71)**

Nombre: SMITHKLINE BEECHAM CORPORATION
Dirección: One Franklin Plaza, Po Box 7929, Philadelphia, Pennsylvania 19101 E.U.A.
Nacionalidad o Domicilio: Estadounidense
Lugar de Constitución: E.U.A.
Teléfono: **Fax:**
E-mail:

IDENTIFICACIÓN
C.C. [ ] **NIT** [ ]
C.E. [ ] **Otro** [ ]
Cual
Número

REPRESENTANTE O APODERADO

Nombre: CARLOS R. OLARTE
Dirección: World Trade Center Torre A, Calle 100 No. 8A-37 Piso 10
Teléfono: 601-7700 **Fax:** 601-7799
E-mail: office@olarteraisbeck.com

IDENTIFICACIÓN
C.C. [X] **NIT** [ ]
C.E. [ ] **Otro** [ ]
Cual
Número 79782747Bta
TP 74.295

INVENTOR (ES) (72)

Nombre: VER PAGINA ADJUNTA
Dirección: VER PAGINA ADJUNTA
Nacionalidad o Domicilio: VER PAGINA ADJUNTA

(5) **PCT (86)**

Solicitud Internacional No. PCT/EP2006/007869 Fecha Agosto 8, 2006

Publicación Internacional No. WO 2007/017262 Fecha Febrero 15, 2007

(6) **Título (54)** **DERIVADOS DE XANTINA COMO AGONISTAS DE HM74A SELECTIVOS**

Clasificación Internacional (51) C07D 473/06, C07D 473/04, A61K 31/495, A61P 3/00, A61P 9/00

Prioridad
SI [X] **NO** [ ]

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
GB	Agosto 10, 2005	0516464.5
GB	Abril 19, 2006	0607736.6
GB	Julio 21, 2006	0614569.2

(9) **Comprobante de pago No.** **08-10,531** **Fecha** **7 de Febrero de 2008**

(10) **ANEXOS**

[x] Comprobante de pago de la tasa de presentación de la solicitud.

[x] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.

[x] Poderes, si fuere el caso. Adjunto copia simple ver expediente No. 06-078.318

[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. Búsqueda Internacional

(11) **FIGURA CARACTERÍSTICA:**

(12) Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTE

FIRMA:

C.C. 79.782.747 Btá T.P. 74.295

RICHARD JONATHAN DANIEL HATLEY
Gunnels Wood Road,
Stevenage Hertfordshire
SG1 2NY
Gran Bretaña
Nacionalidad: Británico

JAG PAUL HEER
New Frontiers Science
Park South, Third Avenue,
Harlow Essex CM19 5 AW
Gran Bretaña
Nacionalidad: Británico

JOHN LIDDLE
Gunnels Wood Road,
Stevenage Hertfordshire
SG1 2NY
Gran Bretaña
Nacionalidad: Británico

ANDREW McMURTRIE MASON,
Gunnels Wood Road,
Stevenage Hertfordshire
SG1 2NY
Gran Bretaña
Nacionalidad: Británico

IVAN LEO PINTO,
New Frontiers Science
Park South, Third Avenue,
Harlow Essex CM19 5 AW
Gran Bretaña
Nacionalidad: Británico

SHAHZAD SHAROOQ RAHMAN,
New Frontiers Science
Park South, Third Avenue,
Harlow Essex CM19 5 AW
Gran Bretaña
Nacionalidad: Británico

IAN EDWARD DAVID SMITH,
Gunnels Wood Road,
Stevenage Hertfordshire
SG1 2NY
Gran Bretaña
Nacionalidad: Británico

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 08-013173- -00000-0000

Fecha: 2008-02-11 12:31:27 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve. 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 703

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 08 - 10,531
FECHA : FEBRERO 7 DE 2008

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBEK	CONSIGNACION	BANCO DE BOGOTA	062754387	2661942	07/02/2008	4,673,000.00

***** 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	501,000.00
		TOTAL : $	501,000.00

SON: QUINIENTOS UN 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

5

APOSTILLA EN PODER DE REPRESENTACIÓN DE

SMITHKLINE BEECHAM CORPORATION

PODER DE REPRESENTACION

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

Certificado de Notario De Pinna en español certificando que Peter John Giddings es apoderado de Smithkline Beecham Corporation, firmado por James Kerr Milligan.

APOSTILLA

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

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

CERTIFICADO

5. En Londres
6. El 14 agosto 2003
7. Por el Secretario de Estado *Principal* de su Majestad para Asuntos exteriores y de la Mancomunidad
8. No. G229470
9. Gran Sello de la Oficina de Asuntos exteriores y de la Mancomunidad
10. Firma legible de J. Garbrah- Por el Secretario de Estado

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

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

Marlen Neira C

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

DE PINNA
NOTARIES

6

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

C E R T I F I C O:

QUE es auténtica la firma "P. Giddings" suscrita al pie del adjunto Poder, por ser del puño y letra del Señor Don **PETER JOHN GIDDINGS**, cuya identidad me consta, Apoderado de la corporación denominada **"SMITHKLINE BEECHAM CORPORATION"**, corporación legalmente constituída y existente de acuerdo con las leyes del Estado de Pensilvania, Estados Unidos de América, con domicilio social en 1, Franklin Plaza, Philadelphia, Pensilvania 19101, Estados Unidos de América;

QUE el citado Señor Don **PETER JOHN GIDDINGS** está debida y suficientemente autorizado para firmar documentos de esta clase, en virtud del Poder otorgado en su favor por la referida Sociedad fechado el 11 de julio de 2002, copia del cual he tenido a la vista.

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

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

JAMES KERR MILLIGAN
Notario Público de Londres, Inglaterra

SCRIVENER NOTARIES

DE PINNA
35 Piccadilly London W1J 0LJ
Telephone:+44 (0)20 7208 2900 Facsimile: +44 (0)20 7208 0066 DX No. 48521 Piccadilly 2

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: **James Kerr Milligan**

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 **14 August 2003**

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

8. Number/sous No **G229470**

9. Stamp:
   timbre:

10. Signature: **J. Garbrah**

FOREIGN AND COMMONWEALTH OFFICE
LONDON

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.

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

Power of Attorney

The undersigned,

SmithKline Beecham Corporation

domiciled in

One Franklin Plaza, P O Box 7929, Philadelphia, PA 19101, United States of America

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,

domiciliado en

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

Signature/Firma: _____

Peter John GIDDINGS as Attorney and Authorised Official

Date/Fecha: 13 August 2003

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

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION RELATING TO
DECLARATION MADE UNDER PCT RULE 4.17

(PCT Rules 26*ter* and 48.2(a)(x)
and Administrative Instructions, Section 419)

To:

EASEMAN, Richard, Lewis
GlaxoSmithKline
Corporate Intellectual Property (CN925.1)
980 Great West Road
Brentford Middlesex TW8 9GS
ROYAUME-UNI

Date of mailing *(day/month/year)* 19 October 2006 (19.10.2006)	
Applicant's or agent's file reference LH/PB62046	**IMPORTANT NOTIFICATION**
International application No. PCT/EP2006/007869	International filing date *(day/month/year)* 08 August 2006 (08.08.2006)

Applicant
SMITHKLINE BEECHAM CORPORATION et al

1. The applicant is hereby **notified** of the following regarding the declaration indicated below in respect of SMEETHKLINE BEECHAM CORPORATION, et al.. :

   (i) ☐ declaration as to the identity of the inventor (Rules 4.17(i) and 51*bis*.1(a)(i) and Section 211)

   (ii) ☒ declaration as to the applicant's entitlement, as at the international filing date, to apply for or be granted a patent (Rules 4.17(ii) and 51*bis*.1(a)(ii) and Section 212)

   (iii) ☒ declaration as to the applicant's entitlement, as at the international filing date, to claim priority of the earlier application (Rules 4.17(iii) and 51*bis*.1(a)(iii) and Section 213)

   (iv) ☒ declaration of inventorship (for the purposes of the designation of the United States of America) (Rules 4.17(iv) and 51*bis*.1(a)(iv) and Section 214)

   (v) ☐ declaration as to non-prejudicial disclosures or exceptions to lack of novelty (Rules 4.17(v) and 51*bis*.1(a)(v) and Section 215)

2. ☒ **Addition or correction of the declaration within the time limit under Rule 26*ter*.1.**

   The added or corrected declaration was received on 21 September 2006 (21.09.2006) , which was within the time limit under Rule 26*ter*.1.

   Any declaration referred to under items 1(i) to (v), whether or not the declaration complies with Rule 4.17, will be published as part of the international application pursuant to Rule 48.2(a)(x).

3. ☐ **Failure to add or correct the declaration within the time limit under Rule 26*ter*.1.**

   The declaration was received on which was **after** the expiration of the time limit under Rule 26*ter*.1; therefore, that declaration, as added or corrected, referred to under items 1(i) to (v) will **not** be published as part of the international application, and any signed declaration referred to under item 1(iv) is attached. **Such declaration should be submitted by the applicant directly to the designated Office(s) concerned.**

4. The applicant's attention is drawn to Rule 51*bis*.2 which provides that the designated Office shall not, unless it may reasonably doubt the veracity of the declaration concerned, require any document or evidence relating to the subject matter of any declaration complying with Rule 4.17(i) to (iv) which is contained in the request or submitted to the International Bureau or directly to the designated Office. Note, however, that Rule 51*bis*.2 may not apply in respect of certain States. For further information, see Notes to the request form, Box No. VIII.

5. A copy of this notification is being sent to the receiving Office and the International Searching Authority.

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Aumaitre Chantal Facsimile No. +41 22 338 70 80

Box No. VIII(iv) DECLARATION: INVENTORSHIP (only for the purposes of the designation of the United States of America). The declaration must conform to the following standardized wording provided for in Section 214; see Notes to Boxes Nos. VIII, VIII(I) to (v) (in general) and the specific Notes to Box No. VIII (iv). If this Box is not used, this sheet should not be included in the request.

Declaration of Inventorship (Rules 4.17(iv) and 51*bis*.1(a)(iv)) for the purposes of the designation of the United States of America:

I hereby declare that I believe I am the original, first and sole (if only one inventor is listed below) or joint (if more than one inventor is listed below) inventor of the subject matter which is claimed and for which a patent is sought.

This declaration is directed to the international application of which it forms a part (if filing declaration with application).

This application is directed to international application No. PCT/EP2006/007869 (if furnishing declaration pursuant to Rule 26*ter*).

I hereby declare that my residence, mailing address, and citizenship are as stated next to my name.

I hereby state that I have reviewed and understand the contents of the above-identified international application, including the claims of said application. I have identified in the request of said application, in compliance with PCT Rule 4.10, any claim to foreign priority, and I have identified below, under the heading "Prior Application," by application number, country or Member of the World Trade Organization, day, month and year of filing, any application for a patent or inventor's certificate filed in a country other than the United States of America, including any PCT international application designating at least one country other than the United States of America, having a filing date before that of the application on which foreign priority is claimed.

Prior Applications: .....

I hereby acknowledge the duty to disclose information that is known by me to be material to patentability as defined by 37 C.F.R. §1.56, including for continuation-in-part applications, material information which became available between the filing date of the prior application and the PCT international filing date of the continuation-in-part.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Name: Richard Jonathan Daniel HATLEY

Residence: Stevenage, Hertfordshire, GB
(city and either US state, if applicable, or country)

Mailing Address: GlaxoSmithKline, Corporate Intellectual Property - UW2220, P.O. Box 1539
King of Prussia, Pennsylvania 19406-0939

Citizenship: British

Inventor's Signature: _____ Date: 12th September 2006
(if not contained in the request, or if declaration is corrected or added under Rule 26*ter* after the filing of the international application. The signature must be that of the inventor, not that of the agent.) (of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26*ter* after the filing of the international application)

Name: Jag Paul HEER

Residence: Harlow, Essex, GB
(city and either US state, if applicable, or country)

Mailing Address: GlaxoSmithKline, Corporate Intellectual Property - UW2220, P.O. Box 1539
King of Prussia, Pennsylvania 19406-0939

Citizenship: British

Inventor's Signature: _____ Date: 11th September 2006
(if not contained in the request, or if declaration is corrected or added under Rule 26*ter* after the filing of the international application. The signature must be that of the inventor, not that of the agent.) (of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26*ter* after the filing of the international application)

☒ This declaration is continued on the following sheet, "Continuation of Box No. VIII(iv)".

Continuation of Box No. VIII(i) to (v) Declaration

If the space is insufficient in any of Boxes Nos. VIII(I) to (v) to furnish all the informatino, including in the case where more than two inventors are to be named in Box No. VIII (iv), in such case, write "Continuation of Box No. VIII " (indicate the item number of the Box) and furnish the information in the same manner as required for the purposes of the Box in which the space was insufficient. If additional space is needed in respect of two or more declarations, a separate continuation box must be used for each such declaration. If this Box is not used, this sheet should not be included in the request.

Name: John LIDDLE

Residence: Stevenage, Hertfordshire, GB
(city and either US state, if applicable, or country)

Mailing Address: GlaxoSmithKline, Corporate Intellectual Property - UW2220, P.O. Box 1539
King of Prussia, Pennsylvania 19406-0939

Citizenship: British

Inventor's Signature: John Liddle Date: 18 Sept 06
(if not contained in the request, or if declaration is corrected or added under Rule 26*ter* after the filing of the international application. The signature must be that of the inventor, not that of the agent.)

(of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26*ter* after the filing of the international application)

Name: Andrew McMurtrie MASON

Residence: Stevenage, Hertfordshire, GB
(city and either US state, if applicable, or country)

Mailing Address: GlaxoSmithKline, Corporate Intellectual Property - UW2220, P.O. Box 1539
King of Prussia, Pennsylvania 19406-0939

Citizenship: British

Inventor's Signature: Andrew Mason Date: 14 Sept 06
(if not contained in the request, or if declaration is corrected or added under Rule 26*ter* after the filing of the international application. The signature must be that of the inventor, not that of the agent.)

(of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26*ter* after the filing of the international application)

Name: Ivan Leo PINTO

Residence: Harlow, Essex, GB
(city and either US state, if applicable, or country)

Mailing Address: GlaxoSmithKline, Corporate Intellectual Property - UW2220, P.O. Box 1539
King of Prussia, Pennsylvania 19406-0939

Citizenship: British

Inventor's Signature: Date: 12th Sept 2006
(if not contained in the request, or if declaration is corrected or added under Rule 26*ter* after the filing of the international application. The signature must be that of the inventor, not that of the agent.)

(of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26*ter* after the filing of the international application)

Name: Shahzad Sharooq RAHMAN

Residence: Harlow, Essex, GB
(city and either US state, if applicable, or country)

Mailing Address: GlaxoSmithKline, Corporate Intellectual Property - UW2220, P.O. Box 1539
King of Prussia, Pennsylvania 19406-0939

Citizenship: British

Inventor's Signature: _____ Date: 11- September - 2006
(if not contained in the request, or if declaration is corrected or added under Rule 26*ter* after the filing of the international application. The signature must be that of the inventor, not that of the agent.)

(of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26*ter* after the filing of the international application)

Name: Ian Edward David SMITH

Residence: Stevenage, Hertfordshire, GB
(city and either US state, if applicable, or country)

Mailing Address: GlaxoSmithKline, Corporate Intellectual Property - UW2220, P.O. Box 1539
King of Prussia, Pennsylvania 19406-0939

Citizenship: British

Inventor's Signature: _____ Date: 14th September, 2006
(if not contained in the request, or if declaration is corrected or added under Rule 26*ter* after the filing of the international application. The signature must be that of the inventor, not that of the agent.)

(of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26*ter* after the filing of the international application)

Box No. VIII(iii) DECLARATION: ENTITLEMENT TO CLAIM PRIORITY

The declaration must conform to the standardized wording provided for in Section 213; see Notes to Boxes Nos. VIII, VIII(i) to (v) (in general) and the specific Notes to Box No. VIII(iii) and 51*bis*.1(a)(iii)

Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application specified below, where the applicant is not the applicant who filed the earlier application or where the applicant's name has changed since the filing of the earlier application (Rules 4.17(iii) and 51*bis*.1(a)(iii)):

in relation to international application No. PCT/EP2006/007869

SMITHKLINE BEECHAM CORPORATION is entitled to claim priority of earlier application Nos. 0516464.5, 0607736.6 and 0614569.2 filed in the United Kingdom by virtue of the following:

(i) transfer of entitlement from ***Richard Jonathan Daniel HATLEY, Jag Paul HEER, John LIDDLE, Andrew McMurtrie MASON, Ivan Leo PINTO, Shahzad Sharooq RAHMAN and Ian Edward David SMITH*** to GlaxoSmithKline Services Unlimited by way of employment contract

(ii) an assignment from GlaxoSmithKline Services Unlimited to SmithKline Beecham Corporation dated 8 September 2006

☐ This declaration is continued on the following sheet, "Continuation of Box No. VIII(iii)".

Box No. VIII(ii) DECLARATION: ENTITLEMENT TO APPLY FOR AND BE GRANTED A PATENT
The declaration must conform to the standardized wording provided for in Section 212; see Notes to Boxes Nos. VIII, VIII(I) to (v) (in general and the specific Notes to Box No. VIII(ii). If this Box is not used, this sheet should not be included in the request.

Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent (Rules 4.17(ii) and 51*bis*.1(a)(ii)), in a case where the declaration under Rule 4.17(iv) is not appropriate:

in relation to international application No. PCT/EP2006/007869

SMITHKLINE BEECHAM CORPORATION is entitled to apply for and be granted a patent by virtue of the following:

(i) transfer of entitlement from inventors ***Richard Jonathan Daniel HATLEY, Jag Paul HEER, John LIDDLE, Andrew McMurtrie MASON, Ivan Leo PINTO, Shahzad Sharooq RAHMAN and Ian Edward David SMITH*** to GlaxoSmithKline Services Unlimited by way of employment contract

(ii) an assignment from GlaxoSmithKline Services Unlimited to SmithKline Beecham Corporation dated 8 September 2006

☐ This declaration is continued on the following sheet, "Continuation of Box No. VIII(ii)".

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
15 February 2007 (15.02.2007)

PCT

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(71) Applicant *(for all designated States except US)*: **SMITHKLINE BEECHAM CORPORATION** [US/US]; One Franklin Plaza, Po Box 7929, Philadelphia, Pennsylvania 19101 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **HATLEY, Richard, Jonathan, Daniel** [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage Hertfordshire SG1 2NY (GB). **HEER, Jag, Paul** [GB/GB]; GlaxoSmithKline, New Frontiers Science Park South, Third Avenue, Harlow Essex CM19 5AW (GB). **LIDDLE, John** [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage Hertfordshire SG1 2NY (GB). **MASON, Andrew, McMurtrie** [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage Hertfordshire SG1 2NY (GB). **PINTO, Ivan, Leo** [GB/GB]; GlaxoSmithKline, New Frontiers Science Park South, Third Avenue, Harlow Essex CM19 5AW (GB). **RAHMAN, Shahzad, Sharooq** [GB/GB]; GlaxoSmithKline, New Frontiers Science Park South, Third Avenue, Harlow Essex CM19 5AW (GB). **SMITH, Ian, Edward, David** [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage Hertfordshire SG1 2NY (GB).

(74) Agent: **EASEMAN, Richard, Lewis**; GlaxoSmithKline, Corporate Intellectual Property (CN925.1), 980 Great West Road, Brentford Middlesex TW8 9GS (GB).

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(54) Title: XANTHINE DERIVATIVES AS SELECTIVE HM74A AGONISTS

(57) Abstract: The present invention relates to compounds Of formula (I), which are xanthine derivatives, processes for the manufacture of said derivatives, pharmaceutical formulations containing the active compounds and the use of the compounds in therapy, for example, in the treatment of diseases where under-activation of the HM74A receptor contributes to the disease or where activation of the receptor will be beneficial.

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XANTHINE DERIVATIVES AS SELECTIVE HM74A AGONISTS

The present invention relates to compounds which are xanthine derivatives, processes for the manufacture of said derivatives, pharmaceutical formulations containing these compounds and the use of the compounds in therapy, for example, in the treatment of diseases where under-activation of the HM74A receptor contributes to the disease or where activation of the receptor will be beneficial.

Dyslipidaemia is a general term used to describe individuals with aberrant lipoprotein profiles. Clinically, the main classes of compounds used for the treatment of patients with dyslipidaemia, and therefore at risk of cardiovascular disease are the statins, fibrates, bile-acid binding resins and nicotinic acid. Nicotinic acid (Niacin, a B vitamin) has been used clinically for over 40 years in patients with various forms of dyslipidaemia. The primary mode of action of nicotinic acid is via inhibition of hormone-sensitive triglyceride lipase (HSL), which results in a lowering of plasma non-esterified fatty acids (NEFA) which in turn alters hepatic fat metabolism to reduce the output of LDL and VLDL (low and very low density lipoprotein). Reduced VLDL levels are thought to lower cholesterol ester transfer protein (CETP) activity to result in increased HDL (high density lipoprotein) levels which may be the cause of the observed cardiovascular benefits. Thus, nicotinic acid produces a very desirable alteration in lipoprotein profiles; reducing levels of VLDL and LDL whilst increasing HDL. Nicotinic acid has also been demonstrated to have disease modifying benefits, reducing the progression and increasing the regression of atherosclerotic lesions and reducing the number of cardiovascular events in several trials.

The observed inhibition of HSL by nicotinic acid treatment is mediated by a decrease in cellular cyclic adenosine monophosphate (cAMP) caused by the G-protein-mediated inhibition of adenylyl cyclase. Recently, the G-protein coupled receptors HM74 and HM74A have been identified as receptors for nicotinic acid (PCT patent application WO02/84298; Wise et. al. J Biol Chem., 2003, 278 (11), 9869-9874). The DNA sequence of human HM74A may be found in Genbank; accession number AY148884. Two further papers support this discovery, (Tunaru et. al. Nature Medicine, 2003, 9(3), 352-255 and Soga et. al. Biochem Biophys Res Commun., 2003, 303 (1) 364-369), however the nomenclature differs slightly. In the Tunaru paper what they term human HM74 we term HM74A and in the Soga paper HM74b is identical to HM74A. Cells transfected to express HM74A and/or HM74 gain the ability to elicit G_i G-protein mediated responses following exposure to nicotinic acid. In mice lacking the homologue of HM74A (m-PUMA-G) nicotinic acid fails to reduce plasma NEFA levels.

Certain xanthine derivatives have been synthesised and disclosed in the prior art. For example, EP0389282 discloses xanthine derivatives as potential mediators of cerebrovascular disorders. A range of xanthine derivatives were identified as

adenosine receptor antagonists by Jacobson et. al. in J. Med. Chem., 1993, 36, 2639-2644.

We now present a group of xanthine derivatives which are selective agonists of the nicotinic acid receptor HM74A and are thus of potential benefit in the treatment, prophylaxis and suppression of diseases where under-activation of this receptor either contributes to the disease or where activation of the receptor will be beneficial.

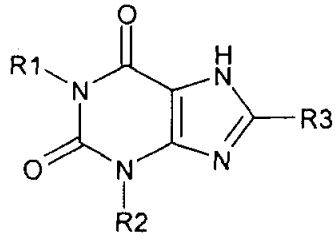
Summary of the Invention

The present invention provides xanthine derivatives and the use of these derivatives in therapy, for example, in the treatment of diseases where under-activation of the HM74A receptor contributes to the disease or where activation of the receptor will be beneficial. For example, in treatment of diseases of lipid metabolism including dyslipidaemia or hyperlipoproteinaemia such as diabetic dyslipidaemia and mixed dyslipidaemia, heart failure, hypercholesteraemia, cardiovascular disease including atherosclerosis, arteriosclerosis, and hypertriglyceridaemia. As such, the compounds may also find favour as therapeutics for coronary artery disease, thrombosis, angina, chronic renal failure, peripheral vascular disease and stroke, as well as the cardiovascular indications associated with type II diabetes mellitus, type I diabetes, insulin resistance, hyperlipidaemia, anorexia nervosa, obesity. The compounds may also be of use in the treatment of inflammatory diseases or conditions, as set out further below.

Intermediates, formulations, methods and processes described herein form further embodiments of the invention.

Detailed Description of the Invention

According to one aspect of this invention we provide at least one chemical entity selected from compounds of formula (I)



(I)

and pharmaceutically acceptable derivatives thereof, wherein

R^1 represents $-(alkylene)_m-X-(alkylene)_n-Y$;

Wherein X represents A, A1, A2 or a direct link;

A represents a group selected from
cycloalkylene, cycloalkenylene, aryl, heteroaryl, heterocyclyl, and $-CH_2-OC(O)-$;

A1 represents a group selected from
$-CH_2-O-(CH_2)_q$aryl$-O-$, $-CH_2-O-(CH_2)_wN(R^5)C(O)O-$, $-CH_2-N(R^5)C(O)O-$,
$-CH_2-N(R^5)C(O)-$, $-CH_2-(O)_p-(CH_2)_qC(O)NR^5-$, $-CH_2-N(R^5)C(O)N(R^5)-$,
$-CH_2-C(O)N((CH_2)_wOH)-$, $-CH_2-NR^5-S(O)_2-$, $CH_2-S(O)_2NR^5-$, $-CH_2-C(O)O-$, $-O-$,
$-NR^5-$, and $-S-$;

A2 represents $-CH(OH)-$;

When X is A, A1 or A2, Y represents a group selected from
heteroaryl, heterocyclyl, aryl, cycloalkyl, cycloalkenyl, -NH-aryl, $-O(CH_2)_n$-aryl,
-O-heteroaryl, $-OR^5$, $-C(O)OR^5$, $-C(O)O-C_6$aryl, $-OC(O)R^4$, $-CH(aryl)_2$,
$-CH(heteroaryl)_2$, and $-C_{1-6}$ haloalkyl;

When X is A1 and Y is selected from
$-O(CH_2)_n$-aryl, -O-heteroaryl, $-OR^5$, $-OC(O)R^4$, and -NH-aryl,
n is an integer selected from 2, 3, 4 and 5;

When X is A1 and Y is $-C_{1-6}$ haloalkyl, or when X is A2, n is an integer selected from 1, 2, 3, 4 and 5;

When X is a direct link, (m + n) is an integer selected from 2 to 10;

When X is a direct link and (m + n) is an integer selected from 3 to 10, Y represents a group selected from
$-C(O)(CH_2)_qOR^4$, -C(O)-aryl, -C(O)-heteroaryl, -C(O)-heterocyclyl, heteroaryl, heterocyclyl, Aryl, 3 or 4 ring fused system, $-CH(aryl)_2$, $-CH(heteroaryl)_2$, $-OR^5$, $-NR^5R^6$, $-NR^5C(O)OR^7$, $-(O)_pC(O)NR^5R^7$, and $-NR^5C(O)R^7$;

When X is a direct link and (m + n) is 2, Y represents a group selected from
$-OR^5$, $-NH_2$, and $-NR^5C(O)OR^8$;

When Y incorporates a ring, that ring may be optionally substituted by one or more of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, $-(CH_2)_qNR^5R^7$,
$-(CH_2)_q-(O)_p-(CH_2)_q-N(R^5)C(O)OR^8$, $-(CH_2)_q-N(R^5)C(O)R^8$,
$-(CH_2)_q-(O)_p-(CH_2)_q-C(O)NR^5R^6$, $-(CH_2)_q-N(R^5)C(O)N(R^5)R^6$,

$-(CH_2)_q-C(O)N((CH_2)_mOH)R^5$, $-(CH_2)_q-N(R^5)-S(O)_2R^8$, $-CH_2-S(O)_2N(R^5)R^6$, $-C_{1-6}$ haloalkyl, $-OCF_3$, $-OCH(F)_2$, $-OCH_2F$, $-C(O)OR^5$, $-OR^5$, $-R^8CN$, $-CN$, $-SO_2R^9$, $-(CH_2)_n$heteroaryl, $-(CH_2)_n$heterocycyl, $-(CH_2)_n$cycloalkyl, $-(CH_2)_n$cycloalkenyl, and $-(CH_2)_n$aryl;

Provided that when X is A1, A1 is -O- and Y is a ring which is substituted by aryl or heteroaryl, then m is an integer selected from 3, 4 and 5;

R^2 is selected from hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, aryl, and heteroaryl, each of which may be optionally substituted by one or more of a group independently selected from: C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, C_{1-6} haloalkyl, halogen, -CN, $-OR^4$, $-(CH_2)_nCOR^4$, $-C(O)OR^4$, $-OCOR^4$, $-(CH_2)_nNR^5R^6$, $-(NH)_pCONR^5R^6$, $-OCONR^5R^7$, and $-NR^5C(O)OR^7$;

R^3 represents a group selected from halogen and CN;

R^4 is selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $-(CH_2)_n$ cycloalkyl, $-(CH_2)_n$ cycloalkenyl, $-(CH_2)_n$ heterocyclyl, $-(CH_2)_n$ aryl, and $-(CH_2)_n$ heteroaryl;

R^5 and R^6 are independently selected from hydrogen and C_{1-4} alkyl;

R^7 represents a group selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $-(CH_2)_t$ cycloalkyl, $-(CH_2)_n$ cycloalkenyl, $-(CH_2)_t$ heterocyclyl, $-(CH_2)_t$ aryl, and $-(CH_2)_t$ heteroaryl;

R^8 represents a group selected from C_{1-4} alkyl;

R^9 represents a group selected from C_{1-6} alkyl C_{2-6} alkenyl, C_{2-6} alkynyl, $-(CH_2)_n$ cycloalkyl, $-(CH_2)_n$cycloalkenyl, $-(CH_2)_n$heterocyclyl, $-(CH_2)_n$ aryl, $-(CH_2)_n$heteroaryl, and CN;

m represents an integer selected from 1, 2, 3, 4 and 5;

n represents an integer selected from 0, 1, 2, 3, 4 and 5;

p represents an integer selected from 0 and 1;

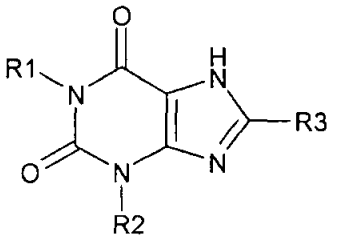
q represents an integer selected from 0, 1 and 2;

t represents an integer selected from 1 and 2; and

w represents an integer selected from 2, 3 and 4.

The compounds are of use in the treatment of diseases where under-activation of the HM74A receptor contributes to the disease or where activation of the receptor will be beneficial. For example in treatment of diseases of lipid metabolism including dyslipidaemia or hyperlipoproteinaemia such as diabetic dyslipidaemia and mixed dyslipidaemia, heart failure, hypercholesteraemia, cardiovascular disease including atherosclerosis, arteriosclerosis, and hypertriglyceridaemia. As such, the compounds may also find favour as therapeutics for coronary artery disease, thrombosis, angina, chronic renal failure, peripheral vascular disease and stroke, as well as the cardiovascular indications associated with type II diabetes mellitus, type I diabetes, insulin resistance, hyperlipidaemia, anorexia nervosa, obesity. As such the compounds of the present invention may find use as agonists or partial agonists of HM74A.

According to another aspect of this invention we provide at least one chemical entity selected from compounds of formula (I)



(I)

and pharmaceutically acceptable derivatives thereof, wherein

R^1 represents $-(alkylene)_m-X-(alkylene)_n-Y$

Wherein X represents A, A1, A2 or a direct link;

A represents a group selected from:
cycloalkylene, cycloalkenylene, aryl, heteroaryl, heterocyclyl, and $-CH_2-OC(O)-$;

A1 represents a group selected from:
$-CH_2-O-(CH_2)_q$aryl$-O-$, $-CH_2-O-(CH_2)_wN(R^5)C(O)O-$, $-CH_2-N(R^5)C(O)O-$, $-CH_2-N(R^5)C(O)-$, $-CH_2-(O)_p-(CH_2)_qC(O)NR^5-$, $-CH_2-N(R^5)C(O)N(R^5)-$, $-CH_2-C(O)N((CH_2)_mOH)-$, $-CH_2-NR^5-S(O)_2-$, $CH_2-S(O)_2NR^5-$, $-CH_2-C(O)O-$, -O-, -NH-, and -S-;

A2 represents:
-CH(OH)-;

When X is A, A1 or A2, Y represents a group selected from:
heteroaryl, heterocyclyl, aryl, cycloalkyl, cycloalkenyl, -NH-aryl, -$O(CH_2)_n$-aryl, -O-heteroaryl, -OR^5, -$C(O)OR^5$, -$C(O)O$-C_6 aryl, -$OC(O)R^5$, -$CH(aryl)_2$, -$CH(heteroaryl)_2$, and -C_{1-6} haloalkyl;

When X is A1 and Y is selected from:
-$O(CH_2)_n$-aryl, -O-heteroaryl, -OR^5, -$OC(O)R^5$, and -NH-aryl,
n is an integer selected from 2, 3, 4 and 5;

When X is A1 and Y is -CF_3, or when X is A2, n is an integer selected from 1, 2, 3, 4 and 5;

When X is a direct link, (m + n) is an integer selected from 2 to 10;

When X is a direct link and (m + n) is an integer selected from 3 to 10, Y represents a group selected from: -$C(O)(CH_2)_qOR^5$, -C(O)-aryl, -C(O)-heteroaryl, -C(O)-heterocyclyl, heteroaryl, heterocyclyl, Aryl, 3 or 4 ring fused system, -$CH(aryl)_2$, -$CH(heteroaryl)_2$, -OR^5, -NR^5R^6, -$NC(O)OR^8$, -$(O)_pC(O)NR^5R^6$, and -$NR^5C(O)R^8$;

When X is a direct link and (m + n) is 2, Y represents a group selected from:
-OR^5, -NH_2, and –$NC(O)OR^8$;

When Y incorporates a ring, that ring may be optionally substituted by one or more of:
C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, -NH_2, -$(CH_2)_q$-$(O)_p$-$(CH_2)_q$-$N(R^5)C(O)OR^8$, -$(CH_2)_q$-$N(R^5)C(O)R^8$, -$(CH_2)_q$-$(O)_p$-$(CH_2)_q$-$C(O)NR^5R^6$, -$(CH_2)_q$-$N(R^5)C(O)N(R^5)R^6$, -$(CH_2)_q$-$C(O)N((CH_2)_mOH)R^5$, -$(CH_2)_q$-$N(R^5)$-$S(O)_2R^8$, -CH_2-$S(O)_2N(R^5)R^6$, -C_{1-6} haloalkyl, -OCF_3, -$OCH(F)_2$, -OCH_2F, -$C(O)OR^5$, -OR^5, -$(R^8)_pCN$, -SO_2R^9, -$(CH_2)_n$heteroaryl, -$(CH_2)_n$heterocycyl, -$(CH_2)_n$cycloalkyl, -$(CH_2)_n$cycloalkenyl, and -$(CH_2)_n$aryl;

Provided that when X is A1, A1 is -O- and Y is a ring which is substituted by aryl or heteroaryl, then m is an integer selected from 3, 4 and 5;

R^2 is selected from: H; or C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, cycloalkyl, cycloalkenyl heterocyclyl, aryl, and heteroaryl, each of which may be optionally substituted by one or more of: C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, C_{1-6} haloalkyl, halogen, -CN, -OR^4, -$(CH_2)_nCOR^4$, -$C(O)OR^4$, -$OCOR^4$, -$(CH_2)_nNR^5R^6$, -$(NH)_pCONR^5R^6$, -$OCONR^5R^7$, and -$NHC(O)OR^7$;

R^3 is selected from: halogen and CN;

R^4 is selected from: H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $-(CH_2)_n$ cycloalkyl, $-(CH_2)_n$ cycloalkenyl, $-(CH_2)_n$ heterocyclyl, $-(CH_2)_n$ aryl, and $-(CH_2)_n$ heteroaryl;

R^5 and R^6 are selected from: hydrogen and C_{1-4} alkyl;

R^7 is selected from: H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $-(CH_2)_t$ cycloalkyl, $-(CH_2)_n$ cycloalkenyl, $-(CH_2)_t$ heterocyclyl, $-(CH_2)_t$ aryl, and $-(CH_2)_t$ heteroaryl;

R^8 is selected from C_{1-4} alkyl;

R^9 is selected from, C_{1-6} alkyl C_{2-6} alkenyl, C_{2-6} alkynyl, $-(CH_2)_n$ cycloalkyl, $-(CH_2)_n$cycloalkenyl, $-(CH_2)_n$heterocyclyl, $-(CH_2)_n$ aryl, and $-(CH_2)_n$heteroaryl, CN;

m represents an integer selected from: 1, 2, 3, 4 and 5;

n represents an integer selected from: 0, 1, 2, 3, 4 and 5;

p represents an integer selected from: 0 and 1;

q represents an integer selected from: 0, 1 and 2;

t represents an integer selected from: 1 and 2;

w represents an integer selected from: 2, 3 and 4.

In one embodiment, X represents A or A1. In a further embodiment, A is selected from heteroaryl, heterocyclyl, and A1 is selected from CH_2-O-$(CH_2)_w$N(R^5)C(O)O-, for example $CH_2O(CH_2)_2NHC(O)O$-, CH_2-N(R^5)C(O)O- for example CH_2-NHC(O)O, CH_2-N(R^5)C(O)- for example, CH_2-NHC(O)-, CH_2-$(O)_p$-$(CH_2)_q$C(O)NR^5- for example $CH_2C(O)NCH_3$- , CH_2-N(R^5)C(O)N(R^5)- for example CH_2-NHC(O)NCH_3-, CH_2-C(O)N($(CH_2)_m$OH)- for example CH_2-C(O)N($(CH_2)_2$OH)-, CH_2-NR^5-$S(O)_2$- for example CH_2-NH-$S(O)_2$-, CH_2-$S(O)_2$NR^5- for example CH_2-$S(O)_2NCH_3$-, and CH_2-C(O)O-. In another embodiment, X represents A and A represents a heteroaryl. In another embodiment A represents a heteroaryl comprising a nitrogen heteroatom, for example, triazolyl, furazanyl, oxadiazolyl, tetrazolyl, imidazolyl or pyrazolyl.

In one embodiment, Y represents an optionally substituted group selected from: aryl, for example phenyl or napthyl, heteroaryl, for example pyridinyl, thiazolyl, thienyl, benzofuranyl or indolyl, and O-aryl, for example O-phenyl.

In a further embodiment, Y is substituted by one or more groups selected from OR^5 for example OH or OCH_3, halogen, for example F or Cl, aryl, for example phenyl,

C_{1-6} haloalkyl for example CF_3 or CH_2CF_3, OCF_3, $(R^8)_pCN$ for example CN, $(CH_2)_q$-$N(R^5)$-$S(O)_2R^8$, for example $NHSO_2CH_3$ and SO_2R^9, for example SO_2CH_3.

In yet a further embodiment Y is substituted by one or more groups selected from OR^5, halogen, C_{1-6} haloalkyl, and $-(CH_2)_q-N(R^5)C(O)R^8$.

In another embodiment, Y is substituted by one or more groups selected from halogen, and C_{1-6} haloalkyl.

In yet a further embodiment, wherein Y is a ring, it is not further substituted.

In one embodiment of the invention, when X represents A or A1, and A represents cycloalkyl, cycloalkenyl, aryl, heteroaryl or heterocyclyl, and A1 represents $-CH_2-O-(CH_2)_wN(R^5)C(O)O-$, $-CH_2-N(R^5)C(O)O-$, $-CH_2-N(R^5)C(O)-$, $-CH_2-(O)_p-(CH_2)_qC(O)NR^5-$, $-CH_2-N(R^5)C(O)N(R^5)-$, or $-CH_2-C(O)N((CH_2)_mOH)-$, and Y represents a ring, for example when X represents oxadizolyl, tetrazolyl or pyrazolyl and Y represents phenyl, pyridinyl, or thienyl, m is an integer selected from 3 and 4 and n is an integer selected from 0 and 1, for example m is 4 and n is 0, or m is 3 and n is 1;

In one embodiment R^2 represents C_{1-10} alkyl which may be optionally substituted by one or more of: cycloalkyl, heterocyclyl, aryl, heteroaryl, C_{1-6} haloalkyl, halogen, -CN, $-OR^4$, $-(CH_2)_nCOR^5$, $-C(O)OR^4$, $-OCOR^4$, $-(CH_2)_nNR^5R^6$, and $-(NH)_pCONR^5R^6$. In a further embodiment, R^2 is selected from C_{1-10} alkyl which may be optionally substituted by one or more of: cycloalkyl, aryl, heteroaryl, C_{1-6} haloalkyl, halogen, -CN, $-OR^4$, $-(CH_2)_nCOR^5$, $-C(O)OR^4$ and $-OCOR^4$. In yet a further embodiment R^2 is selected from C_{1-6} alkyl which may be optionally substituted by one or more of: cycloalkyl, C_{1-6} haloalkyl, halogen, -CN or $-OR^4$. In yet another further embodiment, R^2 is selected from C_{3-6} alkyl, for example butyl or pentyl.

In one embodiment, R^3 represents halogen. In a further embodiment, R^3 is selected from: chlorine and bromine. In another embodiment, R^3 represents chlorine.

With regard to stereoisomers, the compounds of formula (I) may have one or more asymmetric carbon atom and may occur as recemates, racemic mixtures and as individual enantiomers or diastereomers. All such isomeric forms are included within the present invention, including mixtures thereof.

Where a compound of formula (I) contains an alkenyl or alkenylene group, cis (E) and trans (Z) isomerism may also occur. The present invention includes the individual stereoisomers of the compound of the invention and, where appropriate, the individual tautomeric forms thereof, together with mixtures thereof.

Separation of diastereoisomers or cis and trans isomers may be achieved by conventional techniques, e.g. by fractional crystallisation, chromatography or HPLC of a stereoisomeric mixture of the agent may also be prepared from a corresponding optically pure intermediate or by resolution, such as 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.

Furthermore, some of the crystalline forms of the compounds of formula (I) may exist as polymorphs, which are included in the present invention. One form may have an advantage over another form, for example one form may have improved stability over another form.

It is to be understood that the present invention includes any combination of particular embodiments and covers all combinations of particular substituents described hereinabove.

Throughout the present specification and the accompanying claims the words "comprise" and "include" and variations such as "comprises", "comprising", "includes" and "including" are to be interpreted inclusively. That is, these words are intended to convey the possible inclusion of other elements or integers not specifically recited, where the context allows.

As used herein, the term "alkyl" (when used as a group or as part of a group) refers to a straight or branched hydrocarbon chain unless specified otherwise, containing the specified number of carbon atoms. For example, C_3-C_{10}alkyl means a straight or branched hydrocarbon chain containing at least 3 and at most 10 carbon atoms. Examples of alkyl as used herein include, but are not limited to methyl (Me), ethyl (Et), n-propyl and i-propyl.

The term "alkylene" or as used herein means both straight and branched chain, or cyclic saturated hydrocarbon linker groups. Examples of alkylene groups include methylene (-CH_2-), ethylene (-CH_2CH_2-), ethene (-CH=CH-), or cyclopropylene and the like. For example, as used herein, -$(alk)_n$-, where n is 3 represents -$(CH_2)_3$-, -$C(CH_3)_2$-, -CH_2CH=CH-, or -cyclopropylene- and the like. For example as used herein, -$(alk)_m$- where m is 4 represents -$(CH_2)_4$-, -$CH_2C(CH_3)_2$-, -CH_2CH=$CHCH_2$-, or -CH_2cyclopropylene- and the like.

The term "alkenyl" as used herein refers to a straight or branched hydrocarbon chain containing the specified number of carbon atoms which contains one or more double bonds.

The term "alkynyl" as used herein refers to a straight or branched hydrocarbon chain containing the specified number of carbon atoms which contains one or more triple bonds.

The term "cycloalkyl" as used herein refers to a saturated monocyclic hydrocarbon ring of 3 to 8 carbon atoms. Examples of such groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl and the like.

The term "cycloalkylene" as used herein refers to a saturated monocyclic hydrocarbon ring of 3 to 8 carbon linker goups. Examples of such groups include cyclopropylene, cyclobutylene, cyclopentylene, cyclohexylene, cycloheptylene or cyclooctylene and the like.

The term "cycloalkenyl" as used herein refers to an unsaturated non-aromatic monocyclic hydrocarbon ring of 3 to 8 carbon atoms containing one or more carbon-carbon double bonds. Examples of such groups include cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl or cyclooctenyl and the like.

The term "cycloalkenylene" as used herein refers to an unsaturated non-aromatic monocyclic hydrocarbon ring of 3 to 8 carbon linker groups containing one or more carbon-carbon double bonds. Examples of such groups include cyclopropenylene, cyclobutenylene, cyclopentenylene, cyclohexenylene, cycloheptenylene or cyclooctenylene and the like.

The term "aryl" as used herein refers to a C_{6-12} monocyclic, bicyclic or tricyclic hydrocarbon ring wherein at least one ring is aromatic. Examples of such groups include phenyl, naphthyl or tetrahydronaphthalenyl and the like.

The term "heteroaryl" as used herein refers to a 5-6 membered monocyclic aromatic ring or a fused 8-10 membered bicyclic aromatic ring, containing 1 to 4 heteroatoms selected from oxygen, nitrogen and sulphur. There may be one or more optional oxo substituents on the ring carbon atoms. Examples of such monocyclic aromatic rings include thienyl, furyl, furazanyl, pyrrolyl, triazolyl, tetrazolyl, imidazolyl, oxazolyl, thiazolyl, oxadiazolyl, isothiazolyl, isoxazolyl, thiadiazolyl, pyranyl, pyrazolyl, pyrimidyl, pyridazinyl, pyrazinyl, pyridyl, triazinyl, tetrazinyl and the like. Examples of such fused aromatic rings include quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, pteridinyl, cinnolinyl, phthalazinyl, naphthyridinyl, indolyl, isoindolyl, azaindolyl, indolizinyl, indazolyl, purinyl, pyrrolopyridinyl, furopyridinyl, benzofuranyl, isobenzofuranyl, benzothienyl, benzoimidazolyl, benzoxazolyl, benzoisoxazolyl, benzothiazolyl, benzoisothiazolyl, benzoxadiazolyl, benzothiadiazolyl and the like.

The term "heterocyclyl" as used herein refers to a 4-7 membered monocyclic ring or a fused 8-12 membered bicyclic ring which may be saturated or partially unsaturated containing 1 to 4 heteroatoms selected from oxygen, nitrogen or sulphur. There may be one or more optional oxo substituents on the ring carbon atoms. Examples of such monocyclic rings include pyrrolidinyl, azetidinyl, pyrazolidinyl, oxazolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, hydantoinyl, valerolactamyl, oxiranyl, oxetanyl, dioxolanyl, dioxanyl, oxathiolanyl, oxathianyl, dithianyl, dihydrofuranyl, tetrahydrofuranyl, dihydropyranyl, tetrahydropyranyl, tetrahydropyridinyl, tetrahydropyrimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, diazepanyl, azepanyl and the like. Examples of such bicyclic rings include indolinyl, isoindolinyl, benzopyranyl, quinuclidinyl, 2,3,4,5-tetrahydro-1*H*-3-benzazepine, tetrahydroisoquinolinyl and the like.

The term "3 or 4 ring fused system" as used herein refers to a fused 12-18 membered tricyclic or tetracyclic ring which contains 1 to 4 heteroatoms of N and wherein at least one ring is aromatic. There may be one or more optional oxo substituents on the ring carbon atoms. Examples of such fused aromatic rings include carbazolyl, acenaphthyl, naphthotriazolyl and the like.

The terms "halogen" or "halo" as used herein refer to a fluorine, chlorine, bromine or iodine atom.

The term "C_{1-6} haloalkyl" as used herein refers to a C_{1-6} alkyl group as defined herein wherein at least one hydrogen atom is replaced with halogen. Examples of such groups include fluoroethyl, trifluoromethyl or trifluoroethyl and the like.

As used herein, where a group is referred to as being "substituted" by another group or having "one or more substituents" unless a particular position for such a substitution is specified it is to be understood that a substitution may be present at any position in the group.

The term "pharmaceutically acceptable derivative" as used herein refers to any pharmaceutically acceptable derivative of a compound of the present invention, for example, salts, solvates or esters, which upon administration to a mammal, such as a human, is capable of providing (directly or indirectly) such a compound or an active metabolite thereof. Such derivatives are clear to those skilled in the art, without undue experimentation, and with reference to the teaching of Burger's Medicinal Chemistry And Drug Discovery, 5th Edition, Vol 1: Principles And Practice, which is incorporated herein by reference.

As used herein, the term "pharmaceutically acceptable" used in relation to an ingredient (active ingredient, diluent, excipient or carrier) which may be included in a

pharmaceutical formulation for administration to a patient, refers to that ingredient being acceptable in the sense of being compatible with any other ingredients present in the pharmaceutical formulation and not being deleterious to the recipient thereof.

As used herein, the term "solvate" refers to a complex of variable stoichiometry formed by a solute (in this invention, a compound of formula (I) or a pharmaceutically acceptable derivative thereof) and a solvent. Such solvents for the purposes of the present invention may not interfere with the biological activity of the solute. The solvent used may be a pharmaceutically acceptable solvent. Examples of suitable pharmaceutically acceptable solvents include water, ethanol and acetic acid. An example of a solvent that may be used is water, in which case the solvate may be referred to as a hydrate of the solute in question.

It will be appreciated that, for pharmaceutical use, the "salt or solvate" referred to above will be a pharmaceutically acceptable salt or solvate. However, other salts or solvates may find use, for example, in the preparation of a compound of formula (I) or in the preparation of a pharmaceutically acceptable salt or solvate thereof.

Pharmaceutically acceptable salts include those described by Berge, Bighley and Monkhouse, *J. Pharm. Sci.*, 1977, 66, 1-19. Suitable pharmaceutically acceptable salts include alkali metal salts formed from the addition of alkali metal bases such as alkali metal hydroxides. Examples of suitable alkali metal salts include sodium salts and potassium salts. Other suitable pharmaceutically acceptable salts include alkaline earth metal salts such as calcium salts and magnesium salts, ammonium salts; or salts with organic bases such as ethanolamine, triethanolamine, ethylene diamine, triethylmine, choline and meglumine; or salts with amino acids such as arginine, lysine and histidine.

Esters may be active in their own right and/or be hydrolysable under *in vivo* conditions in the human body. Suitable pharmaceutically acceptable *in vivo* hydrolysable ester groups include those which break down readily in the human body to leave the parent acid or its salt. An ester may be formed at a carboxylic acid (-C(O)OH) group, by methods well known in the art involving reaction with the corresponding alcohol. For example, esters may be C_{1-6}alkyl esters, e.g. methyl esters, ethyl esters, and the like.

As used herein, the term "compounds of the invention" means the compounds according to Formula I and the pharmaceutically acceptable derivatives thereof. The term "a compound of the invention" means any one of the compounds of the invention as defined above.

As used herein the term "at least one chemical entity" means at least one chemical substance chosen from the group of compounds consisting of compounds of formula I and pharmaceutically acceptable derivatives thereof.

In one aspect of the invention there is provided substantially crystalline 3-Butyl-8-chloro-1-{4-[5-(2-pyridinyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione form 1. In another aspect of the invention there is provided substantially crystalline 3-Butyl-8-chloro-1-{4-[5-(2-pyridinyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione form 2.

Thermal analysis on samples of substantially crystalline 3-Butyl-8-chloro-1-{4-[5-(2-pyridinyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione forms 1 and 2 was carried out. Thus, there is provided substantially crystalline 3-Butyl-8-chloro-1-{4-[5-(2-pyridinyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione (form 1 or form 2) having a melting point onset measured by DSC (± 0.5°C) of: 160 °C or greater and 147°C or greater, respectively.

Samples of substantially crystalline 3-Butyl-8-chloro-1-{4-[5-(2-pyridinyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione form 1, and 3-Butyl-8-chloro-1-{4-[5-(2-pyridinyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione form 2, prepared as described hereinafter, gave the X-ray powder diffraction patterns of Figures 1-2. The X-ray diffraction pattern is unique to the crystalline form. The substantially crystalline forms exhibit diffraction patterns with a unique set of diffraction peaks which can be expressed in 2 theta angles (°).

2 Theta diffraction angles account for positions of various peaks in the X-ray diffraction pattern. Slight variations in observed 2 theta angles are expected based on the specific diffractometer employed and the analyst's sample preparation technique.

The substantially crystalline forms of 3-Butyl-8-chloro-1-{4-[5-(2-pyridinyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione can be identified by the presence of a characteristic 2 theta angle peak, or by multiple 2 theta angles which are reasonably characteristic of the particular crystalline forms. To identify substantially crystalline 3-Butyl-8-chloro-1-{4-[5-(2-pyridinyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione (form 1), these peaks occur at the following positions, expressed in 2 theta angles (±0.1 degrees): 5.4, 6.7, 9.7, 11.1, 12.9, 14.0, 15.6, 16.3, 16.7, 23.1 degrees. To identify substantially crystalline 3-Butyl-8-chloro-1-{4-[5-(2-pyridinyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione (form 2), these peaks occur at the following positions, expressed in 2 theta angles (±0.1 degrees): 5.2, 6.6, 10.4, 11.2, 13.4, 15.6, 18.1, 19.5, 20.9 degrees. In one embodiment at least one of the foregoing 2 theta angles are employed to identify substantially crystalline 3-Butyl-8-chloro-1-{4-[5-(2-pyridinyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione

form 1 and substantially crystalline 3-Butyl-8-chloro-1-{4-[5-(2-pyridinyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione form 2. In other embodiments at least 2, 3, 4 or 5 (where applicable) of the foregoing 2 theta angles are employed to identify substantially crystalline 3-Butyl-8-chloro-1-{4-[5-(2-pyridinyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione form 1, substantially crystalline 3-Butyl-8-chloro-1-{4-[5-(2-pyridinyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione form 2.

Some margin of error is present in each of the 2 theta angle assignments. The margin of error in the foregoing 2 theta angles is approximately ±0.1 degrees for each of the foregoing peak assignments.

Since some margin of error is possible in the assignment of 2 theta angles, the preferred method of comparing X-ray powder diffraction patterns in order to identify a particular crystalline form is to overlay the X-ray powder diffraction pattern of the unknown form over the X-ray powder diffraction pattern of a known form. For example, one skilled in the art can overlay an X-ray powder diffraction pattern of an unidentified form of 3-Butyl-8-chloro-1-{4-[5-(2-pyridinyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione, obtained using the methods described herein, see Figure 3 for example, and readily determine whether the X-ray diffraction pattern of the unidentified form is substantially the same as the X-ray powder diffraction pattern of substantially crystalline 3-Butyl-8-chloro-1-{4-[5-(2-pyridinyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione Form 1 or 2. If the X-ray powder diffraction pattern is substantially the same as that shown in any of Figures 1-2, the previously form can be readily and accurately identified.

As used herein, the term "substantially crystalline form" means that it is substantially free of amorphous form 3-Butyl-8-chloro-1-{4-[5-(2-pyridinyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione. By "substantially free" is meant containing less than 50% of the amorphous form, in one aspect less than 20% of the amorphous form, in another aspect less than 10% of the amorphous form, in another aspect less than 5% of the amorphous form, in another aspect less than 2% of the amorphous form, in another aspect less than 1% of the amorphous form.

The present invention provides a method for the preparation of substantially crystalline 3-Butyl-8-chloro-1-{4-[5-(2-pyridinyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione form as described herein.

Compounds of formula (I) are of potential therapeutic benefit in the treatment and amelioration of the symptoms of many diseases of lipid metabolism including dyslipidaemia and hyperlipoproteinaemia such as diabetic dyslipidaemia and mixed dyslipidaemia, heart failure, hypercholesteraemia, cardiovascular disease including

atherosclerosis, arteriosclerosis, and hypertriglyceridaemia, type II diabetes mellitus, type I diabetes, insulin resistance, hyperlipidaemia, anorexia nervosa, obesity. As such, the compounds may also find favour as therapeutics for coronary artery disease, thrombosis, angina, chronic renal failure, peripheral vascular disease and stroke.

It has been reported that the HM74 and HM74A receptors are involved in inflammation (WO02084298). Inflammation represents a group of vascular, cellular and neurological responses to trauma. Inflammation can be characterised as the movement of inflammatory cells such as monocytes, neutrophils and granulocytes into the tissues. This is usually associated with reduced endothelial barrier function and oedema into the tissues. Inflammation with regards to disease typically is referred to as chronic inflammation. Such chronic inflammation may manifest itself through disease symptoms. The aim of anti-inflammatory therapy is therefore to reduce this chronic inflammation and allow for the physiological process of healing and tissue repair to progress.

Examples of inflammatory diseases or conditions for which the compounds of the present invention may demonstrate utility include those of the joint, for example arthritis (e.g. rheumatoid arthritis, osteoarthritis, prosthetic joint failure), or the gastrointestinal tract (e.g. ulcerative colitis, Crohn's disease, and other inflammatory bowel and gastrointestinal diseases, gastritis and mucosal inflammation resulting from infection, the enteropathy provoked by non-steroidal anti-inflammatory drugs), of the lung (e.g. adult respiratory distress syndrome, asthma, cystic fibrosis, or chronic obstructive pulmonary disease), of the heart (e.g. myocarditis), of nervous tissue (e.g. multiple sclerosis), of the pancreas, (e.g. inflammation associated with diabetes melitus and complications thereof, of the kidney (e.g. glomerulonephritis), of the skin (e.g. dermatitis, psoriasis, eczema, urticaria, burn injury), of the eye (e.g. glaucoma) as well as of transplanted organs (e.g. rejection) and multi-organ diseases (e.g. systemic lupus erythematosis, sepsis) and inflammatory sequelae of viral or bacterial infections and inflammatory conditions associated with atherosclerosis and following hypoxic or ischaemic insults (with or without reperfusion), for example in the brain or in ischaemic heart disease.

In one embodiment, the compounds of this invention are useful in the treatment and prevention of inflammation, diabetes and cardiovascular diseases or conditions including atherosclerosis, arteriosclerosis, hypertriglyceridemia, and mixed dyslipidaemia.

Nicotinic acid has a significant side effect profile, possibly because it is dosed at high level (gram quantities daily). The most common side effect is an intense cutaneous flushing. In certain embodiments of the present invention the compounds may exhibit reduced side effects compared to nicotinic acid. HM74A has been identified as a high

affinity receptor for nicotinic acid whilst HM74 is a lower affinity receptor. The compounds of the present invention show greater affinity for HM74A than for HM74 therefore may find use as selective HM74A agonists or partial agonists.

The potential for compounds of formula (I) to activate HM74A may be demonstrated, for example, using the following in vitro whole cell assays:

In-vitro testing

For transient transfections, HEK293T cells (HEK293 cells stably expressing the SV40 large T-antigen) were maintained in DMEM containing 10% foetal calf serum and 2mM glutamine. Cells were seeded in 90mm culture dishes and grown to 60-80% confluence (18-24h) prior to transfection. Human HM74A (GenBank™ accession number AY148884) was subcloned in to a mammalian expression vector (pcDNA3; Invitrogen) and transfected using Lipofectamine reagent. For transfection, 9μg of DNA was mixed with 30μl Lipofectamine in 0.6ml of Opti-MEM (Life Technologies Inc.) and was incubated at room temperature for 30min prior to the addition of 1.6ml of Opti-MEM. Cells were exposed to the Lipofectamine/DNA mixture for 5h and 6ml of 20% (v/v) foetal calf serum in DMEM was then added. Cells were harvested 48h after transfection. Pertussis toxin treatment was carried out by supplementation into media at 50ngml^{-1} for 16h. All transient transfection studies involved co-transfection of receptor together with the $G_{i/o}$ G protein, $G_{o1}\alpha$.

For generation of stable cell lines the above method was used to transfect CHO-K1 cells seeded in six well dishes grown to 30% confluence. These cells were maintained in DMEM F-12 HAM media containing 10% foetal calf serum and 2mM glutamine. 48h post-transfection the media was supplemented with 400μg/ml Geneticin (G418, Gibco) for selection of antibiotic resistant cells. Clonal CHO-K1 cell lines stably expressing HM74A were confirmed by [^{35}S]-GTPγS binding measurements, following the addition of nicotinic acid.

P2 membrane preparation - Plasma membrane-containing P2 particulate fractions were prepared from cell pastes frozen at –80°C after harvest. All procedures were carried out at 4°C. Cell pellets were resuspended in 1 ml of 10mM Tris-HCl and 0.1mM EDTA, pH 7.5 (buffer A) and by homogenisation for 20s with a Ultra Turrax followed by passage (5 times) through a 25-gauge needle. Cell lysates were centrifuged at 1,000*g* for 10 min in a microcentrifuge to pellet the nuclei and unbroken cells and P2 particulate fractions were recovered by microcentrifugation at 16,000*g* for 30min. P2 particulate fractions were resuspended in buffer A and stored at –80°C until required.

[^{35}S]-GTPγS binding - assays were performed at room temperature in 384-well format based on methods described previously, (Wieland, T. and Jakobs, K.H. (1994)

Methods Enzymol. **237,** 3-13). Briefly, the dilution of standard or test compounds were prepared and added to a 384-well plate in a volume of 10µl. Membranes (HM74A or HM74) were diluted in assay buffer (20mM HEPES, 100mM NaCl, 10mM $MgCl_2$, pH7.4) supplemented with saponin (60µg/ml), Leadseeker WGA beads (Amersham; 250µg/well) and 10µM GDP, so that the 20µl volume added to each well contains 5µg of membranes. [^{35}S]-GTPγS (1170 Ci/mmol, Amersham) was diluted (1:1500) in assay buffer and 20µl added to each well. Following the addition of the radioligand, the plates were sealed, pulse spun and incubated for 4hours at room temperature. At the end of the incubation period the plates were read on a Leadseeker machine (VIEWLUX PLUS; Perkin-Elmer) to determine the levels of specific binding.

These assays were refined by reducing the final assay volume to 10 µl. For this 10 µl assay a revised protocol was used. This involved the use of only 100 nl of standard or test compound per well of a 384-well plate and 1.5 µg membrane and 100 µg Leadseeker WGA beads. For the low volume protocol, membrane, beads and [^{35}S]-GTPγS were mixed together and then 10 µl of this mix were dispensed to each well. Incubation and plate read were identical for the 10µl and 50 µl assays.

All exemplified compounds were tested in one or both of the [^{35}S]-GTPγS binding assays described above (i.e. the 10µl and 50µl assays).

Data was analysed by curve fitting as carried out using a Four Parameter Logistical equation using the XC50 software package (max 2 points deleted from any one curve). Specific binding is expressed as pEC_{50} and as % efficacy compared to the maximal response of nicotinic acid binding.

In-vivo testing

HM74A agonists can be tested in male Spague-Dawley rats (200-250g) which have been fasted for at least 12 hours prior to the study. The compounds are dosed intravenously at either 1 or 3mg/kg (5ml/kg) or by oral gavage at doses ranging from 1-30mg/kg (10ml/kg). Blood samples (0.3ml tail vein bleed) can be taken pre-dose and at three times post-dose (times ranging from 15 minutes to 6 hours post-dose). Each blood sample is transferred to a heparin tube (Becton Dickinson Microtainer, PST LH) and centrifuged (10,000*g* for 5 minutes) to produce a plasma sample. The plasma samples are assayed for levels of non-esterified fatty acids (NEFA) using a commercially available kit (Randox). Inhibition of plasma NEFA levels, relative to pre-dose levels, are used as a surrogate for HM74A agonist activity.

In order to determine whether HM74A compounds exhibit the flushing response associated with nicotinic acid they can be dosed to conscious guinea-pigs. Male

Dunkin Hartley guinea pigs (300-600g; n=10-20 per group) are fasted for at least 12 hours, but not in excess of 24 hours prior to experimention. Pre-study blood samples (0.5ml) are taken from each animal by cardiac puncture under recovery anaesthesia (Isoflurane 3.5% with additional O2 (1L/min)). Ear temperature measurements are taken by placing the left ear of each animal over an infra-red temperature probe. Measurements are taken at one minute intervals from 5 minutes pre-dose to 30 minutes post-dose. Temperature measurements are then taken at 15 minute intervals up to 2 hours post-dose. Animals receive test compounds by oral gavage (5ml/kg). Blood samples (0.5ml) are taken by cardiac puncture under terminal anaesthesia. Blood samples are taken from individual animals to provide data at 0.5, 1, 2, 3, and 4 hours post-dose. All blood samples are placed on a blood roller for 5 minutes then stored on ice until the end of the study. Following centrifugation (12000g for 5min) the plasma is transferred into fresh tubes and stored at -20°C until assayed for NEFA concentrations.

Compounds according to Formula (I) have been synthesised (see synthetic examples below) and tested in the [^{35}S]-GTPγS binding assays discussed above.

Some compounds according to formula (I) including:

3-butyl-8-chloro-1-[3-(dimethylamino)propyl]-3,7-dihydro-1H-purine-2,6-dione;
8-chloro-3-(3,3-dimethylbutyl)-1-[2-(ethyloxy)ethyl]-3,7-dihydro-1H-purine-2,6-dione;
3-butyl-8-chloro-1-[3-(5-phenyl-1,2,4-oxadiazol-3-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione;
1-[3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)propyl]-1H-naphtho[2,3-d][1,2,3]triazole-4,9-dione;
2-({4-[3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)propyl]phenyl}oxy)ethyl acetate.

have utility as intermediates in the production of other compounds according to formula (I).

The exemplified compounds (Examples 1 - 894) have a pEC_{50} of 4.3 (+/- 0.3 log unit) or greater and an efficacy of 30% or greater (in relation to nicotinic acid) in the [^{35}S]-GTPγS binding assays described above, in which they were tested.

The following compounds were tested and found to have activity lower than a pEC_{50} of 4.3 (+/- 0.3 log unit) and an efficacy of less than 30% (in relation to nicotinic acid) in the [^{35}S]-GTPγS binding assays described above, in which they were tested.

8-chloro-1-(3-{3-[(2,4-difluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3-[2-(1-piperidinyl)ethyl]-3,7-dihydro-1*H*-purine-2,6-dione;

8-chloro-1-(3-{3-[(2,4-difluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3-[2-(hexahydro-1*H*-azepin-1-yl)ethyl]-3,7-dihydro-1*H*-purine-2,6-dione;
8-chloro-1-(3-{3-[(2,4-difluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3-[2-(1-pyrrolidinyl)ethyl]-3,7-dihydro-1*H*-purine-2,6-dione;
8-chloro-1-(3-{3-[(2,4-difluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3-[2-(dimethylamino)-2-methylpropyl]-3,7-dihydro-1*H*-purine-2,6-dione;
8-chloro-1-(3-{3-[(2,4-difluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3-[3-(dimethylamino)propyl]-3,7-dihydro-1*H*-purine-2,6-dione;
8-chloro-1-(3-{3-[(2,4-difluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3-[3-(4-methyl-1-piperazinyl)propyl]-3,7-dihydro-1*H*-purine-2,6-dione;
8-chloro-1-(3-{3-[(2,4-difluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3-[2-(dimethylamino)ethyl]-3,7-dihydro-1*H*-purine-2,6-dione.

General purification and analytical methods:

LC/MS: Method
Analytical HPLC was conducted on a Supelcosil™ ABZ+PLUS column (Supelco) (3µm, 3.3cm x 4.6mm ID) eluting with 0.1% HCO_2H and 0.01 M ammonium acetate in water (solvent A), and 95% MeCN and 5% water (containing 0.5% HCO_2H) (solvent B), using the following elution gradient 0-0.7min 0%B, 0.7-4.2min 0→100%B, 4.2-4.6minutes 100%B, 4.6-4.8min 100→0%B at a flow rate of 3 ml/min. The diode array UV detection was carried out in the range 215 to 330nm. The mass spectra (MS) were recorded on a Waters ZQ mass spectrometer using electrospray positive ionisation [(ES+ve to give MH^+ and $M(NH_4)^+$ molecular ions] or electrospray negative ionisation [(ES-ve to give $(M-H)^-$ molecular ion] modes. Only the parent ion of major isotopes quoted.

^1H NMR spectra were recorded using a Bruker DPX 400MHz spectrometer using tetramethylsilane as the standard.

Biotage™ chromatography refers to purification carried out using either the Flash 40i or Flash 150i purification systems, sold by Biotage AB, using cartridges pre-packed with KPSil (silica).

Companion™ system refers to the Teledyne Isco Combiflash Companion™ purification system. This is a gradient controlled purification system with integral, variable wavelength UV detection with the capability to trigger automated fraction collection by UV threshold.

Mass directed autoprep (MDAP) refers to methods where the material was purified by high performance liquid chromatography using either a Supelcosil ABZ+ 5µm column (10cm x 20mm i.d.) or a Supelcosil ABZ+ 10µm column (15cm x 30mm i.d.) with a suitable gradient of solvent A: 0.1% HCO_2H in water and solvent B: 95% MeCN, 5%

water (containing 0.5% HCO_2H). The Waters 2767 inject / collector was triggered by a MicroMass ZQ Mass Spectrometer on detecting the mass of interest (using Micromass MassLynx software).

Preparative HPLC (Autoprep HPLC or Autoprep) refers to methods where the material was purified by high performance liquid chromatography on a Supelcosil ABZ+ 5µm column (10cm x 21.2mm i.d.) with a suitable gradient of 0.1% HCO_2H in water and MeCN (with 0.5% HCO_2H). The Gilson 233 fraction collector was triggered by UV detection.

SPE (solid phase extraction) refers to the use of polyethylene cartridges which are pre-packed with sorbent used for purification. The sorbent contained in these cartridges will be specified. Examples used are detailed below:

C18 SPE refers to the use of cartridges pre-packed with 40µM C18 funtionalised silica sorbent (sold by by Varian Inc.). The compound was loaded, typically in 50:50 DMSO / MeOH, onto a cartridge previously conditioned with MeCN and equilibrated with 5% MeCN in water. The product was eluted with a suitable gradient of 0.1% HCO_2H in water and MeCN (0.5% HCO_2H).

Aminopropyl SPE or column refers to the use of cartridges pre-packed with 40µm-120µm aminopropyl functionalized silica (sold by Varian Inc.). The crude product is typically loaded in DCM / MeOH mixtures onto a cartridge previously conditioned with MeOH. The neutral components were eluted with MeOH and/or DCM (3 or 4 column volumes) and the acidic components usually eluted with an eluent containing a proportion of AcOH (2-20%).

Oasis™ Cartridges / Oasis™ SPE's refer to SPE cartridges packed with a polymeric sorbent manufactured by the Waters Corporation. These are typically conditioned with 3 column volumes of MeOH and equilibrated with water before the sample is loaded. Salts and inorganics are eluted with water and the product typically eluted with MeOH or MeCN.

GreenHouse™ refers to a 24 reaction parallel synthesiser platform available from RDT Ltd, UK

As indicated above, compounds of Formula (I) may find use in human or veterinary medicine, for example as activators of HM74A, in the management of dyslipidaemia and hyperlipoproteinaemia.

Thus, there is provided as another embodiment of the present invention at least one compound of formula (I) or a pharmaceutically acceptable derivative thereof, for use in human or veterinary medicine, for example in the treatment of disorders of lipid metabolism including dyslipidaemia and hyperlipoproteinaemia such as diabetic

dyslipidaemia and mixed dyslipidaemia, heart failure, hypercholesteraemia, cardiovascular disease including atherosclerosis, arteriosclerosis, and hypertriglyceridaemia, type II diabetes mellitus, type I diabetes, insulin resistance, hyperlipidaemia, anorexia nervosa and obesity. As such, the compounds are also provided for use in the treatment of coronary artery disease, thrombosis, angina, chronic renal failure, peripheral vascular disease and stroke.

There is provided as a further embodiment of the present invention at least one compound of formula (I) or a pharmaceutically acceptable derivative thereof, for use in the manufacture of a medicament for the treatment of disorders of lipid metabolism including dyslipidaemia and hyperlipoproteinaemia such as diabetic dyslipidaemia and mixed dyslipidaemia, heart failure, hypercholesteraemia, cardiovascular disease including atherosclerosis, arteriosclerosis, and hypertriglyceridaemia, type II diabetes mellitus, type I diabetes, insulin resistance, hyperlipidaemia, anorexia nervosa, obesity. As such, the compounds are also provided for use in the treatment of coronary artery disease, thrombosis, angina, chronic renal failure, peripheral vascular disease and stroke.

It will be appreciated that references herein to treatment extend to prophylaxis, prevention of recurrence and suppression of symptoms as well as the treatment of established conditions.

In one embodiment of the invention, there is provided at least one compound of formula (I) or a pharmaceutically acceptable derivative thereof for use in the treatment of disorders of lipid metabolism including dyslipidaemia and hyperlipoproteinaemia. For example, the use is provided of at least one compound of Formula (I) or a pharmaceutically acceptable derivative thereof in the treatment of diabetic dyslipidaemia, mixed dyslipidaemia, heart failure, hypercholesteraemia, type II diabetes mellitus, type I diabetes, insulin resistance, hyperlipidaemia, anorexia nervosa, obesity, coronary artery disease, thrombosis, angina, chronic renal failure, stroke and cardiovascular disease including atherosclerosis, arteriosclerosis, and hypertriglyceridaemia.

It is to be understood that this embodiment of the present invention includes any combination of particular embodiments and covers all combinations of particular substituents described herein above for compounds of Formula (I).

Additionally, the present invention provides the use of at least one compound of formula (I) or a pharmaceutically acceptable derivative thereof, in the manufacture of a medicament for the treatment of inflammatory diseases or conditions of the joint, for example, arthritis (e.g. rheumatoid arthritis, osteoarthritis, prosthetic joint failure), or of the gastrointestinal tract (e.g. ulcerative colitis, Crohn's disease, and other

inflammatory bowel and gastrointestinal diseases, gastritis and mucosal inflammation resulting from infection, the enteropathy provoked by non-steroidal anti-inflammatory drugs), of the lung (e.g. adult respiratory distress syndrome, asthma, cystic fibrosis, or chronic obstructive pulmonary disease), of the heart (e.g. myocarditis), of nervous tissue (e.g. multiple sclerosis), of the pancreas, (e.g. inflammation associated with diabetes melitus and complications thereof, of the kidney (e.g. glomerulonephritis), of the skin (e.g. dermatitis, psoriasis, eczema, urticaria, burn injury), of the eye (e.g. glaucoma) as well as of transplanted organs (e.g. rejection) and multi-organ diseases (e.g. systemic lupus erythematosis, sepsis) and inflammatory sequelae of viral or bacterial infections and inflammatory conditions associated with atherosclerosis and following hypoxic or ischaemic insults (with or without reperfusion), for example in the brain or in ischaemic heart disease.

In a further or alternative embodiments there is provided a method for the treatment of a human or animal subject with a condition where under-activation of the HM74A receptor contributes to the condition or where activation of the receptor will be beneficial, which method comprises administering to said human or animal subject an effective amount of at least one compound of formula (I) or a pharmaceutically acceptable derivative thereof.

Again, it is to be understood that this embodiment of the present invention includes any combination of particular embodiments and covers all combinations of particular substituents described herein above for compounds of Formula (I).

In one embodiment, the present invention provides a method for the treatment of disorders of lipid metabolism including dyslipidaemia and hyperlipoproteinaemia such as diabetic dyslipidaemia and mixed dyslipidaemia, heart failure, hypercholesteraemia, cardiovascular disease including atherosclerosis, arteriosclerosis, and hypertriglyceridaemia, type II diabetes mellitus, type I diabetes, insulin resistance, hyperlipidaemia, anorexia nervosa and obesity, which method comprises administering to said human or animal subject an effective amount of at least one compound of formula (I) or a pharmaceutically acceptable derivative thereof. As such, these compounds may also find favour in methods for the treatment of coronary artery disease, thrombosis, angina, chronic renal failure, peripheral vascular disease and stroke, which methods comprise administering to said human or animal subject an effective amount of at least one compound of formula (I) or a pharmaceutically acceptable derivative thereof.

The amount of a compound of formula (I) or a pharmaceutically acceptable derivative thereof which is required to achieve the desired biological effect will, of course, depend on a number of factors, for example, the mode of administration and the precise clinical condition of the recipient. In general, the daily dose will be in the range of 0.1mg -

1g/kg, typically 0.1 - 100mg/kg. An intravenous dose may, for example, be in the range of 0.01mg to 0.1g/kg, typically 0.01mg to 10mg/kg, which may conveniently be administered as an infusion of from 0.1μg to 1mg, per minute. Infusion fluids suitable for this purpose may contain, for example, from 0.01μg to 0.1mg, per millilitre. Unit doses may contain, for example, from 0.01μg to 1g of a compound of the invention. Thus ampoules for injection may contain, for example, from 0.01μg to 0.1g and orally administrable unit dose formulations, such as tablets or capsules, may contain, for example, from 0.1mg to 1g, for example from 5mg to 50mg.

A compound of formula (I) or a pharmaceutically acceptable derivative thereof may be employed as the compound *per se* in the treatment of a disease where under-activation of the HM74A receptor contributes to the disease or where activation of the receptor will be beneficial, an example of this is where a compound of the present invention is presented with an acceptable carrier in the form of a pharmaceutical formulation. The carrier must, of course, be acceptable in the sense of being compatible with the other ingredients of the formulation and must not be deleterious to the recipient. The carrier may be a solid or a liquid, or both, and may be formulated with the compound of the invention as a unit-dose formulation, for example, a tablet, which may contain from 0.05% to 95% by weight of the compound of the invention.

The formulations include those suitable for oral, rectal, topical, buccal (e.g. sub-lingual) and parenteral (e.g. subcutaneous, intramuscular, intradermal or intravenous) administration.

There is also provided according to the invention a process for preparation of such a pharmaceutical composition which comprises mixing the ingredients.

Formulations suitable for oral administration may be presented in discrete units, such as capsules, cachets, lozenges or tablets, each containing a predetermined amount of a a compound of formula (I) or a pharmaceutically acceptable derivative thereof; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water or water-in-oil emulsion. In general, the formulations are prepared by uniformly and intimately admixing the compound of formula (I) or a pharmaceutically acceptable derivative thereof, with a liquid or finely divided solid carrier, or both, and then, if necessary, shaping the product. For example, a tablet may be prepared by compressing or moulding a powder or granules of the compound of formula (I) or a pharmaceutically acceptable derivative thereof optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing, in a suitable machine, the compound in a free-flowing form, such as a powder or granules optionally mixed with a binder, lubricant, inert diluent and/or surface active/dispersing agent(s). Moulded tablets may be made by moulding, in a suitable machine, the powdered compound moistened with an inert liquid diluent.

Tablets and capsules for oral administration may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, mucilage of starch or polyvinyl pyrrolidone; fillers, for example, lactose, microcrystalline cellulose, sugar, maize- starch, calcium phosphate or sorbitol; lubricants, for example, magnesium stearate, stearic acid, talc, polyethylene glycol or silica; disintegrants, for example, potato starch, croscarmellose sodium or sodium starch glycollate; or wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in the art. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example, sorbitol syrup, methyl cellulose, glucose/sugar syrup, gelatin, hydroxymethyl cellulose, hydroxypropylmethyl cellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats; emulsifying agents, for example, lecithin, sorbitan mono-oleate or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, fractionated coconut oil, oily esters, propylene glycol or ethyl alcohol; or preservatives, for example, methyl or propyl p-hydroxybenzoates or sorbic acid. The preparations may also contain buffer salts, flavouring, colouring and/or sweetening agents (e.g. mannitol) as appropriate.

Formulations suitable for buccal (sub-lingual) administration include lozenges comprising a compound of the invention in a flavoured base, usually sucrose and acacia or tragacanth, and pastilles comprising the compound of the invention in an inert base such as gelatin and glycerin or sucrose and acacia.

Formulations of the present invention suitable for parenteral administration conveniently comprise sterile aqueous preparations of a compound of formula (I) or a pharmaceutically acceptable derivative thereof, the formulation may be isotonic with the blood of the intended recipient. These preparations could be administered intravenously, although administration may also be effected by means of subcutaneous, intramuscular, or intradermal injection. Such preparations may conveniently be prepared by admixing the compound of formula (I) or a pharmaceutically acceptable derivative thereof with water and rendering the resulting solution sterile and isotonic with the blood. Injectable compositions according to the invention will generally contain from 0.1 to 5% w/w of the compound of formula (I) or a pharmaceutically acceptable derivative thereof.

Thus, formulations of the present invention suitable for parenteral administration comprising a compound of formula (I) or a pharmaceutically acceptable derivative thereof may be formulated for parenteral administration by bolus injection or continuous infusion and may be presented in unit dose form, for instance as ampoules, vials, small

volume infusions or pre-filled syringes, or in multi-dose containers with an added preservative. The compositions may take such forms as solutions, suspensions, or emulsions in aqueous or non-aqueous vehicles, and may contain formulatory agents such as anti-oxidants, buffers, antimicrobial agents and/or toxicity adjusting agents. Examples of formulations suitable for oral administration include formulations comprising a compound of formula (I) or a pharmaceutically acceptable derivative thereof, in 10% DMSO and 90% sodium hydrogen carbonate in sterile saline. Examples of formulations suitable for intravenous administration include formulations comprising a compound of formula (I) or a pharmaceutically acceptable derivative thereof, in 5% or 10% DMSO and 95% or 90% sodium hydrogen carbonate in sterile water. Alternatively, the therapeutically active agent may be in powder form for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use. The dry solid presentation may be prepared by filling a sterile powder aseptically into individual sterile containers or by filling a sterile solution aseptically into each container and freeze-drying.

Formulations suitable for rectal administration may be presented as unit-dose suppositories. These may be prepared by admixing a a compound of formula (I) or a pharmaceutically acceptable derivative thereof with one or more conventional solid carriers, for example, cocoa butter or glycerides and then shaping the resulting mixture.

Formulations suitable for topical application to the skin may take the form of an ointment, cream, lotion, paste, gel, spray, aerosol, or oil. Carriers which may be used include vaseline, lanolin, polyethylene glycols, alcohols, and combinations of two or more thereof. The compound of formula (I) or a pharmaceutically acceptable derivative thereof is generally present at a concentration of from 0.1 to 15% w/w of the composition, for example, from 0.5 to 2%.

By topical administration as used herein, we include administration by insufflation and inhalation. Examples of various types of preparation for topical administration include ointments, creams, lotions, powders, pessaries, sprays, aerosols, capsules or cartridges for use in an inhaler or insufflator or drops (e.g. eye or nose drops).

Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents and/or solvents. Such bases may thus, for example, include water and/or an oil such as liquid paraffin or a vegetable oil such as arachis oil or castor oil or a solvent such as a polyethylene glycol. Thickening agents which may be used include soft paraffin, aluminium stearate, cetostearyl alcohol, polyethylene glycols, microcrystalline wax and beeswax.

Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilising agents, dispersing agents, suspending agents or thickening agents.

Powders for external application may be formed with the aid of any suitable powder base, for example, talc, lactose or starch. Drops may be formulated with an aqueous or non-aqueous base also comprising one or more dispersing agents, solubilising agents or suspending agents.

Spray compositions may be formulated, for example, as aqueous solutions or suspensions or as aerosols delivered from pressurised packs, with the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, 1,1,1,2,3,3,3-heptafluoropropane, 1,1,1,2- tetrafluorethane, carbon dioxide or other suitable gas.

Capsules and cartridges for use in an inhaler or insufflator, of for example gelatin, may be formulated containing a powder mix of a compound of the invention and a suitable powder base such as lactose or starch.

The pharmaceutical compositions according to the invention may also be used in combination with other therapeutic agents, for example in combination with other classes of dyslipidaemic drugs (e.g. statins, fibrates, bile-acid binding resins or nicotinic acid).

The compounds of the instant invention may be used in combination with one or more other therapeutically active agents for example in combination with other classes of dyslipidaemic drugs e.g. 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (statins) or fibrates or bile acid binding resins or nicotinic acid. The invention thus provides, in a further embodiment, the use of such a combination in the treatment of diseases where under-activation of the HM74A receptor contributes to the disease or where activation of the receptor will be beneficial and the use of at least one compound of formula (I) or a pharmaceutically acceptable derivative thereof in the manufacture of a medicament for the combination therapy of disorders of lipid metabolism including dyslipidaemia and hyperlipoproteinaemia such as diabetic dyslipidaemia and mixed dyslipidaemia, heart failure, hypercholesteraemia, cardiovascular disease including atherosclerosis, arteriosclerosis, and hypertriglyceridaemia, type II diabetes mellitus, type I diabetes, insulin resistance, hyperlipidaemia, anorexia nervosa and obesity.

When the compounds of the present invention are used in combination with other therapeutically active agents, the compounds may be administered either together or separately, sequentially or simultaneously by any convenient route.

The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above optimally together with a pharmaceutically acceptable carrier or excipient comprise a further embodiment of the invention. The individual components of such combinations may be administered either together or separately, sequentially or simultaneously in separate or combined pharmaceutical formulations.

When combined in the same formulation it will be appreciated that the two components must be stable and compatible with each other and the other components of the formulation and may be formulated for administration. When formulated separately they may be provided in any convenient formulation, conveniently in such a manner as are known for such compounds in the art.

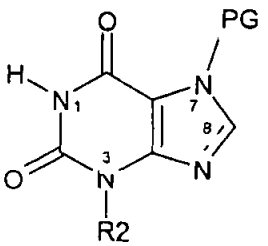
When in combination with a second therapeutic agent active against the same disease, the dose of each component may differ from that when the compound is used alone. Appropriate doses will be readily appreciated by those skilled in the art.

The invention thus provides, in a further embodiment, a combination comprising at least one compound of formula (I) or a pharmaceutically acceptable derivative thereof together with another therapeutically active agent.

The combination referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above together with a pharmaceutically acceptable carrier thereof represent a further embodiment of the invention.

The compounds of the present invention and pharmaceutically acceptable derivatives thereof may be prepared by the methodology described hereinafter, constituting a further embodiment of this invention.

In one embodiment the present invention provides a method for the preparation of compound(s) of formula (I) from an appropriate starting material, for example compound(s) of formula (II):



(II)

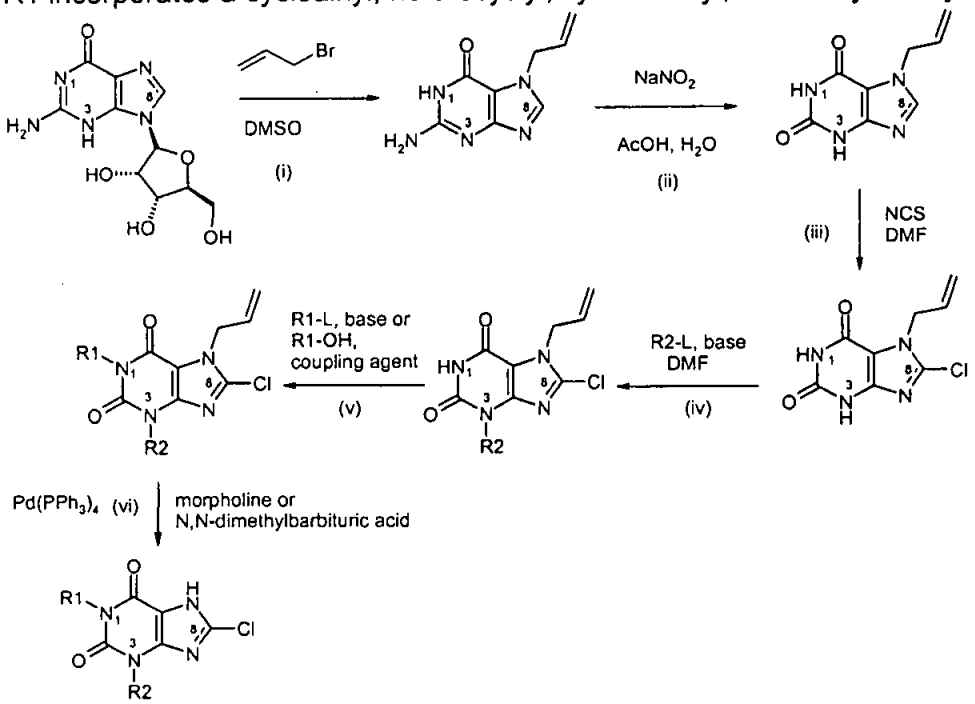
wherein PG = protecting group, the method comprising:

(i) alkylation at N1 of an N7 protected xanthine;
(ii) alkylation at N3 of an N7 protected xanthine;
(iii) halogenation at C8; and
(iv) de-protection of N7;

in any order providing de-protection is carried out after alkylation.

Process 1:

A process according to the invention for preparing compound(s) of formula (I) in which R1 incorporates a cycloalkyl, heterocyclyl, cycloalkenyl, heteroaryl or aryl.

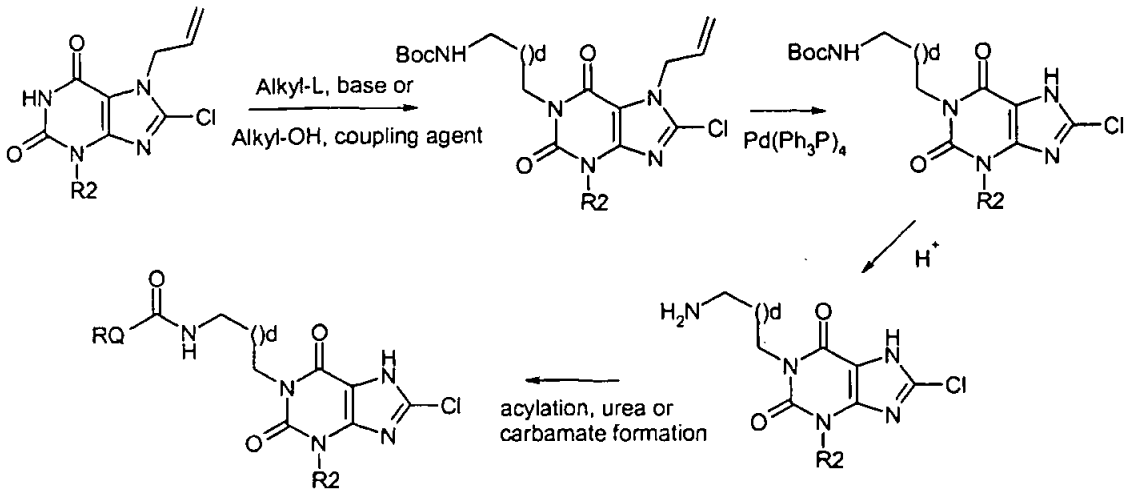


i) Alkylation of guanine with allyl bromide
ii) Diazotisation with sodium nitrite followed by hydrolysis to form the xanthine
iii) Chlorination
iv) Alkylation at N3
v) Alkylation at N1
vi) Palladium catalysed removal of the allyl group

wherein L represents a leaving group, for example halogen.

Process 2:

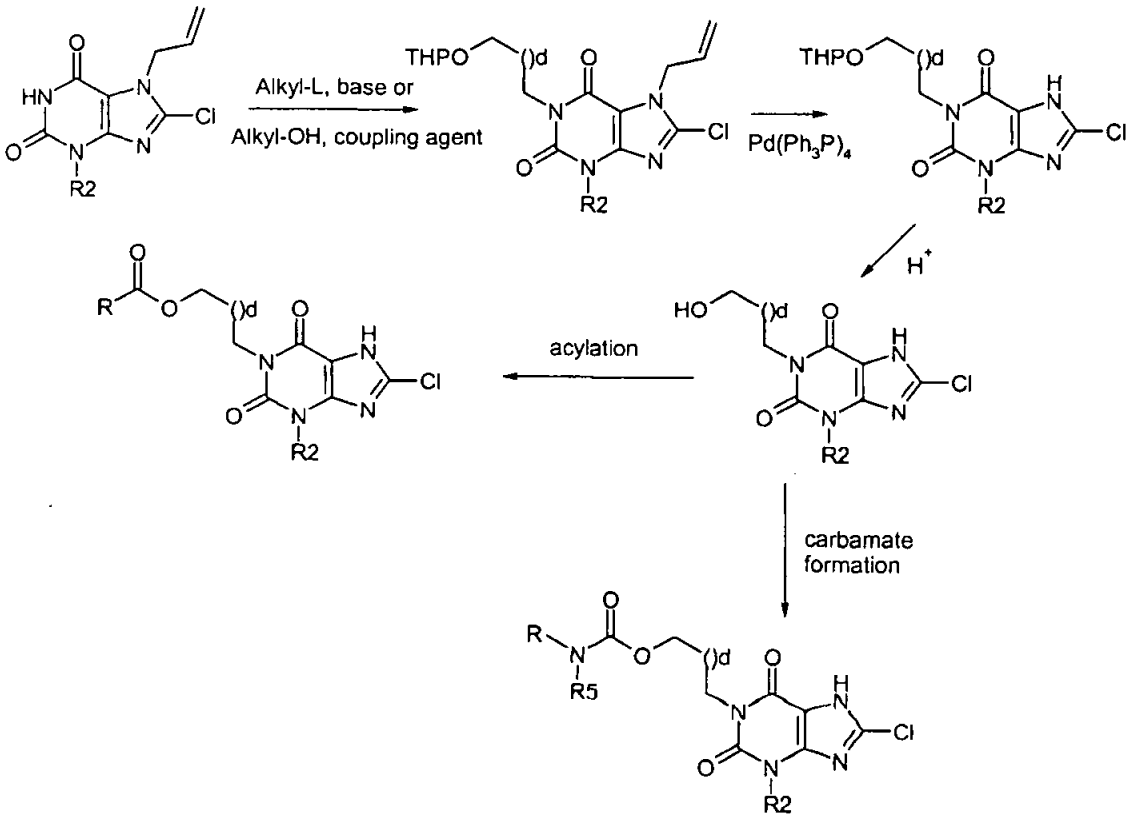
A process according to the invention for preparing compound(s) of formula (I) in which R1 incorporates an amide, carbamate or urea



wherein L represents a leaving group, for example halogen, d represents (m-1) (i.e. d together with the preceding methylene = m), R represents -(alkylene)$_n$-Y and Q may or may not be present, and if present represents either O or NR5.

Process 3:

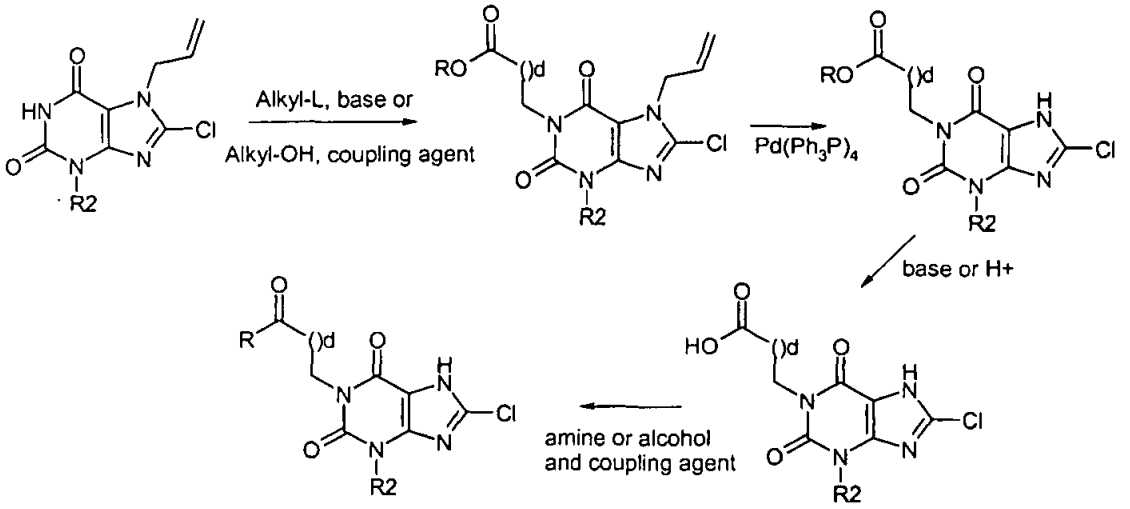
A process according to the invention for preparing compound(s) of formula (I) in which R1 incorporates a 'reverse' carbamate or ester



wherein L represents a leaving group, for example halogen, d represents (m-1), and R represents -(alk)$_n$-Y.

Process 4:

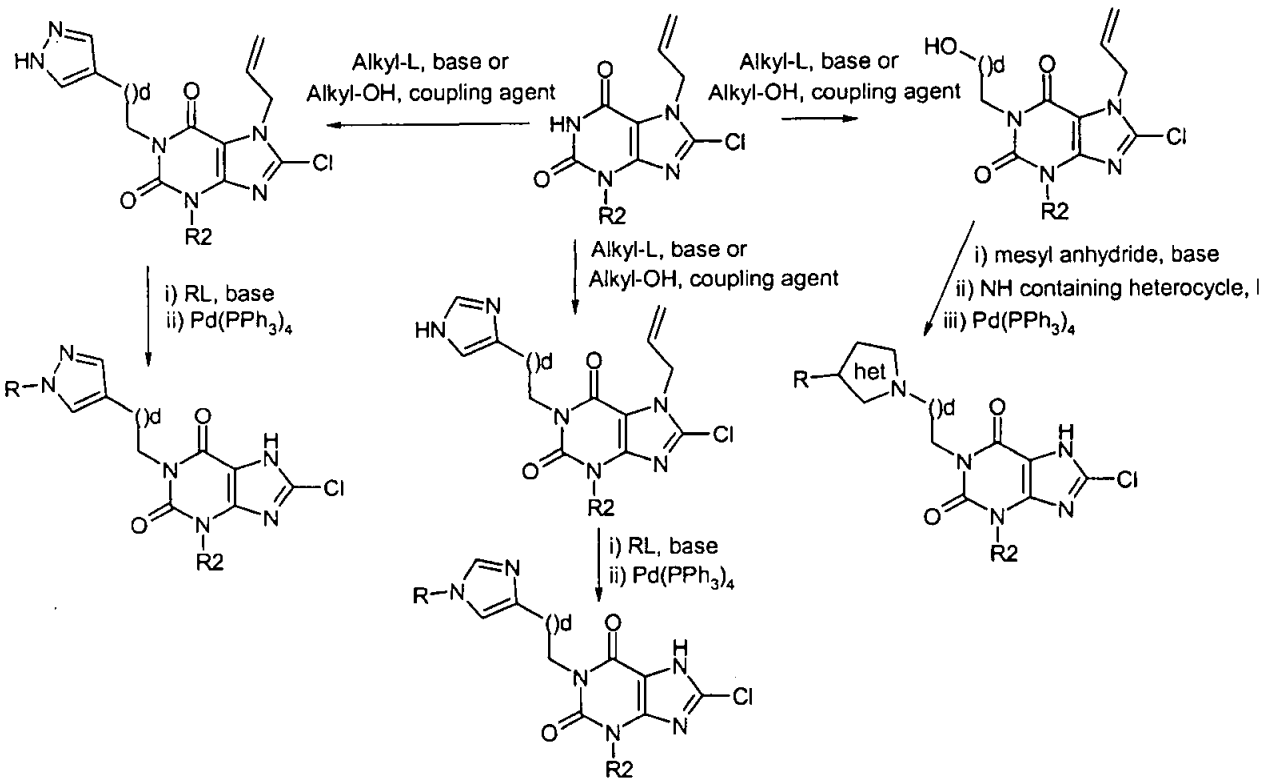
A process according to the invention for preparing compound(s) of formula (I) in which R1 incorporates an ester or amide



wherein L represents a leaving group, for example halogen, d represents (m-1), and R represents -NR^5R^7 or -OR^5.

Process 5:

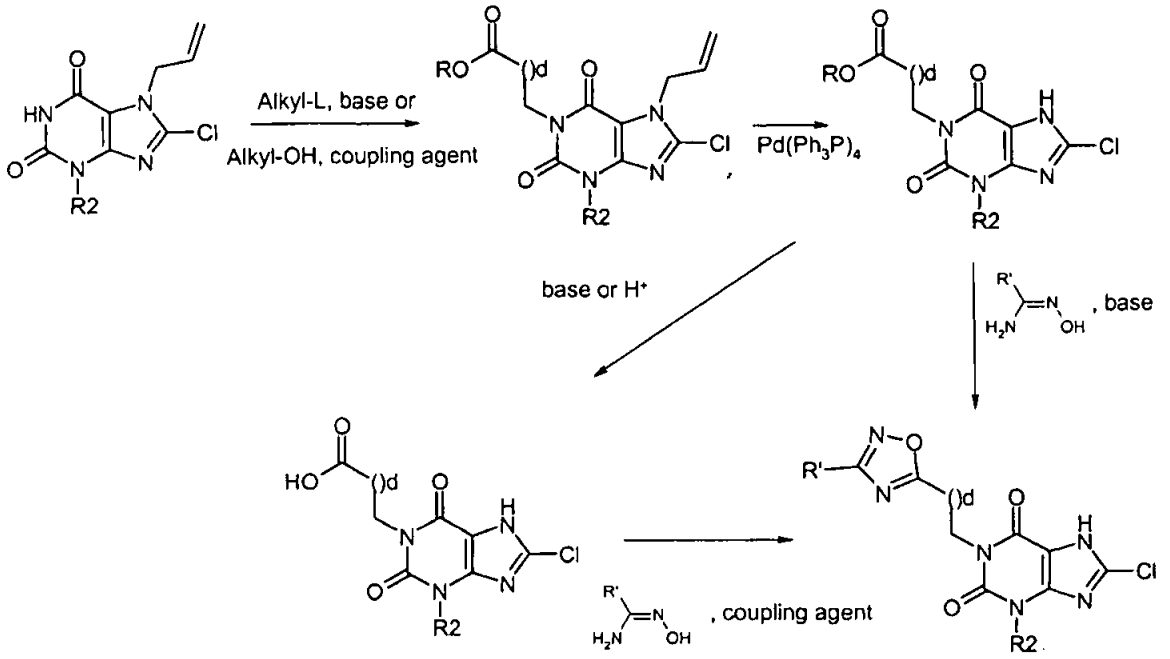
A process according to the invention for preparing compound(s) of formula (I) in which R1 incorporates a pyrazole, imidazole or tetrazole.



wherein L represents a leaving group, for example halogen, d represents (m-1), and R represents -(alk)$_n$-Y.

Process 6:

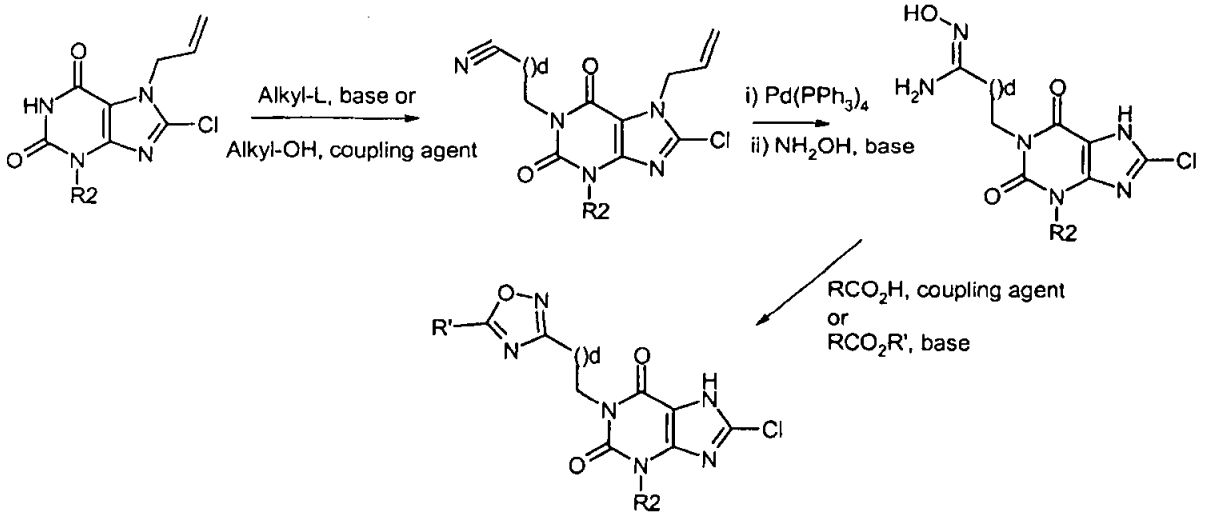
A process according to the invention for preparing compound(s) of formula (I) in which R1 incorporates an oxadiazole.



wherein L represents a leaving group, for example halogen, d represents (m-1), R represents an alkyl group and R' represents -(alk)$_n$-Y.

Process 7:

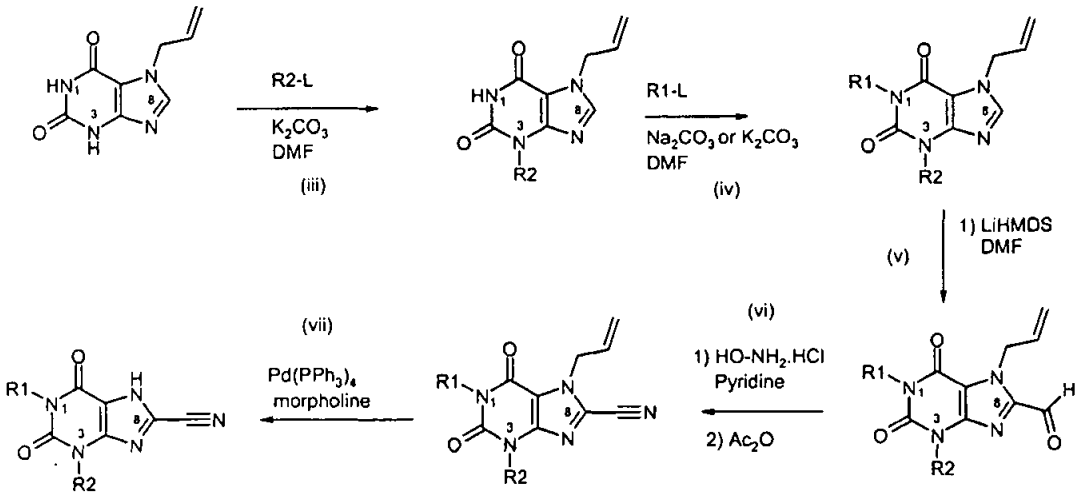
A process according to the invention for preparing compound(s) of formula (I) in which R1 incorporates an oxadiazole



wherein L represents a leaving group, for example halogen, d represents (m-1), R represents an alkyl group and R' represents -(alk)$_n$-Y.

Process 8:

A process according to the invention for preparing compound(s) of formula (I) in which R^3 is CN comprises steps (i) and (ii) of Process 1 followed by:



iii) Alkylation at N3

iv) Alkylation at N1

v) Formation of aldehyde at C8 by lithiation with LiHMDS and DMF quench

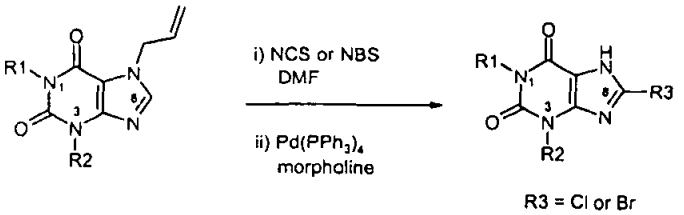
vi) Conversion of the aldehyde to the nitrile

vii) Palladium catalysed removal of the allyl group

wherein L represents a leaving group.

Process 9:

A process according to the invention for preparing compound(s) of formula (I) in which R^3 is Cl or Br comprises steps (i) to (iv) of Process 8 followed by:

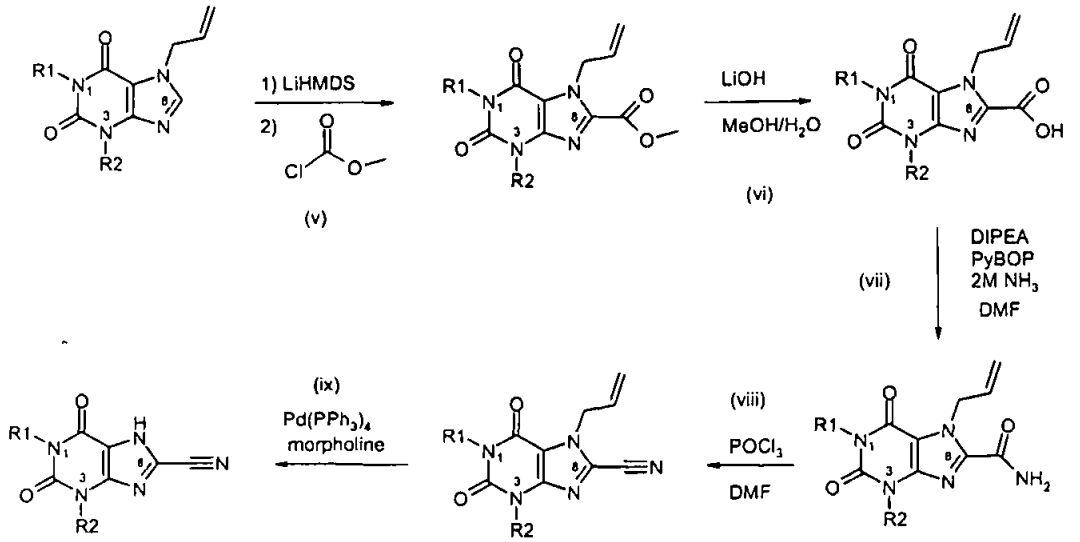


i) Halogenation at C8 using NCS or NBS

ii) Palladium catalysed removal of the allyl group

Process 10:

A process according to the invention for preparing compound(s) of formula (I) in which R^3 is CN comprises steps (i) to (iv) of Process 8 followed by:



v) Formation of ester

vi) Hydrolysis of the methyl ester

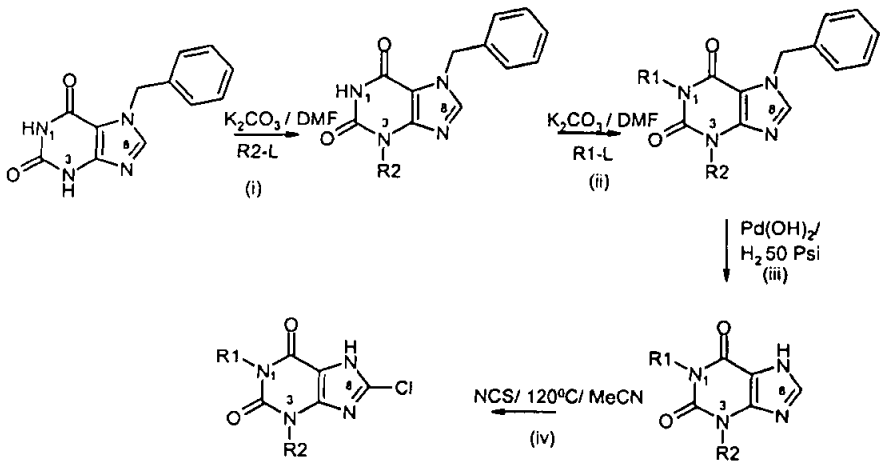
vii) Conversion of the acid to the amide.

viii) Conversion of the amide to the nitrile

ix) Palladium catalysed removal of the allyl group

Process 11:

A process according to the invention for preparing compound(s) of formula (I) in which R^3 is Cl comprises:



i) Alkylation at N3

ii) Alkylation at N1

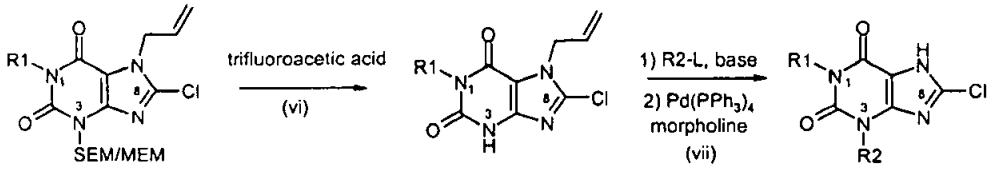
iii) Debenzylation

iii) Chlorination at C8

wherein L represents a leaving group

Process 12:

A process according to the invention for preparing compound(s) of formula (I) in which R^1 differs from R^2 and R^3 is Cl comprises steps (i) to (v) of Process 1 (where R^2 from process 1 is specifically SEM or MEM) followed by:



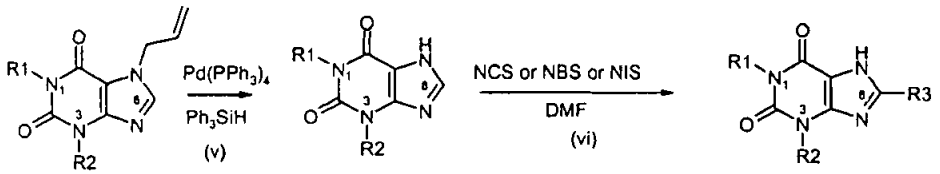
vi) Cleavage of MEM or SEM protecting group group

vii) Alkylation of N3 followed by palladium catalysed removal of the allyl group

wherein L represents a leaving group

Process 13:

A process according to the invention for preparing compound(s) of formula (I) in which R^3 is Cl, Br or I comprises steps (i) to (iv) of Process 8 followed by:

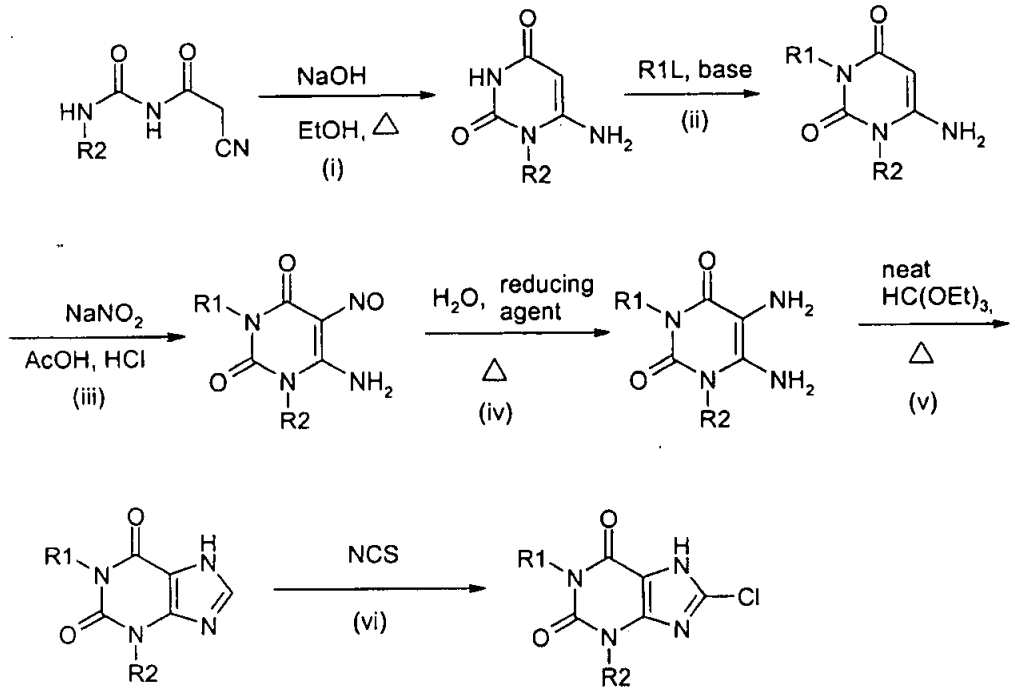


v) Palladium catalysed removal of allyl group

vi) Halogenation at C8 using NCS, NBS or NIS

Process 14:

A process according to the invention for preparing compound(s) of formula (I) comprises:

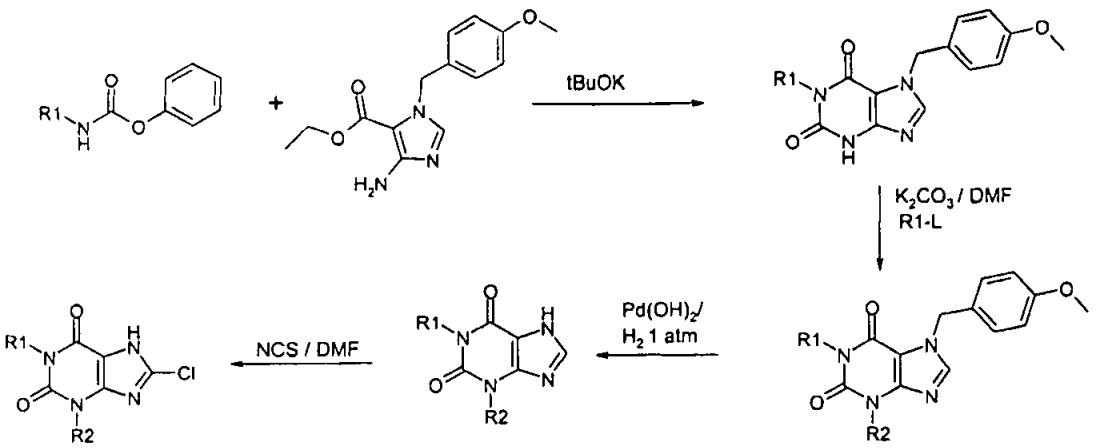


i) Pyrimidinedione formation
ii) Alkylation at N1
iii) Nitrosation
iv) Reduction using $Na_2S_2O_4$ or a similar reducing agent
v) Xanthine formation
vi) Halogenation at C8 using NCS

wherein L represents a leaving group

Process 15:

A process according to the invention for preparing compound(s) of formula (I):



50

wherein L represents a leaving group.

As an additional step to the general processes described above, and in particular for use in the preparation of the examples below, there are several ways of purifying resulting compounds, one or more of which may be of use in the present invention, for example the use of MDAP, by recrystallisation from one or more suitable solvents such as ethyl acetate, absolute ethanol, acetonitrile or methanol, or by use of purification column such as Silica Redisep cartridges and subsequent eluting with a suitable solvent such as dichloromethane containing ethyl acetate.

Where desired or necessary, as a final stage in any of the above synthetic processes, a resultant compound of formula (I) can be converted into a pharmaceutically acceptable salt form or vice versa or converting one salt form into another pharmaceutically acceptable salt form.

ABBREVIATIONS

AcOH	Acetic acid
atm	Atmosphere
br	Broad (NMR)
CDI	Carbonyldiimidazole
d	Doublet (NMR)
DBAD	Di-*t*-butylazodicarboxylate
DCM	Dichloromethane
DIPEA	Diisopropylethylamine
DMSO	Dimethylsulfoxide
DMF	N,N-Dimethylformamide
EtOAc	Ethyl acetate
EtOH	Ethanol
h	Hour(s)
IPA	Isopropyl alcohol
m	Multiplet (NMR)
MDAP	Mass directed autoprep
MeCN	Acetonitrile
MeOH	Methanol
min	Minute(s)
NCS	N-Chlorosuccinimide
NBS	N-bromosuccinimide
NIS	N-iodosuccinimide
q	Quartet (NMR)
rt	Room temperature
RT	Retention time
s	Singlet (NMR)
SPE	Solid phase extraction cartridge
t	Triplet (NMR)
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
DMEM	Dulbecco's Modified Eagle's Medium
HEPES	4-(2-Hydroxyethyl)piperazine-1-ethanesulphonic acid
LiHMDS	Lithium hexamethyldisilylamide
△	Heat
SEM	2-(trimethylsilyl)ethoxymethyl
MEM	2-methoxyethoxymethyl
Boc	t-butoxycarbonyl
THP	tetrahydropyran

Brief description of Figures

Figure 1: XRPD data of substantially crystalline 3-Butyl-8-chloro-1-{4-[5-(2-pyridinyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione form 1.

Figure 2: XRPD data of substantially crystalline 3-Butyl-8-chloro-1-{4-[5-(2-pyridinyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione form 2.

Figure 3: Overlay of XRPD data for substantially crystalline 3-Butyl-8-chloro-1-{4-[5-(2-pyridinyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione Form 1 and Form 2.

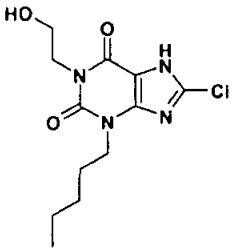
The following non-limiting examples illustrate the present invention:

Synthetic Examples

It should be noted that the assignment of (Z)-stereochemistry set out in the compounds exemplified below has not been confirmed by experimental data. The person skilled in the art will also recognise that there can be interconversion between E & Z isomers. (Dondoni, Alessandro; Lunazzi, Lodovico; Giorgianni, Patrizia; Macciantelli, Dante. Carbon-nitrogen rotational barrier as a stereochemical probe of benzamidoximes. Journal of Organic Chemistry (1975), 40(20), 2979-80)

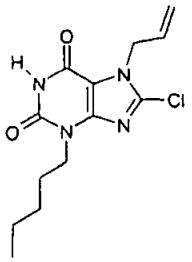
Example 1: 8-Chloro-1-(2-hydroxyethyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione

a) 8-Chloro-1-(2-hydroxyethyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione



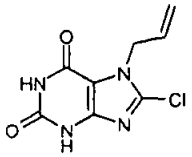
8-Chloro-3-pentyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (1.5g, 5.1mmol), Cs_2CO_3 (1.8g, 5.6mmol) and 2-chloroethanol (509µL, 7.7mmol) were reacted together in DMF (20ml) at 60°C for 18h. The reaction was allowed to cool to rt and the mixture was degassed by applying a vacuum and then nitrogen was introduced. $Pd(PPh_3)_4$ (428mg, 0.37mmol) was added and the mixture degassed once more. Morpholine (2.1ml, 24.7mmol) was added and the mixture was stirred under nitrogen for 3h, and then partitioned between 2M HCl (aq) and EtOAc. The organic layer was separated, washed with brine, dried ($MgSO_4$) and concentrated. The residue was taken up into MeOH and then passed down an aminopropyl column with the product eluting with 3% AcOH/MeOH. The product fractions were combined and concentrated then purified by recrystallisation from EtOAc. The resulting solid was collected by filtration and washed with EtOAc to give the title compound as a white solid (713mg, 47%).
LC/MS: m/z 301 $[MH]^+$, RT 2.7min.
^1H NMR (DMSO-d_6) δ: 0.86 (t, 3H, J = 7Hz), 1.22-1.36 (m, 4H), 1.63 (m, 2H), 3.50 (br t, 2H, J = 6Hz), 3.90 (t, 2H, J = 7.5Hz), 3.95 (t, 2H, J = 6.5Hz), 4.75 (br s, 1H), 14.5 (br s, 1H).

b) 8-Chloro-3-pentyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione



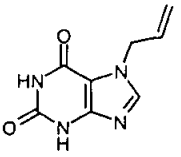
To a solution of 8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (100mg, 0.44mmol) in anhydrous DMF (3ml) was added sodium carbonate (0.051g, 0.484mmol). After 10min stirring at rt pentyl iodide (0.063ml, 0.484mmol) was added and stirring continued under nitrogen at rt for 18h. The reaction mixture was diluted with water (25ml) and extracted with EtOAc (2x25ml). The combined organic extracts were dried ($MgSO_4$) filtered and evaporated. Purification by SPE (Si, 5g) eluting with 4:1 EtOAc/cyclohexane afforded the title compound as a white solid (96mg, 74%).
LC/MS: m/z 297 $[MH]^+$.

c) 8-Chloro-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione



To a solution of 7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione) (10.52g, 54.7mmol) in anhydrous DMF (60ml) was added NCS (8.04g, 60.2mmol). The reaction mixture was left to stir under nitrogen at 20°C for 6h. The reaction mixture was concentrated *in vacuo* to give an amber oil. MeOH was added and left to stand for 18h. The resulting residue was filtered and dried under vacuum to give the title compound (7.69g, 62%).
LC/MS: m/z 227 $[MH]^+$.

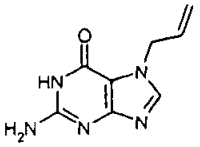
d) 7-(2-Propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione



A mixture of 2-amino-7-(2-propen-1-yl)-1,7-dihydro-6*H*-purin-6-one (40g, 0.209mol) in AcOH (900ml) and water (100ml) was heated at 55°C. Sodium nitrite (57.74g, 0.837mol) in water (100ml) was added dropwise. Care; toxic fumes. After the addition was complete (ca. 25min) the reaction mixture was allowed to cool to ambient temperature and then concentrated to ca. 1/3 of its original volume. Water (500ml) was added and the resulting precipitate collected by filtration. The residue was washed with water then dried at 50°C over P_2O_5 and under vacuum for 2h to give the title compound (17.20g). The aqueous fraction was concentrated and water added (100ml). Again the resulting solid was filtered and dried. This gave more of the title compound (2.31g). Combined product (19.52g, 49%).

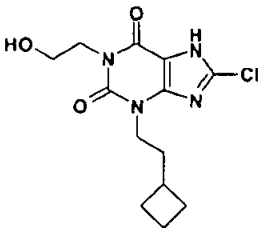
LC/MS: m/z 193 $[MH]^+$.

e) 2-Amino-7-(2-propen-1-yl)-1,7-dihydro-6*H*-purin-6-one



A mixture of guanosine (20g, 0.071mol), allyl bromide (14.7ml, 0.169mol) and anhydrous DMSO (100ml) was stirred at rt, under nitrogen, for 18h. Conc. HCl (50ml of 37%) was added in one portion and the mixture stirred for 45min then poured into MeOH (600ml). The methanolic solution was neutralised with 2M NaOH (aq) solution and the resulting white precipitate collected by filtration. The white solid was dried under vacuum at 50°C for 18h to afford the title compound (16g) which was used without further purification.
LC/MS: m/z 192 $[MH]^+$.

Example 2: 8-Chloro-3-(2-cyclobutylethyl)-1-(2-hydroxyethyl)-3,7-dihydro-1*H*-purine-2,6-dione



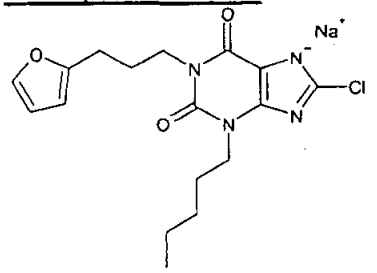
7-(2-Propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (575mg, 2.54mmol) was stirred in dry THF (20ml) with 2-cyclobutylethanol (c.73 mol%, remainder 1-butanol) (254mg). Dibenzyl azodicarboxylate (94%, 1.57g, 4.95mmol) was added, the mixture cooled to 0°C and a solution of triphenylphosphine (1.302g, 4.97mmol) in dry THF (10ml) was added dropwise. The mixture was stirred for 30min. at 0°C then at rt for 18h under nitrogen. The solvent was evaporated and the residue purified on a Biotage system (100g) eluting with EtOAc-cyclohexane (2:3). The material thus obtained (0.53g) was a mixture of the required compound, the corresponding n-butyl analogue and dibenzyl hydrazinedicarboxylate, and was alkylated without further purification.
This mixture (256mg) and Cs_2CO_3 (326mg, 1mmol) were stirred in dry DMF (5ml). 2-Chloroethanol (80.5mg, 1mmol) was added and the mixture was stirred and heated at 55 ° C for 65h. After cooling, it was thoroughly degassed, tetrakis(triphenylphosphine)palladium(0) (200mg) and morpholine (0.7ml) were added, and the mixture was stirred for 6h. EtOAc and 2M HCl were added and the mixture filtered, the organic phase washed with brine, dried (Na_2SO_4) and evaporated and the residue separated from non-acidic material by aminopropyl SPE (5g, MeOH-THF and MeOH wash, elution with DCM-MeOH with 5% added AcOH). The material obtained

from the acid wash (105mg) was further purified by MDAP to provide the title compound (42.7mg).

LC/MS: m/z 313 $[MH]^+$, RT 2.58min.

^{1}H NMR (DMSO-d_6) δ: 1.53-1.64 (m, 2H), 1.71-1.84 (m, 4H), 1.94-2.02 (m, 2H), 2.21-2.30 (m, 1H), 3.47-3.53 (m, 2H), 3.84 (t, 2H, J = 7Hz), 3.95 (t, 2H, J = 7Hz), 4.76 (br s, 1H), 14.45 (br s, 1H)

Example 3: 8-Chloro-1-[3-(2-furanyl)propyl]-3-pentyl-3,7-dihydro-1H-purine-2,6-dione, sodium salt



A GreenHouse™ tube equipped with a stirrer was charged with a 0.25ml aliquot of a 0.54M solution of 8-chloro-3-pentyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (0.13mmol) in THF. To the mixture was added 3-(2-furanyl)-1-propanol (21mg, 0.16mmol, 1.2eq) in THF (0.25ml), followed by a 0.25ml aliquot of a 0.71M solution of bis(1,1-dimethylethyl) (*E*)-1,2-diazenedicarboxylate (0.18mmol) in THF and then a 0.25ml aliquot of a 0.71M solution of triphenylphosphine (0.18mmol) in THF. The solution was stirred in a GreenHouse™ under nitrogen for 16h. To the mixture was added a further 0.25ml aliquot of a 1.4M solution of bis(1,1-dimethylethyl) (*E*)-1,2-diazenedicarboxylate (0.36mmol) in THF and then a further 0.25ml aliquot of a 1.4M solution of triphenylphosphine (0.36mmol) in THF. The mixture was stirred for 16h under a stream of nitrogen.

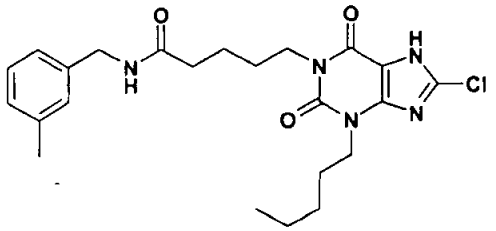
Tetrakis(triphenylphosphine)palladium(0) (16mg, 0.014mmol) and morpholine (0.12ml, 1.35mmol) were added to the mixture which was stirred for 16h under a stream of nitrogen. The reaction mixture was concentrated under nitrogen and the crude material dissolved in aqueous NaOH solution (0.5ml, 2M). The resulting solution was purified using aminopropyl SPE (eluting with AcOH in DCM and MeOH). Further purification using C18 SPE (eluting with a water, ammonia and MeCN mixture) afforded the title compound as a clear gum (22mg, 45%).

LC/MS: m/z 365 $[MH]^+$, RT 3.48min.

^{1}H NMR (DMSO-d_6) δ: 0.85 (t, 3H, J = 7Hz), 1.35-1.19 (m, 4H), 1.62 (m, 2H), 1.79 (m, 2H), 2.59 (t, 2H, J = 8Hz), 3.93 – 3.80 (m, 4H), 6.14 (d, 1H, J = 3Hz), 6.32 (dd, 1H, J = 3 and 2Hz), 7.48 (d, 1H, J = 2Hz).

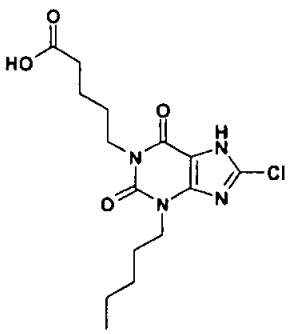
Example 4: 5-(8-Chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)-*N*-[(3-methylphenyl)methyl]pentanamide

a) 5-(8-Chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)-*N*-[(3-methylphenyl)methyl]pentanamide



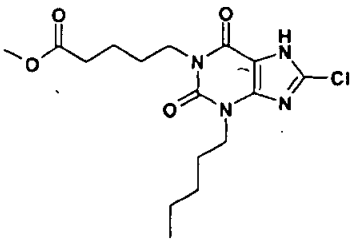
A mixture of 5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)pentanoic acid (50mg, 0.14mmol) in DCM (3ml) was treated with CDI (27mg, 0.17mmol) and left to stir at rt for 1h. [(3-Methylphenyl)methyl]amine (25µl, 0.20mmol) was added and left to stir for a further 1h. The mixture was concentrated then purified by aminopropyl SPE. The title compound was eluted with 2-3% AcOH/MeOH then concentrated to give the title compound as a white solid (56mg, 87%).
LC/MS: m/z 460 $[MH]^+$, RT 3.3min.

b) 5-(8-Chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)pentanoic acid



A mixture of methyl 5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)pentanoate (8.40g, 0.023mol), LiOH (1.63g, 0.068mol), MeOH (150ml) and water (10ml) was left to stir at ambient temperature for 64h. The mixture was partitioned between water and EtOAc and the aqueous acidified. The organic layer was separated and the aqueous extracted again with EtOAc. The combined extracts were washed with brine, dried ($MgSO_4$) and concentrated, giving the title compound as an off-white solid (9.09g).
LC/MS: m/z 357 $[MH]^+$, RT 3.0min.

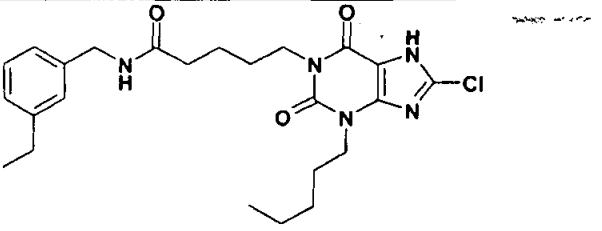
c) Methyl 5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)pentanoate



A solution of 8-chloro-3-pentyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (2.0g, 6.7mmol) in anhydrous DMF (40ml) was treated with Cs_2CO_3 (2.42g, 7.4mmol) and methyl 5-bromovalerate (1.16ml, 8.1mmol). The mixture was heated at 50°C for 18h then allowed to cool to rt and degassed under a gentle vacuum, then nitrogen introduced. This was repeated twice. $Pd(PPh_3)_4$ (779mg, 0.67mmol) was added and the mixture degassed once more. Morpholine (5.9ml, 67mmol) was added and left to stir for 3h at rt. The mixture was partitioned between 2M HCl (aq) and EtOAc. The organic layer was separated, washed with brine, dried ($MgSO_4$) and concentrated, giving a yellow residue/oil (5.16g). The residue was taken up in MeOH and divided into two equal portions, and then each passed down an aminopropyl SPE (20g), eluting with MeOH followed by 5% AcOH/MeOH then 10% AcOH/MeOH and finally 15% AcOH/MeOH. The product fractions were combined and concentrated giving the title compound as an off-white solid (2.28g, 91%).

LC/MS: m/z 371 $[MH]^+$, RT 3.1min.

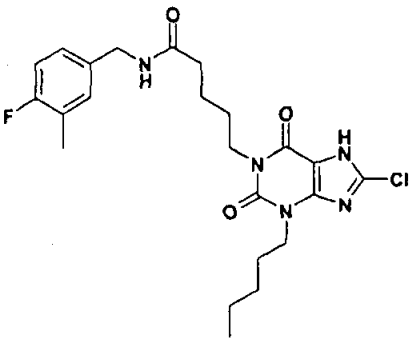
Example 5 : 5-(8-Chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)-*N*-[(3-ethylphenyl)methyl]pentanamide



A mixture of 5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)pentanoic acid (50mg, 0.14mmol) in DCM (3ml) was treated with CDI (27mg, 0.17mmol) and left to stir at rt for 1h. [(3-ethylphenyl)methyl]amine (25µl 0.20mmol) was added and left to stir for a further 1h. The mixture was concentrated then purified on an aminopropyl SPE. The title compound was eluted with 2-3% AcOH/MeOH to give a white solid (61mg, 92%).

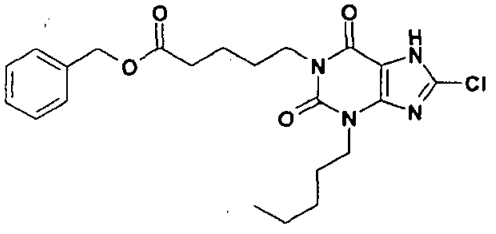
LC/MS: m/z 474 $[MH]^+$, RT 3.5min.

Example 6 : 5-(8-Chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)-*N*-[(4-fluoro-3-methylphenyl)methyl]pentanamide



A mixture of 5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)pentanoic acid (50mg, 0.14mmol) and DCM (3ml) was treated with CDI (27mg, 0.17mmol) and stirred at rt for 1h. 1-(4-Fluoro-3-methylphenyl)methanamine (27mg, 0.20mmol) and DIPEA (24µl 0.14mmol) were added. After 1h the mixture was concentrated and then the residue taken up into MeOH and passed down an aminopropyl SPE. The product was eluted with 2% AcOH/MeOH and further purified by MDAP to give the title compound as a solid (15mg, 22%).
LC/MS: m/z 478 $[MH]^+$, RT 3.4min.

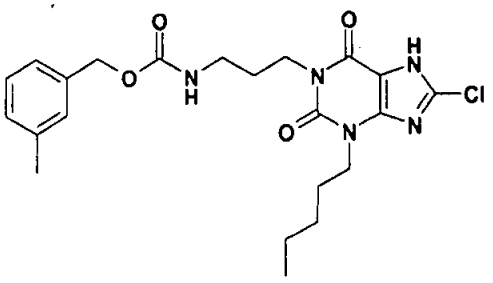
Example 7: Phenylmethyl 5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)pentanoate



A mixture of 5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)pentanoic acid (50mg, 0.14mmol) in DCM (3ml) was treated with CDI (27mg, 0.17mmol) and left to stir at rt for 1h. Benzyl alcohol (21µl, 0.20mmol) was added and left to stir for a further 1h. The reaction mixture was concentrated and DMF (3ml) was added then heated at 50°C for 2h. The mixture was concentrated then purified by MDAP giving the title compound as a white solid (33mg, 53%).
LC/MS: m/z 447 $[MH]^+$, RT 3.7min.

Example 8: (3-Methylphenyl)methyl [3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)propyl]carbamate

a) (3-Methylphenyl)methyl [3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)propyl]carbamate

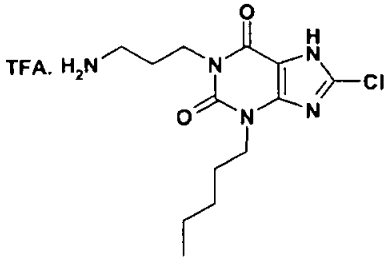


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A solution of 3-methylbenzyl alcohol (16µl, 0.13mmol) in DCM (3ml) was treated with CDI (24mg, 0.15mmol) and allowed to stir at rt for 1h. 1-(3-aminopropyl)-8-chloro-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione trifluoroacetate (50mg, 0.16mmol) was added followed by DIPEA (28µl, 0.16mmol) then heated at 50°C for 56h. The reaction mixture was concentrated, the residue taken up into MeOH and purified by aminopropyl SPE. The title compound eluted with 2% AcOH/MeOH and a white solid collected (40mg, 58%).

LC/MS: m/z 462 $[MH]^+$, RT 3.6min.

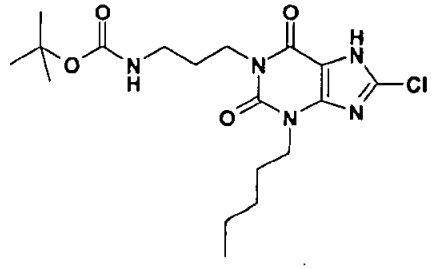
b) 1-(3-Aminopropyl)-8-chloro-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione trifluoroacetate



A solution of 1,1-dimethylethyl [3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)propyl]carbamate (1.59g, 4.38mmol) in DCM (16ml) was treated with TFA (16ml) and stirred at rt for 2h then concentrated *in vacuo*. Residual TFA was removed by azeotroping with DCM then the residue was triturated with Et_2O to give the title compound as a solid (1.48g, quant.).

LC/MS: m/z 314 $[MH]^+$, RT 2.1min.

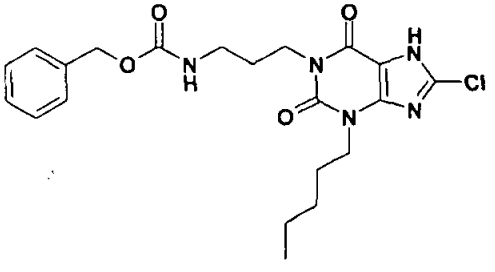
c) 1,1-Dimethylethyl [3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)propyl]carbamate



A solution of 1,1-dimethylethyl (3-hydroxypropyl)carbamate (1.0ml, 6.1mmol) in THF (40ml) was treated with 8-chloro-3-pentyl-1-[3-(tetrahydro-2*H*-pyran-2-yloxy)propyl]-

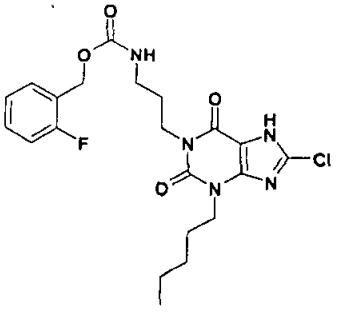
3,7-dihydro-1*H*-purine-2,6-dione (1.5g, 5.1mmol) and PPh_3 (1.73g, 6.6mmol) at rt under nitrogen. DBAD (1.52g, 6.6mmol) was added in one portion and stirred for 18h. The mixture was degassed by applying a vacuum and then nitrogen was introduced. $Pd(PPh_3)_4$ (586mg, 0.51mmol) was added and the mixture degassed once more. Morpholine (4.4ml, 50.7mmol) was added and the mixture was stirred under nitrogen for 3h, then partitioned between 2M HCl (aq) and EtOAc. The organic layer was separated, washed with brine, dried ($MgSO_4$) and concentrated, giving a yellow oil. MeOH was added and then passed down an aminopropyl SPE with the product eluting with 2-3% AcOH/MeOH. The product fractions were combined and concentrated, giving the title compound as a clear gummy solid (1.59g, 75%).
LC/MS: m/z 414 $[MH]^+$, RT 3.4min.

Example 9 : Phenylmethyl [3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)propyl]carbamate



1-(3-Aminopropyl)-8-chloro-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione trifluoroacetate (50mg, 0.12mmol) in DCM (3ml) was treated with DIPEA (51µl, 0.29mmol) and benzyl chloroformate (20µl, 0.14mmol). After 1h the reaction mixture was concentrated and purified on an aminopropyl SPE. The title compound eluted with 2% AcOH/MeOH and a white solid collected (35mg, 67%).
LC/MS: m/z 448 $[MH]^+$, RT 3.4min.

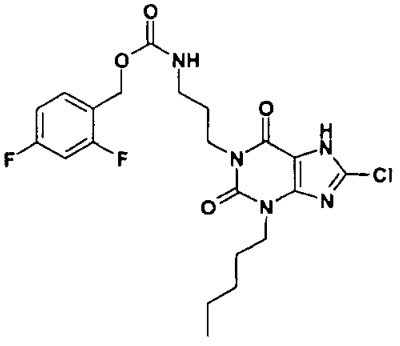
Example 10 : (2-Fluorophenyl)methyl [3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)propyl]carbamate



(2-Fluorophenyl)methanol (11µl, 0.10mmol) in DCM (3ml) was reacted with CDI (17mg, 0.11mmol) under nitrogen for 1h. 1-(3-Aminopropyl)-8-chloro-3-pentyl-3,7-dihydro-1*H*-

purine-2,6-dione trifluoroacetate (50mg, 0.16mmol) was added followed by DIPEA (20µl, 0.12mmol) then heated at reflux for 18h. THF (3ml) was added and heated at 75°C for 5h. After cooling, the mixture was concentrated *in vacuo* and purified by MDAP to give the title compound as a solid (21mg, 39%).
LC/MS: m/z 466 $[MH]^+$, RT 3.4min.

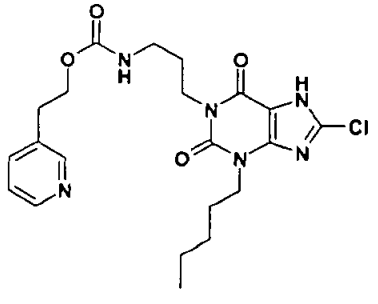
Example 11 : (2,4-Difluorophenyl)methyl [3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)propyl]carbamate



(2,4-Difluorophenyl)methanol (11µL, 0.10mmol) in DCM (3ml) was reacted with CDI (17mg, 0.11mmol) under nitrogen for 1h. 1-(3-Aminopropyl)-8-chloro-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione trifluoroacetate (50mg, 0.16mmol) was added followed by DIPEA (20µl, 0.12mmol) then heated at reflux for 18h. THF (3ml) was added and heated at 75°C for 5h. After cooling, the mixture was concentrated *in vacuo* and purified by MDAP to give the title compound as a solid (29mg, 21%).
LC/MS: m/z 484 $[MH]^+$, RT 3.4min.

Example 12 : 2-(3-Pyridinyl)ethyl [3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)propyl]carbamate

a) 2-(3-Pyridinyl)ethyl [3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)propyl]carbamate

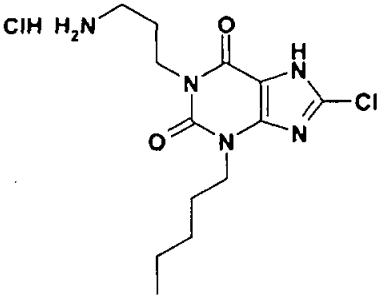


A solution of CDI (21mg, 0.13mmol) in THF (2ml) was treated with 2-(3-pyridinyl)ethanol (16mg, 0.13mmol) and heated at reflux for 1h before the addition of 1-

(3-aminopropyl)-8-chloro-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione hydrochloride (50mg, 0.14mmol) and DIPEA (25µl, 0.14mmol). The reaction was left at reflux for 18h then concentrated and purified by MDAP to provide the title compound as a solid (30mg, 24%).

LC/MS: m/z 463 $[MH]^+$, RT 2.6min.

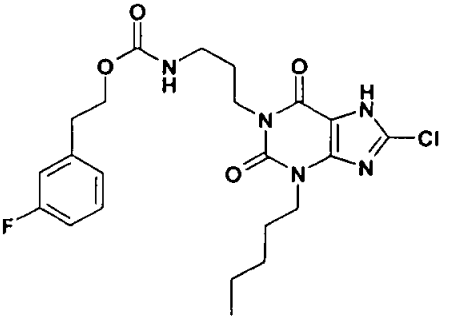
b) 1-(3-Aminopropyl)-8-chloro-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione hydrochloride



A mixture of 1,1-dimethylethyl [3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)propyl]carbamate (5.19g, 12.5mmol) and 4M HCl in 1,4-dioxane (80ml) was stirred at rt for 3h. The mixture was concentrated *in vacuo* and dried under vacuum to provide the title product as a white solid (4.49g, quant.).

LC/MS: m/z 314 $[MH]^+$, RT 2.2min.

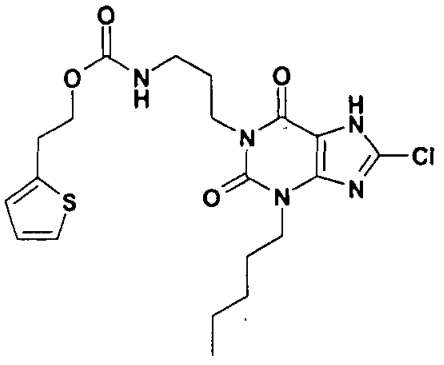
Example 13 : 2-(3-Fluorophenyl)ethyl [3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)propyl]carbamate



A solution of CDI (21mg, 0.13mmol) in THF (2ml) was treated with 2-(3-fluorophenyl)ethanol (16µl, 0.13mmol) and heated at reflux for 1h before the addition of 1-(3-aminopropyl)-8-chloro-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione hydrochloride (50mg, 0.14mmol) and DIPEA (25µL, 0.14mmol). The reaction was left at reflux for 18h then concentrated and purified by MDAP to provide the title compound as a solid (27mg, 39%).

LC/MS: m/z 480 $[MH]^+$, RT 3.5min.

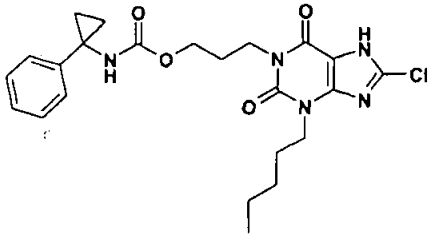
Example 14 : 2-(2-Thienyl)ethyl [3-(8-chlor -2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)propyl]carbamate



A solution of CDI (21mg, 0.13mmol) in THF (2ml) was treated with 2-(2-thienyl)ethanol (15μl, 0.13mmol) and heated at reflux for 1h before the addition of 1-(3-aminopropyl)-8-chloro-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione hydrochloride (50mg, 0.14mmol) and DIPEA (25μL, 0.14mmol). The reaction was left at reflux for 18h then concentrated and purified by MDAP to provide the title compound as a solid (34mg, 51%).
LC/MS: m/z 468 $[MH]^+$, RT 3.4min.

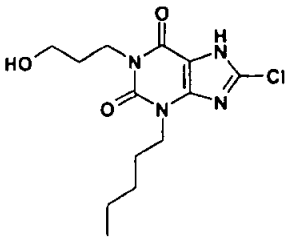
Example 15 : 3-(8-Chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)propyl (1-phenylcyclopropyl)carbamate

a) 3-(8-Chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)propyl (1-phenylcyclopropyl)carbamate



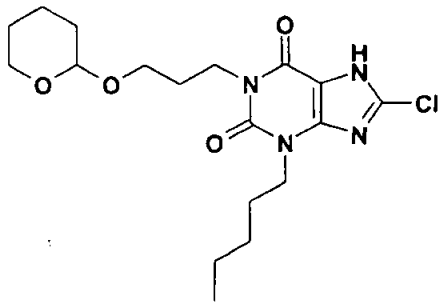
A solution of 8-chloro-1-(3-hydroxypropyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione (50mg, 0.16mmol) was treated with CDI (28mg, 0.18mmol) and allowed to stir at rt for 1h. 1-Phenylcyclopropanamine (30mg, 0.20mmol) was added and the mixture heated at reflux under nitrogen for 18h. Another aliquot of 1-phenylcyclopropanamine (30mg, 0.20mmol) was added followed by THF (3ml). The reaction was heated at 75°C for 18h then concentrated and purified by MDAP. This gave the title compound as a white solid (13mg, 18%).
LC/MS: m/z 474 $[MH]^+$, RT 3.5min.

b) 8-Chloro-1-(3-hydroxypropyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione



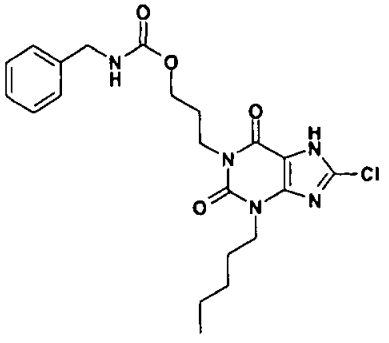
A solution of 8-chloro-3-pentyl-1-[3-(tetrahydro-2*H*-pyran-2-yloxy)propyl]-3,7-dihydro-1*H*-purine-2,6-dione (5.87g, 14.8mmol) in EtOH (100ml) was treated with pTsOH (2.8g, 14.8mmol) and stirred at rt for 18.5h. The mixture was partitioned between 1M HCl (aq) and EtOAc. The organic layer was separated and the aqueous layer extracted once more. The combined extracts were washed with water (x5), brine, then dried ($MgSO_4$) and concentrated, giving a pale yellow solid. The solid was washed with Et_2O and collected by filtration giving a white solid (2.42g, 52%).
LC/MS: m/z 315 $[MH]^+$, RT 2.7min.

c) 8-Chloro-3-pentyl-1-[3-(tetrahydro-2*H*-pyran-2-yloxy)propyl]-3,7-dihydro-1*H*-purine-2,6-dione



8-Chloro-3-pentyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (5.0g, 16.8mmol), Cs_2CO_3 (6.0g, 18.5mmol) and 2-(3-bromopropoxy)tetrahydro-2H-pyran (3.4ml, 20mmol) were reacted together in DMF (100ml) at 50°C under nitrogen for 24h. The reaction was allowed to cool to rt and the mixture was degassed by applying a vacuum and then nitrogen was introduced. $Pd(PPh_3)_4$ (1.4g, 1.2mmol) was added and the mixture degassed once more. Morpholine (14.7ml, 170mmol) was added and the mixture was stirred under nitrogen for 3h, then partitioned between 2M HCl (aq) and EtOAc. The organic layer was separated, washed with brine, dried ($MgSO_4$) and concentrated, giving a yellow residue (5.16g). MeOH was added and then passed down an aminopropyl SPE with the product eluting with 5% AcOH/MeOH. The product fractions were combined and concentrated, giving the title compound as a pale yellow solid (5.97g, 89%).
LC/MS: m/z 399 $[MH]^+$, RT 3.3min.

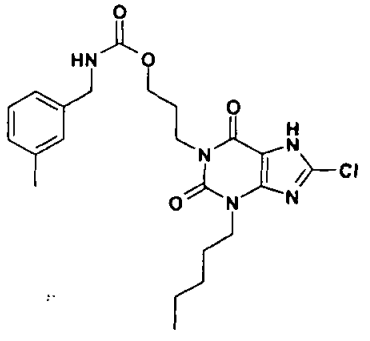
Example 16 : 3-(8-Chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)propyl (phenylmethyl)carbamate



A solution of 8-chloro-1-(3-hydroxypropyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione (50mg, 0.16mmol) in THF (3ml) was treated with triphosgene (47mg, 0.16mmol) and pyridine (13µl, 0.16mmol). After 30min benzylamine (217µl, 2.0mmol) was added and left to stir for a further 30min. The mixture was partitioned between 2M HCl (aq) and EtOAc. The organic layer was separated, washed with brine, dried ($MgSO_4$) and concentrated. The residue was taken up into MeOH and purified by passing down an aminopropyl SPE, the product eluted with 2-5% AcOH/MeOH. The title compound was obtained as an off-white solid (67mg, 94%).

LC/MS: m/z 448 $[MH]^+$, RT 3.2min.

Example 17 : 3-(8-Chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)propyl [(3-methylphenyl)methyl]carbamate

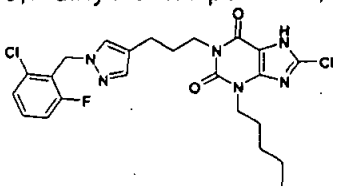


A solution of 8-chloro-1-(3-hydroxypropyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione (50mg, 0.16mmol) in DCM (3ml) was treated with CDI (31mg, 0.19mmol) and stirred at rt for 1h. 3-Methylbenzylamine (26µl, 0.21mmol) was added and heated at reflux for 18h. Another aliquot of methylbenzylamine (4µl, 0.03mmol) was added and the mixture left for 4h at reflux. The mixture was concentrated then taken up into MeOH and passed down an aminopropyl SPE. The product was eluted with 2% AcOH/MeOH and then purified further by MDAP. This gave the title compound as a white solid (42mg, 57%).

LC/MS: m/z 462 $[MH]^+$, RT 3.5min.

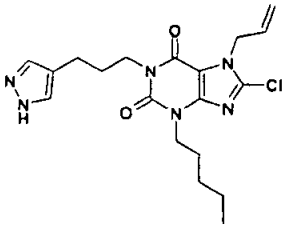
Example 18 : 8-Chloro-1-(3-{1-[(2-chloro-6-fluorophenyl)methyl]-1*H*-pyrazol-4-yl}propyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione

a) 8-Chloro-1-(3-{1-[(2-chloro-6-fluorophenyl)methyl]-1*H*-pyrazol-4-yl}propyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione



8-Chloro-3-pentyl-7-(2-propen-1-yl)-1-[3-(1*H*-pyrazol-4-yl)propyl]-3,7-dihydro-1*H*-purine-2,6-dione (61mg, 0.15mmol) in dry DMF (2ml) was stirred with sodium carbonate (64mg, 0.6mmol) and 2-chloro-6-fluorobenzyl bromide (134mg, 0.6mmol) and heated at 45°C for 18h under nitrogen. After cooling to rt the mixture was degassed by evacuating and readmitting nitrogen, and stirred with tetrakis(triphenylphosphine)palladium(0) (35mg, 0.303mmol) and morpholine (0.13ml) for 5.5h. The mixture was partitioned between EtOAc and 2M HCl, the organic phase separated and evaporated and the residue purified by aminopropyl SPE (5g, washing with THF-MeOH (1:1) then neat MeOH and finally eluting with DCM-MeOH (1:1) containing 5% AcOH) to give the title compound (57mg) as a solid.
LC/MS: m/z 507 $[MH]^+$, RT 3.64min.

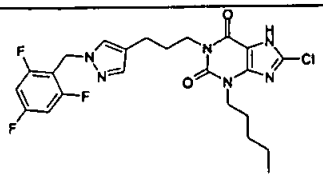
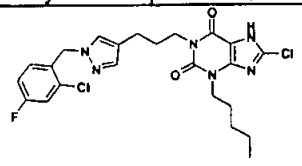
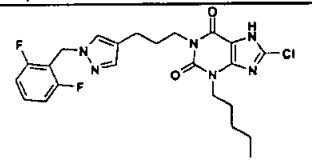
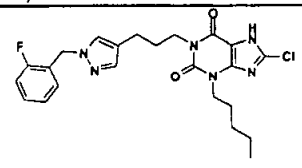
b) 8-Chloro-3-pentyl-7-(2-propen-1-yl)-1-[3-(1*H*-pyrazol-4-yl)propyl]-3,7-dihydro-1*H*-purine-2,6-dione



3-Pentyl-8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (5g, 16.86mmol) and 3-(1*H*-pyrazol-4-yl)propan-1-ol (2.12g, 16.8mmol) were stirred in dry THF (150ml) at 3°C. Dibenzyl azodicarboxylate (10.05g, 33.7mmol) was added followed by the dropwise addition of triphenylphosphine (8.83g, 33.7mmol) in dry THF (70ml). The mixture was allowed to warm to rt and stirred for 18h. Water (1ml) was added and the solvents evaporated. The residue was taken up in Et_2O (200ml) from which a white solid, mostly triphenylphosphine oxide, crystallised and was filtered off. The filtrate was concentrated and further by-products crystallised from ether-cyclohexane. The remaining filtrate was concentrated (19.2g) and purified on a Biotage™ system (400g) eluting with EtOAc-cyclohexane (2:1) to afford the title compound as a white solid (2.89g).
LC/MS: m/z 405 $[MH]^+$, RT 3.19min.

The following compounds (Table 1) were prepared using a method analogous to that for Example 18, from the corresponding benzyl halides.

Table 1

Example	structure	Yield (mg)	LC/MS:
19	 8-chloro-3-pentyl-1-(3-{1-[(2,4,6-trifluorophenyl)methyl]-1*H*-pyrazol-4-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione	68	m/z 509 $[MH]^+$ RT 3.58 min
20	 8-chloro-1-(3-{1-[(2-chloro-4-fluorophenyl)methyl]-1*H*-pyrazol-4-yl}propyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione	56	m/z 507 $[MH]^+$ RT 3.73 min
21	 8-chloro-1-(3-{1-[(2,6-difluorophenyl)methyl]-1*H*-pyrazol-4-yl}propyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione	29	m/z 491 $[MH]^+$ RT 3.53 min
22	 8-chloro-1-(3-{1-[(2-fluorophenyl)methyl]-1*H*-pyrazol-4-yl}propyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione	32*	m/z 473 $[MH]^+$ RT 3.55 min

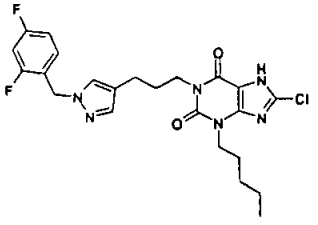
* after additional purification by MDAP.

NMR details for selected examples from Table 1

Example 19: 8-chloro-3-pentyl-1-(3-{1-[(2,4,6-trifluorophenyl)methyl]-1*H*-pyrazol-4-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione

^{1}H NMR (DMSO-d_6) δ: 0.85 (t, 3H, J = 7 Hz), 1.20-1.40 (m, 4H), 1.60-1.70 (m, 2H), 1.70-1.82 (m, 2H), 2.39 (t, 2H, J = 8 Hz), 3.83-3.94 (m, 4H), 5.24 (s, 2H), 7.18-7.30 (m, 3H), 7.57 (s, 1H).

Example 23: 8-Chloro-1-(3-{1-[(2,4-difluorophenyl)methyl]-1*H*-pyrazol-4-yl}propyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione



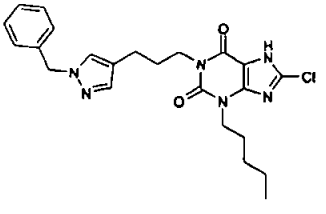
8-Chloro-3-pentyl-7-(2-propen-1-yl)-1-[3-(1*H*-pyrazol-4-yl)propyl]-3,7-dihydro-1*H*-purine-2,6-dione (81mg, 0.2mmol) and sodium carbonate (85mg, 0.8mmol) were stirred in dry DMF (2ml) with 2,4-difluorobenzyl bromide (166mg, 0.8mmol) at 45°C for 18h. The mixture was degassed and stirred with tetrakis(triphenylphosphine)palladium(0) (46mg, 0.04mmol) and morpholine (176mg, 2mmol) at rt for 6h. The reaction was worked up and purified by aminopropyl SPE (5g, washing with THF-MeOH (1:1) then neat MeOH, eluting with DCM-MeOH (1:1) with 5% added AcOH) to yield the title compound (37.7mg) as a solid.

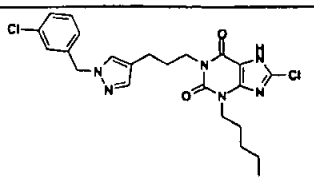
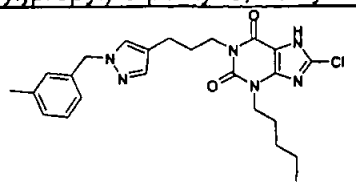
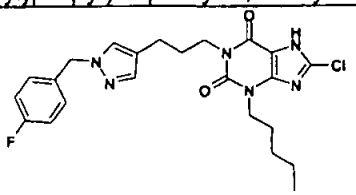
LC/MS: m/z 491 $[MH]^+$, RT 3.42min.

^{1}H NMR (d^6 DMSO) 0.85 (3H, t, J = 7Hz), 1.21-1.34 (4H, m), 1.58-1.68 (2H, m), 1.71-1.80 (2H, m), 2.41 (2H, t, J = 8Hz), 3.84-3.93 (4H, m), 5.26 (2H, s), 7.02-7.09 (1H, m), 7.15-7.29 (2H, m), 7.31 (1H, s), 7.61 (1H, s).

The following compounds (Table 1) were prepared using a method analogous to that for Example 23, from the corresponding benzyl halides.

Table 2

Example	Structure	Yield (mg)	LC/MS:
24	 8-chloro-3-pentyl-1-{3-[1-(phenylmethyl)-1*H*-pyrazol-4-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione	17*	m/z 455 $[MH]^+$ RT 3.52 min

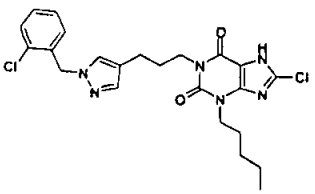
25	 8-chloro-1-(3-{1-[(3-chlorophenyl)methyl]-1*H*-pyrazol-4-yl}propyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione	11.6*	m/z 489 $[MH]^+$ RT 3.52 min
26	 8-chloro-1-(3-{1-[(3-methylphenyl)methyl]-1*H*-pyrazol-4-yl}propyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione	33	m/z 469 $[MH]^+$ RT 3.54 min
27	 8-chloro-1-(3-{1-[(4-fluorophenyl)methyl]-1*H*-pyrazol-4-yl}propyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione	42	m/z 473 $[MH]^+$ RT 3.44 min

*after additional purification by MDAP.

NMR details for selected examples from Table 2

Example 24: 8-chloro-3-pentyl-1-{3-[1-(phenylmethyl)-1*H*-pyrazol-4-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione; ^{1}H NMR (DMSO-d_6) δ: 0.87 (t, 3H, J = 7 Hz), 1.20-1.36 (m, 4H), 1.60-1.70 (m, 2H), 1.72-1.85 (m, 2H), 2.42 (t, 2H, J = 8 Hz), 3.83-3.95 (m, 4H), 5.24 (s, 2H), 7.13-7.38 (m, 6H), 7.61 (s, 1H).

Example 28: 8-Chloro-1-(3-{1-[(2-chlorophenyl)methyl]-1*H*-pyrazol-4-yl}propyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione

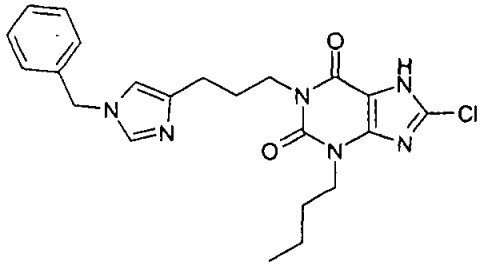


Prepared by the method for 8-chloro-1-(3-{1-[(2,4-difluorophenyl)methyl]-1*H*-pyrazol-4-yl}propyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione but from 2-chlorobenzyl bromide (164mg, 0.8mmol). However, in order to complete the deprotection step further tetrakis(triphenylphosphine)palladium(0) (40mg) and morpholine (0.15ml) were added and stirring continued for a further 5.5h. Purification by aminopropyl SPE as above afforded the title compound as a solid (42mg).

LC/MS: m/z 489 $[MH]^+$, RT 3.67min.

Example 29: 3-Butyl-8-chloro-1-{3-[1-(phenylmethyl)-1*H*-imidazol-4-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione

a) 3-Butyl-8-chloro-1-{3-[1-(phenylmethyl)-1*H*-imidazol-4-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione

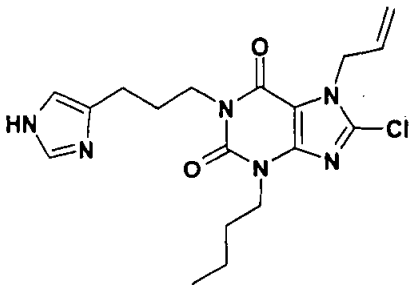


A solution of 3-butyl-8-chloro-1-[4-(1*H*-imidazol-4-yl)butyl]-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (300mg, 0.77mmol) in anhydrous THF (5ml) was treated with benzyl bromide (144mg, 0.84mmol) and DIPEA (147µl, 0.84mmol). The mixture was left to stir at rt under nitrogen for 4 days. The mixture was partitioned between EtOAc and 2M HCl (aq). The organic layer was separated, washed with brine, dried ($MgSO_4$) and concentrated. The crude was purified by a silica SPE column using a 0.5-5% MeOH/DCM gradient. The product fractions were combined and concentrated under high vacuum. The product was dissolved in THF (5ml) then $Pd(PPh_3)_4$ (88mg, 0.077mmol) and morpholine (670µl, 7.67mmol) were added and the mixture left to stir at rt under nitrogen for 3h. 88mg of $Pd(PPh_3)_4$ (0.077mmol) was added and the mixture was left to stir at rt under nitrogen for 16h. The mixture was partitioned between EtOAc and H_2O. The organic layer was separated and the aqueous layer was extracted with EtOAc (x2). The organic layers were combined, washed with brine, dried ($MgSO_4$) and concentrated. The crude product was purified by MDAP to give the title compound as a white solid (9mg, 2%).

LC/MS: m/z 441 $[MH]^+$, RT 2.50min.

^1H NMR (DMSO-d_6) δ: 0.89 (t, 3H, J = 7.5 Hz), 1.28 (m, 2H), 1.60 (m, 2H), 1.79 (m, 2H), 2.48 (t overlapping with DMSO, 2H, J =7.5 Hz), 3.89 (m, 4H), 5.17 (s, 2H), 7.08 (s, 1H), 7.31, (m, 6H), 8.03 (s, 1H).

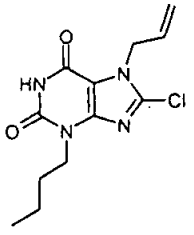
b) 3-Butyl-8-chloro-1-[3-(1*H*-imidazol-4-yl)propyl]-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione



A solution of 3-butyl-8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1H-purine-2,6-dione (2.8g, 9.9mmol) in anhydrous THF (60ml) was treated with 3-(1*H*-imidazol-4-yl)-1-propanol (1.5g, 12mmol) in anhydrous THF (10ml) and PPh_3 (3.4g, 13mmol). DBAD (2.9g, 13mmol) was added in one portion and the mixture was left to stir at rt, under nitrogen for 18h. The mixture was partitioned between EtOAc and H_2O. The aqueous layer was extracted and washed with EtOAc. The organic layers were combined, washed with brine, dried ($MgSO_4$) and concentrated. The crude product was purified by a silica SPE cartridge using a MeOH/EtOAc gradient (0.5%-7% MeOH). The product fractions were combined and concentrated by to give the title compound as a white solid (2.16g, 55%).

LC/MS: m/z 391 $[MH]^+$, RT 2.40min.

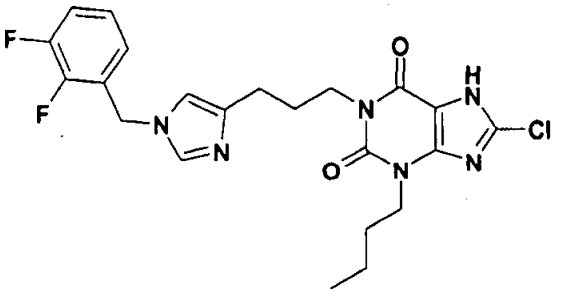
c) 3-Butyl-8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione



To a solution of 3-butyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (3.34g, 13.4mmol) in anhydrous DMF (19ml) was added NCS (1.97g, 14.8mmol) and left to stir at rt under nitrogen for 22h. The mixture was concentrated *in vacuo* to give a yellow solid which was filtered and washed with MeOH to provide a first crop. The filtrate was concentrated to a solid and washed with MeOH to provide a second crop and repeated a further two occasions to provide the title compound. On the final wash the filtrate was further purified by SPE (Si, 20g) cartridge eluting with EtOAc:cyclohexane (1:1). The combined solids were dried under vacuum to afford the title compound (2.42g, 64%).

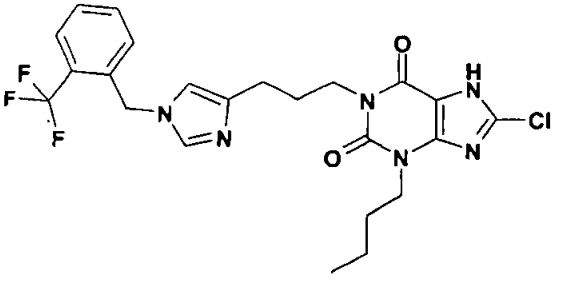
LC/MS: m/z 283 $[MH]^+$.

Example 30: 3-Butyl-8-chloro-1-(3-{1-[(2,3-difluorophenyl)methyl]-1*H*-imidazol-4-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione



A solution of 3-butyl-8-chloro-1-[4-(1*H*-imidazol-4-yl)butyl]-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (150mg, 0.38mmol) in anhydrous DMF (3ml) was treated with 1-(bromomethyl)-2,4-difluorobenzene (54µl, 0.42mmol) and DIPEA (73µl, 0.42mmol). The mixture was left to stir at rt under nitrogen for 3 days. The mixture was partitioned between EtOAc and 2M HCl (aq). The organic layer was separated, washed with brine, dried ($MgSO_4$) and concentrated. The crude product was purified on a silica SPE column using a DCM to load the material onto the column and wash through the impurities then a 0-5% MeOH/DCM gradient to elute the compound. The product fractions were combined and concentrated and the residues dissolved in anhydrous DMF (3ml). The solution was degassed then $Pd(PPh_3)_4$ (39mg, 0.034mmol) and morpholine (200µl, 2.3mmol) were added and the mixture left to stir at rt under nitrogen for 3h. The crude product was purified by an aminopropyl SPE using MeOH to load the compound onto the column and wash through the impurities then a 0-5% AcOH/MeOH gradient to elute the product. The product fractions were combined and concentrated by high vacuum to leave the title compound as a white solid (14mg, 7%).
LC/MS: m/z 477 $[MH]^+$, RT 2.54min.

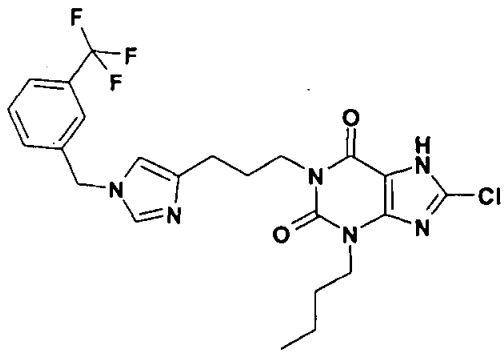
Example 31 : 3-Butyl-8-chloro-1-[3-(1-{[2-(trifluoromethyl)phenyl]methyl}-1*H*-imidazol-4-yl)propyl]-3,7-dihydro-1*H*-purine-2,6-dione



A solution of 3-butyl-8-chloro-1-[4-(1*H*-imidazol-4-yl)butyl]-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (150mg, 0.38mmol) in anhydrous DMF (3ml) was treated with 1-(chloromethyl)-2-(trifluoromethyl)benzene (61µl, 0.42mmol) and DIPEA (73µl, 0.42mmol). The mixture was left to stir at rt under nitrogen for 3 days. The mixture was partitioned between EtOAc and 2M HCl (aq). The organic layer was separated, washed with brine, dried ($MgSO_4$) and concentrated. The crude product was purified on a silica SPE column using DCM to load the material onto the column and wash through the impurities then a 0-5% MeOH/DCM gradient to elute the compound. The product

fractions were combined and concentrated and the residues dissolved in anhydrous DMF (3ml). The solution was degassed then $Pd(PPh_3)_4$ (35mg, 0.030mmol) and morpholine (174µl, 2.0mmol) were added and the mixture left to stir at rt under nitrogen for 3h. The crude product was purified by an aminopropyl SPE using MeOH to load the compound onto the column and wash through the impurities then a 0-5% AcOH/MeOH gradient to elute the product. The product fractions were combined and concentrated by high vacuum to leave the title compound as a white solid (50mg, 26%).
LC/MS: m/z 509 $[MH]^+$, RT 2.64min.

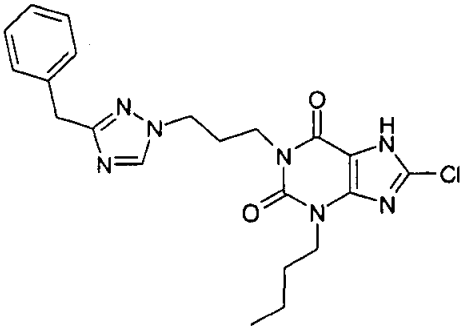
Example 32 : 3-Butyl-8-chloro-1-[3-(1-{[3-(trifluoromethyl)phenyl]methyl}-1*H*-imidazol-4-yl)propyl]-3,7-dihydro-1*H*-purine-2,6-dione



A solution of 3-butyl-8-chloro-1-[4-(1*H*-imidazol-4-yl)butyl]-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (150mg, 0.38mmol) in anhydrous DMF (3ml) was treated with 1-(chloromethyl)-3-(trifluoromethyl)benzene (65µl, 0.42mmol) and DIPEA (73µl, 0.42mmol). The mixture was left to stir at rt under nitrogen for 3 days. The mixture was partitioned between EtOAc and 2M HCl (aq). The organic layer was separated, washed with brine, dried ($MgSO_4$) and concentrated. The crude product was purified on a silica SPE column using a DCM to load the material onto the column and wash through the impurities then a 0-5% MeOH/DCM gradient to elute the compound. The product fractions were combined and concentrated and the residues dissolved in anhydrous DMF (3ml). The solution was degassed then $Pd(PPh_3)_4$ (30mg, 0.027mmol) and morpholine (156µl, 1.8mmol) were added and the mixture left to stir at rt under nitrogen for 3h. The crude product was purified by an aminopropyl SPE using MeOH to load the compound onto the column and wash through the impurities then a 0-5% AcOH/MeOH gradient to elute the product. The product fractions were combined and concentrated by high vacuum to leave the title compound as a white solid (18mg, 9%).
LC/MS: m/z 509 $[MH]^+$, RT 2.78min.

Example 33 : 3-Butyl-8-chloro-1-{3-[3-(phenylmethyl)-1*H*-1,2,4-triazol-1-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione

a) 3-Butyl-8-chloro-1-{3-[3-(phenylmethyl)-1*H*-1,2,4-triazol-1-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione

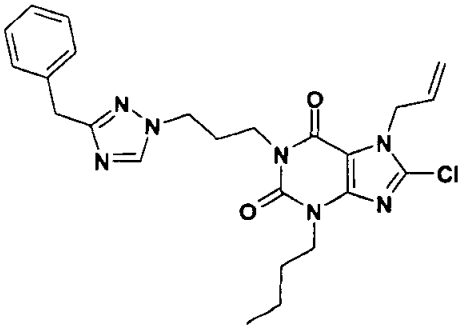


A solution of 3-butyl-8-chloro-1-{3-[3-(phenylmethyl)-1*H*-1,2,4-triazol-1-yl]propyl}-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (669mg, 1.39mmol) in THF (7ml) was degassed by applying a vacuum and then nitrogen was introduced. $Pd(PPh_3)_4$ (160mg, 0.14mmol) was added and the mixture degassed once more. Morpholine (1.2ml, 13.9mmol) was added and the mixture was stirred under nitrogen for 18h, then partitioned between 2M HCl (aq) and EtOAc. The organic layer was separated and the aqueous layer extracted again with EtOAc. The combined extracts were washed with brine, dried ($MgSO_4$) and concentrated, giving a yellow residue. MeOH was added and then passed down an aminopropyl SPE with the product eluting with 2-3% AcOH/ MeOH. The product fractions were combined and concentrated giving a pale yellow solid (380mg). Approximately a quarter of the material was purified by autoprep HPLC and rest was crystallised from MeOH:DMSO (1:1) giving the title compound as a white solid (125mg, 31%).

LC/MS: m/z 442 $[MH]^+$, RT 3.0min.

^{1}H NMR (DMSO-d_6) δ: 0.89 (t, 3H, J = 7Hz), 1.30 (m, 2H), 1.62 (m, 2H), 2.07 (m, 2H), 3.90 (m, 6H), 4.13 (t, 2H, J = 7Hz), 7.24 (m, 5H), 8.36 (1H, s), 14.5 (br s, 1H).

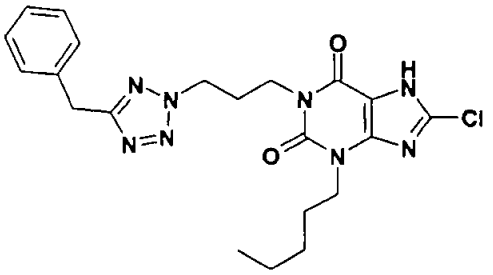
b) 3-Butyl-8-chloro-1-{3-[3-(phenylmethyl)-1*H*-1,2,4-triazol-1-yl]propyl}-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione



A solution of 3-(phenylmethyl)-1*H*-1,2,4-triazole (2.1g, 13.2mmol) in MeOH (40ml) was treated with 0.5M NaOMe in MeOH (29ml) followed by 1,3-dibromopropane (1.7ml). After stirring for 5h at 50°C the mixture was partitioned between 2M HCl (aq) and

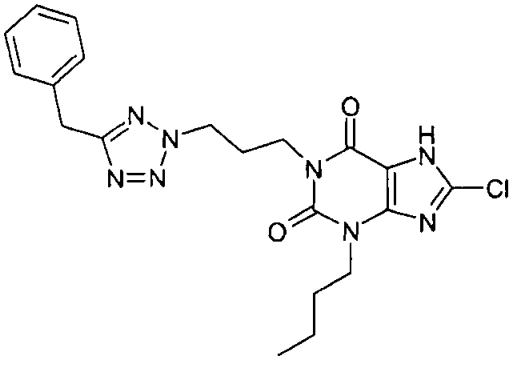
EtOAc. The organic layer was separated, washed with brine, dried ($MgSO_4$) and concentrated, giving an oily residue (1.0g). To this was added butyl-8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (917mg, 3.2mmol) and Cs_2CO_3 (1.2g, 3.6mmol). DMF (15ml) was added and the mixture was stirred at 50°C for 20h then partitioned between 2M HCl (aq) and EtOAc. The organic layer was separated, washed with brine, dried ($MgSO_4$) and concentrated. The resulting oil (1.52g) was passed down a silica SPE (50g) column eluting with EtOAc/ cyclohexane mixtures. Two isomeric products of the triazole were obtained as a 2:1 mixture, in favour of the title compound, as a yellow paste (697mg, 67% based on ratio of isomers present).
LC/MS: m/z 482 $[MH]^+$, RT 3.3min.

Example 34 : 8-Chloro-3-pentyl-1-{3-[5-(phenylmethyl)-2*H*-tetrazol-2-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione



A solution of 5-benzyl-1H-tetrazole (1.0g, 6.24mmol) in MeOH (5ml) was treated with 1-chloro-3-iodopropane (1.0ml, 9.36mmol) and a solution of 0.5M NaOMe in MeOH (4.7ml, 9.36mmol). The reaction was heated at reflux for 18h then partitioned between 2M HCl (aq) and EtOAc. The organic layer was separated and the aqueous layer extracted once more with EtOAc. The combined extracts were washed with brine, dried ($MgSO_4$) and concentrated, giving a yellow solid. (796mg). 700mg of this material was reacted with 8-chloro-3-pentyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (732mg, 2.47mmol) and Cs_2CO_3 (967mg, 3.0mmol) in DMF (20ml) at 75°C for 24h. The reaction was allowed to cool to rt and the mixture was degassed by applying a vacuum and then nitrogen was introduced. $Pd(PPh_3)_4$ (428mg, 0.37mmol) was added and the mixture degassed once more. Morpholine (2.1ml, 24.7mmol) was added and the mixture was stirred under nitrogen for 3h, then partitioned between 2M HCl (aq) and EtOAc. The organic layer was separated and the aqueous layer extracted once more. The combined extracts were concentrated, giving a yellow residue. MeOH was added and then passed down an aminopropyl SPE, the product eluting with 2-3% AcOH/MeOH. The product fractions were combined and concentrated then purified by the MDAP to give the title compound as a white solid (35mg, 3%).
LC/MS: m/z 457 $[MH]^+$, RT 3.5min.
^1H NMR; (DMSO-d_6) δ: 0.85 (t, 3H, J = 7Hz), 1.21-1.34 (m, 4H), 1.62 (m, 2H), 2.22 (m, 2H), 3.88 (t, 2H, J = 7Hz), 3.97 (t, 2H, J = 7Hz), 4.17 (s, 2H), 4.67 (t, 2H, J = 7Hz), 7.20-7.32 (m, 5H), 14.5 (br s, 1H).

Example 35: 3-Butyl-8-chloro-1-{3-[5-(phenylmethyl)-2*H*-tetrazol-2-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione



A solution of 5-benzyl-1H-tetrazole (1.8g, 11.2mmol) in MeOH (30ml) was treated with 1,3-dibromopropane (5.7ml, 56.2mmol) and 0.5M NaOMe in MeOH (31.5ml) then stirred at 40°C under nitrogen for 60h. The mixture was partitioned between 2M HCl (aq) and EtOAc. The organic layer was separated, washed with brine, dried ($MgSO_4$) and concentrated. Partial purification by SPE (20g silica, cyclohexane/EtOAc mixtures) and by the Companion™ system (silica SPE, cyclohexane/EtOAc mixtures) gave an oil (1.98g, 62% of a mixture of isomers, 2:1 in favour of 2-(3-bromopropyl)-5-(phenylmethyl)-2*H*-tetrazole) which was taken on crude in the next step.

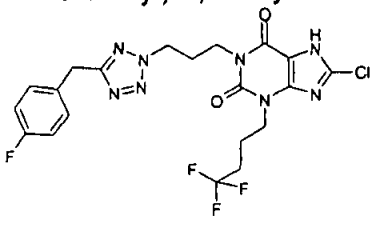
A mixture of 3-butyl-8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (1.74g, 6.1mmol), crude 2-(3-bromopropyl)-5-(phenylmethyl)-2*H*-tetrazole) (1.9g, 6.8mmol), Cs_2CO_3 (2.2g, 6.8mmol) and DMF (60ml) was stirred at 45°C under nitrogen for 24h. The mixture was degassed by applying a vacuum and then nitrogen was introduced. $Pd(PPh_3)_4$ (705mg, 0.61mmol) was added and the mixture degassed once more. Morpholine (5.4ml, 61.4mmol) was added and the mixture was stirred under nitrogen for 4h, and then partitioned between 2M HCl (aq) and EtOAc. The organic layer was separated, washed with brine, dried ($MgSO_4$) and concentrated, giving a yellow residue. MeOH was added and then passed down an aminopropyl column with the product eluting with 2% AcOH/MeOH. The product was further purified by the Companion™ system using EtOAc/cyclohexane mixtures. The resulting solid was stirred with boiling Et_2O and filtered after cooling to rt. The title compound was collected as a white solid (1.01g, 37%) and dried at 50°C under vacuum.

LC/MS: m/z 443 $[MH]^+$, RT 3.3min.

^1H NMR (DMSO-d_6) δ: 0.89 (t, 3H, J = 7Hz), 1.29 (m, 2H), 1.61 (m, 2H), 2.22 (m, 2H), 3.89 (t, 2H, J = 7Hz), 3.97 (t, 2H, J = 7Hz), 4.17 (s, 2H), 4.67 (t, 2H, J = 7Hz), 7.20-7.32 (m, 5H), 14.5 (br s, 1H).

Example 36: 8-Chloro-1-(3-{5-[(4-fluorophenyl)methyl]-2*H*-tetrazol-2-yl}propyl)-3-(4,4,4-trifluorobutyl)-3,7-dihydro-1*H*-purine-2,6-dione

a) 8-Chloro-1-(3-{5-[(4-fluorophenyl)methyl]-2*H*-tetrazol-2-yl}propyl)-3-(4,4,4-trifluorobutyl)-3,7-dihydro-1*H*-purine-2,6-dione

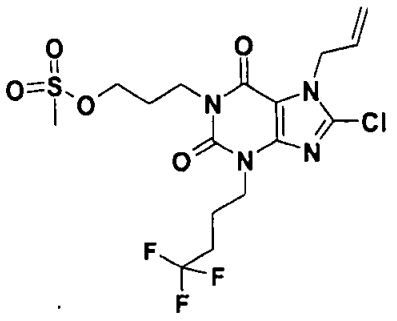


5-[(4-Fluorophenyl)methyl]-1H-tetrazole (75mg, 0.4mmol) was treated with potassium carbonate (100mg, 0.7mmol) and DMF (3ml). The mixture was treated with a solution of 3-[8-chloro-2,6-dioxo-7-(2-propen-1-yl)-3-(4,4,4-trifluorobutyl)-2,3,6,7-tetrahydro-1H-purin-1-yl]propyl methanesulfonate (100mg, 0.2mmol) in DMF (0.5ml). The mixture was stirred and heated at 60°C 3 hours then cooled and evaporated. The residue was partitioned between chloroform (4ml) and water (2cm^3). 1cm^3 of saturated aqueous sodium bicarbonate (3ml) was added to each. The mixture was separated and the organic phase evaporated. The residue was dissolved in anhydrous THF (3ml) and the mixture degassed by the cautious successive application of vacuum and nitrogen pressure to the mixture. The mixture was treated with tetrakis(triphenylphosphine)palladium(0) (10mg, 0.008mmol) and morpholine (0.2ml, 2.3mmol) and then stirred in a nitrogen atmosphere for 2h. The mixture was evaporated and partitioned between chloroform (4ml) and saturated aqueous ammonium chloride (3ml). The mixture was separated, and the aqueous phase re-extracted with chloroform. The organic phase was evaporated and the residue dissolved in MeOH (3ml). The solution was added to the top of a 2g aminopropyl SPE and washed with MeOH (15ml). The desired product was eluted from the cartridge with a 3% v/v solution of AcOH in MeOH (20ml). Product containing fractions were combined and evaporated and the residue subjected to purification by flash column chromatography (gradient elution from 10:1 cyclohexane/EtOAc to EtOAc). Product-containing fractions were combined and evaporated to yield the product as a colourless oil. Trituration in minimal diethyl ether caused the product to solidify and this was thoroughly dried to yield the title compound as a white solid (18.7mg, 18%).

LC/MS: m/z 515 $[MH]^+$, RT 3.31min.

^{1}H NMR ($CDCl_3$) δ: 2.06 (m, 2H), 2.21 (m, 2H), 2.45 (m, 2H), 4.17 (m, 4H), 4.24 (t, 2H, J = 7.0Hz), 4.70 (t, 2H, J = 7.2Hz), 6.96 (m, 2H), 7.25 (m, 2H).

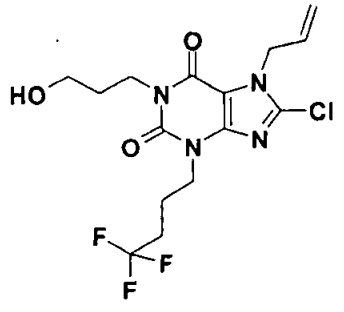
b) 3-[8-Chloro-2,6-dioxo-7-(2-propen-1-yl)-3-(4,4,4-trifluorobutyl)-2,3,6,7-tetrahydro-1H-purin-1-yl]propyl methanesulfonate



A solution of 8-chloro-1-(3-hydroxypropyl)-7-(2-propen-1-yl)-3-(4,4,4-trifluorobutyl)-3,7-dihydro-1H-purine-2,6-dione (0.82g, 2.1mmol) in DCM (20ml) was treated with triethylamine (0.42ml, 3.1mmol) and methanesulfonic anhydride (0.40g, 2.3mmol). After 1h the mixture was treated with saturated aqueous sodium bicarbonate (20ml). The mixture was separated and the organic phase dried ($MgSO_4$), filtered and evaporated to give the title compound (0.91g), which was used without further purification.

LC/MS: m/z 473 $[MH]^+$, RT 3.17min.

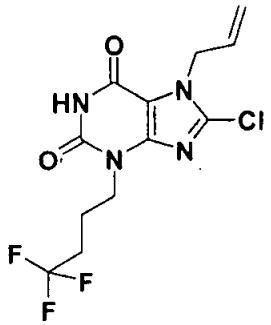
c) 8-Chloro-1-(3-hydroxypropyl)-7-(2-propen-1-yl)-3-(4,4,4-trifluorobutyl)-3,7-dihydro-1*H*-purine-2,6-dione



A solution of 8-chloro-7-(2-propen-1-yl)-3-(4,4,4-trifluorobutyl)-3,7-dihydro-1H-purine-2,6-dione (1.0g, 3.0mmol) in DMF (15ml) was treated with caesium carbonate (1.16g, 3.6mmol) and 3-bromo-1-propanol (0.3ml, 3.3mmol). The mixture was heated at 60°C for 4h and then cooled and evaporated. The residue was partitioned between EtOAc (50ml) and water (50ml). The organic phase was dried ($MgSO_4$), filtered and evaporated. The product was purified by flash chromatography using a gradient elution from cyclohexane to EtOAc. Product-containing fractions were combined and evaporated to give the title compound as a colourless oil (0.82g, 75%).

LC/MS: m/z 395 $[MH]^+$, RT 2.90min.

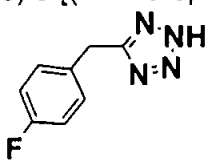
d) 8-Chloro-7-(2-propen-1-yl)-3-(4,4,4-trifluorobutyl)-3,7-dihydro-1*H*-purine-2,6-dione



A solution of 8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1H-purine-2,6-dione (2.0g, 8.8mmol) in DMF (20ml) was treated with sodium carbonate (1.15g, 10.8mmol) and 4-bromo-1,1,1-trifluorobutane (1.86g, 9.7mmol). The mixture was stirred at 50°C for 18h then cooled and evaporated. The residue was partitioned between EtOAc (100ml) and saturated aqueous sodium bicarbonate (50ml). The organic phase was dried ($MgSO_4$), filtered and evaporated. The residue was triturated in a mixture of diethyl ether and cyclohexane then the product filtered off and dried to yield the title compound as a white solid (1.18g, 40%).

LC/MS: m/z 337 $[MH]^+$, RT 2.83min.

e) 5-[(4-Fluorophenyl)methyl]-1H-tetrazole

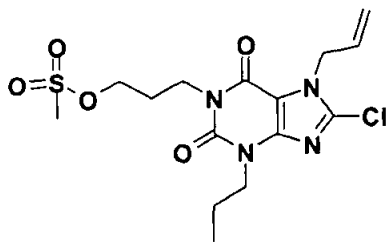


A mixture of triethylammonium chloride (4.14g, 30mmol) and sodium azide (1.95g, 30mmol) was treated with a solution of (4-fluorophenyl)acetonitrile (1.35g, 10mmol) in toluene (14ml) and the mixture was stirred and heated at 100°C for 5h. The cooled mixture was treated with water (10ml) and the mixture separated. The aqueous phase was stirred and treated dropwise with concentrated hydrochloric acid until the product had precipitated from solution. The precipitated product was filtered off, washed with water and dried to yield the title compound as a white solid (1.27g, 72%).
LC/MS: m/z 179 $[MH]^+$, RT 2.24min.

The compounds in Table 3 were prepared using a method analogous to that for Example 36: 8-chloro-1-(3-{5-[(4-fluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3-(4,4,4-trifluorobutyl)-3,7-dihydro-1*H*-purine-2,6-dione, with the appropriate methanesulfonate and tetrazole. MDAP was employed to further purify those compounds insufficiently pure following normal phase chromatography.

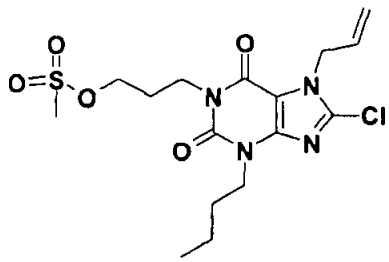
Methanesulfonates intermediates and their precursor alcohols were prepared according to the following procedures:

3-[8-Chloro-2,6-dioxo-7-(2-propen-1-yl)-3-propyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl]propyl methanesulfonate



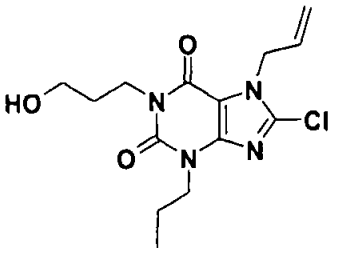
A solution of 8-chloro-1-(3-hydroxypropyl)-7-(2-propen-1-yl)-3-propyl-3,7-dihydro-1*H*-purine-2,6-dione (1.99g, 6.1mmol) in DCM (50ml) was treated with triethylamine (1.2ml, 8.6mmol) and methanesulfonic anhydride (1.2g, 6.9mmol). After 1.5h the mixture was treated with water (50ml). The mixture was separated and the aqueous phase extracted with DCM (25ml), the combined organic phases dried ($MgSO_4$), filtered and evaporated to give the title compound as a pale yellow oil (2.38g), which was used without further purification.
LC/MS: m/z 405 $[MH]^+$, RT 2.93min.

3-[3-Butyl-8-chloro-2,6-dioxo-7-(2-propen-1-yl)-2,3,6,7-tetrahydro-1*H*-purin-1-yl]propyl methanesulfonate



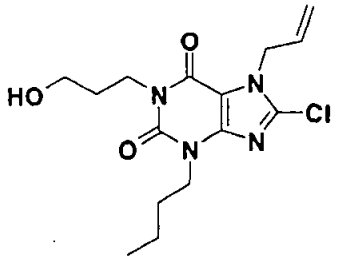
Prepared according to the method used for 3-[8-chloro-2,6-dioxo-7-(2-propen-1-yl)-3-propyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl]propyl methanesulfonate to give the title compound as a pale yellow oil (2.44g).
LC/MS: m/z 419 $[MH]^+$, RT 3.14min.

8-Chloro-1-(3-hydroxypropyl)-7-(2-propen-1-yl)-3-propyl-3,7-dihydro-1*H*-purine-2,6-dione



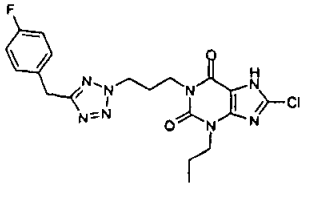
A solution of 8-chloro-7-(2-propen-1-yl)-3-propyl-3,7-dihydro-1*H*-purine-2,6-dione (3.0g, 11.1mmol) in DMF (20ml) was treated with caesium carbonate (3.7g, 11.4mmol) and 3-bromo-1-propanol (1.6g, 11.5mmol). The mixture was heated at 60°C for 4h and then cooled and evaporated. The residue was partitioned between EtOAc (60ml) and saturated aqueous sodium bicarbonate (50ml). The aqueous phase was extracted with EtOAc (60ml), the combined organic phases were dried ($MgSO_4$), filtered and evaporated. The product was purified using the Companion™ system and a gradient elution from cyclohexane to EtOAc. Product containing fractions were combined and evaporated to give the title compound as a colourless oil (2.6g).
LC/MS: m/z 327 $[MH]^+$, RT 2.62min.

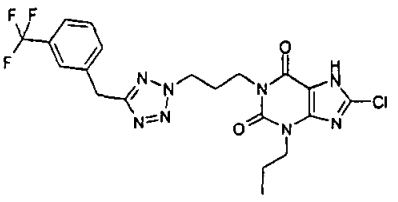
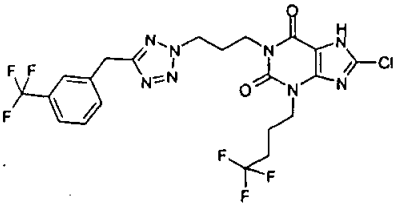
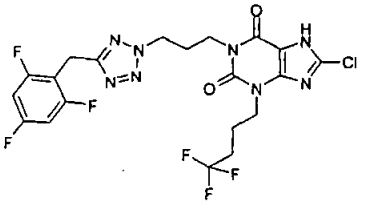
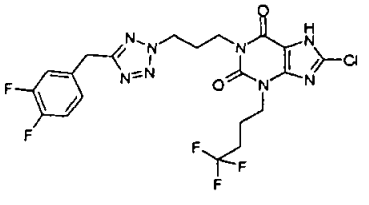
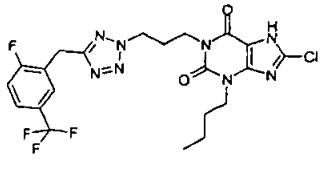
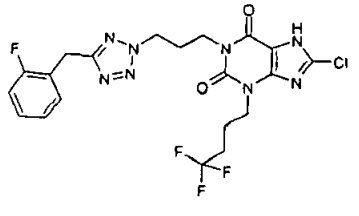
3-Butyl-8-chloro-1-(3-hydroxypropyl)-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione

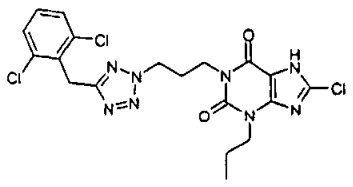
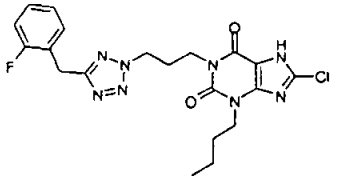
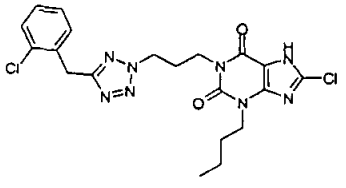
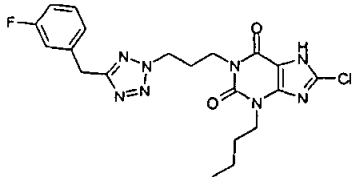
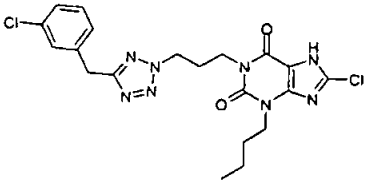
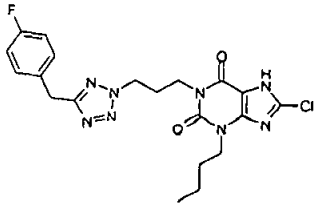


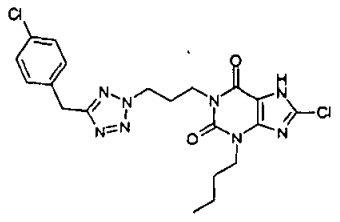
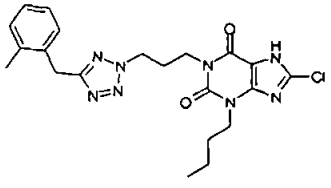
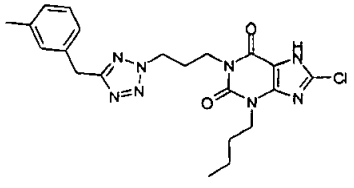
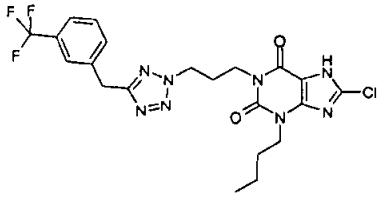
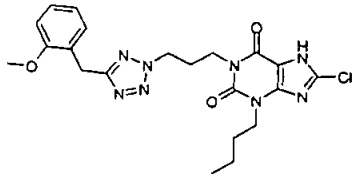
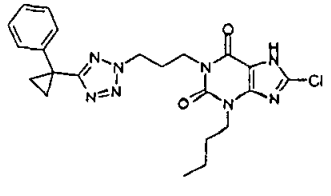
Prepared according to the method used for 8-chloro-1-(3-hydroxypropyl)-7-(2-propen-1-yl)-3-propyl-3,7-dihydro-1*H*-purine-2,6-dione to give the title compound as a colourless oil (2.3g).
LC/MS: m/z 341 $[MH]^+$, RT 2.85min.

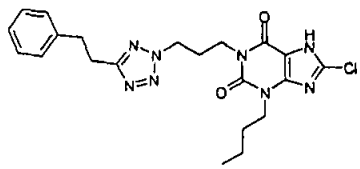
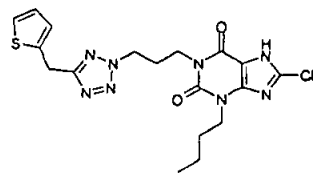
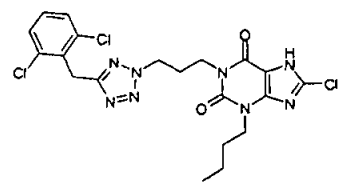
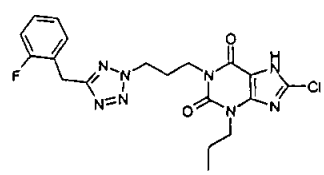
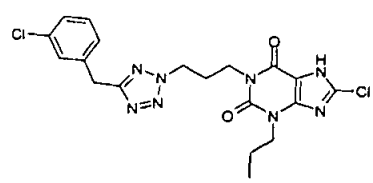
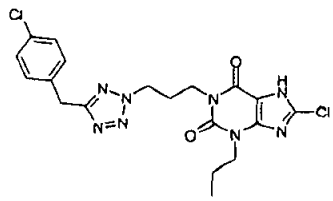
Table 3

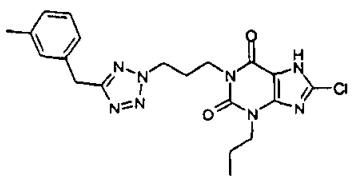
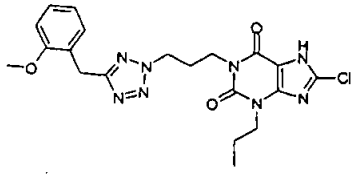
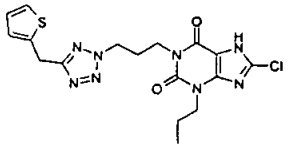
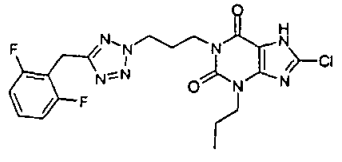
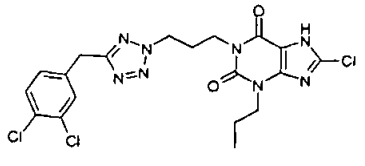
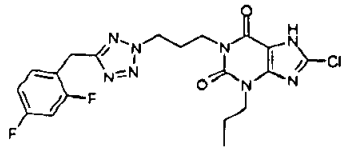
#	Structure	Name	Yield	LC/MS:
37		8-chloro-1-(3-{5-[(4-fluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3-propyl-3,7-dihydro-1H-purine-2,6-dione	12.4mg (14%)	m/z 447 $[MH]^+$ RT 3.14 min

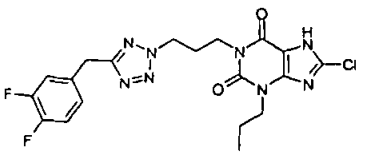
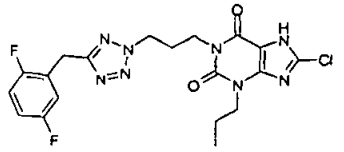
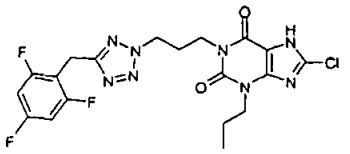
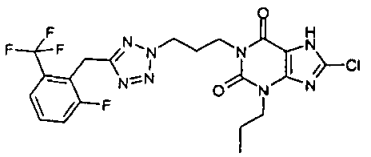
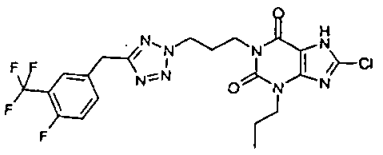
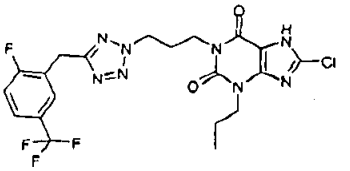
38		8-chloro-3-propyl-1-[3-(5-{[3-(trifluoromethyl)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione	8.0mg (8%)	m/z 497 $[MH]^+$ RT 3.36 min
39		8-chloro-3-(4,4,4-trifluorobutyl)-1-[3-(5-{[3-(trifluoromethyl)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione	21.0mg (19%)	m/z 565 $[MH]^+$ RT 3.34 min
40		8-chloro-3-(4,4,4-trifluorobutyl)-1-(3-{5-[(2,4,6-trifluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	17.0mg (15%)	m/z 551 $[MH]^+$ RT 3.27 min
41		8-chloro-1-(3-{5-[(3,4-difluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3-(4,4,4-trifluorobutyl)-3,7-dihydro-1H-purine-2,6-dione	19.1mg (18%)	m/z 533 $[MH]^+$ RT 3.36 min
42		3-butyl-8-chloro-1-[3-(5-{[2-fluoro-5-(trifluoromethyl)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione	23.9mg (23%)	m/z 529 $[MH]^+$ RT 3.50 min
43		8-chloro-1-(3-{5-[(2-fluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3-(4,4,4-trifluorobutyl)-3,7-dihydro-1H-purine-2,6-dione	19.8mg (19%)	m/z 515 $[MH]^+$ RT 3.31 min

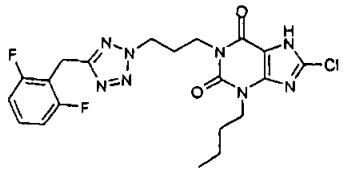
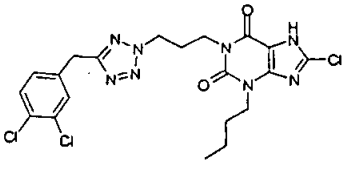
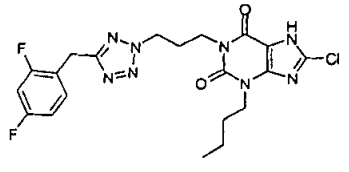
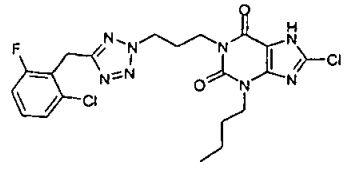
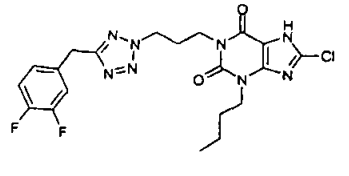
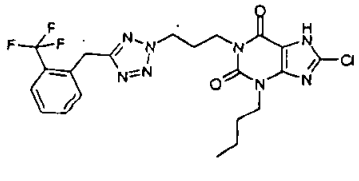
44		8-chloro-1-(3-{5-[(2,6-dichlorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3-propyl-3,7-dihydro-1H-purine-2,6-dione	50.7mg (51%)	m/z 497 $[MH]^+$ RT 3.33 min
45		3-butyl-8-chloro-1-(3-{5-[(2-fluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	46.4mg (48%)	m/z 461 $[MH]^+$ RT 3.27 min
46		3-butyl-8-chloro-1-(3-{5-[(2-chlorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	25.4mg (27%)	m/z 477 $[MH]^+$ RT 3.40 min
47		3-butyl-8-chloro-1-(3-{5-[(3-fluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	36.8mg (40%)	m/z 461 $[MH]^+$ RT 3.31 min
48		3-butyl-8-chloro-1-(3-{5-[(3-chlorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	38.5mg (40%)	m/z 477 $[MH]^+$ RT 3.45 min
49		3-butyl-8-chloro-1-(3-{5-[(4-fluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	31.6mg (34%)	m/z 461 $[MH]^+$ RT 3.31 min

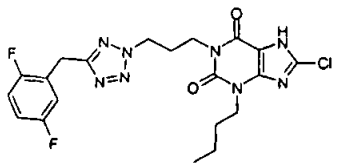
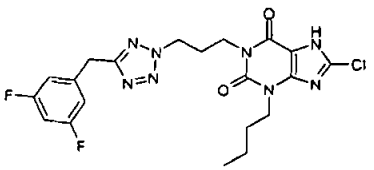
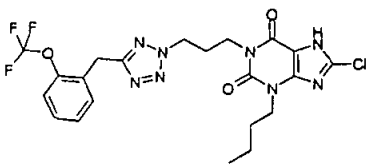
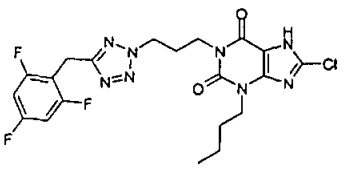
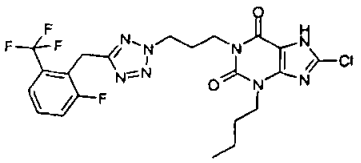
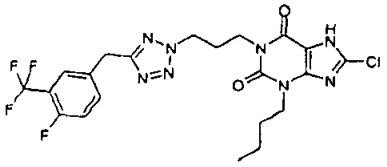
50		3-butyl-8-chloro-1-(3-{5-[(4-chlorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	33.1mg (35%)	m/z 477 $[MH]^+$ RT 3.46 min
51		3-butyl-8-chloro-1-(3-{5-[(2-methylphenyl)methyl]-2H-tetrazol-2-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	39.5mg (43%)	m/z 457 $[MH]^+$ RT 3.37 min
52		3-butyl-8-chloro-1-(3-{5-[(3-methylphenyl)methyl]-2H-tetrazol-2-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	36.5mg (40%)	m/z 457 $[MH]^+$ RT 3.40 min
53		3-butyl-8-chloro-1-[3-(5-{[3-(trifluoromethyl)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione	43.7mg (43%)	m/z 511 $[MH]^+$ RT 3.50 min
54		3-butyl-8-chloro-1-[3-(5-{[2-(methyloxy)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione	28.6mg (30%)	m/z 473 $[MH]^+$ RT 3.29 min
55		3-butyl-8-chloro-1-{3-[5-(1-phenylcyclopropyl)-2H-tetrazol-2-yl]propyl}-3,7-dihydro-1H-purine-2,6-dione	44.2mg (47%)	m/z 469 $[MH]^+$ RT 3.41 min

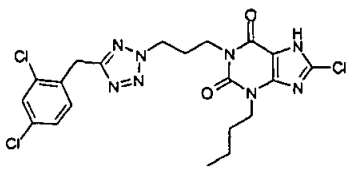
56		3-butyl-8-chloro-1-{3-[5-(2-phenylethyl)-2H-tetrazol-2-yl]propyl}-3,7-dihydro-1H-purine-2,6-dione	39.2mg (43%)	m/z 457 $[MH]^+$ RT 3.36 min
57		3-butyl-8-chloro-1-{3-[5-(2-thienylmethyl)-2H-tetrazol-2-yl]propyl}-3,7-dihydro-1H-purine-2,6-dione	33.4mg (37%)	m/z 449 $[MH]^+$ RT 3.20 min
58		3-butyl-8-chloro-1-(3-{5-[(2,6-dichlorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	36.4mg (36%)	m/z 511 $[MH]^+$ RT 3.49 min
59		8-chloro-1-(3-{5-[(2-fluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3-propyl-3,7-dihydro-1H-purine-2,6-dione	5.6mg (6%)	m/z 447 $[MH]^+$ RT 3.10 min
60		8-chloro-1-(3-{5-[(3-chlorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3-propyl-3,7-dihydro-1H-purine-2,6-dione	5.9mg (6%)	m/z 463 $[MH]^+$ RT 3.29 min
61		8-chloro-1-(3-{5-[(4-chlorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3-propyl-3,7-dihydro-1H-purine-2,6-dione	14.9mg (16%)	m/z 463 $[MH]^+$ RT 3.30 min

62		8-chloro-1-(3-{5-[(3-methylphenyl)methyl]-2H-tetrazol-2-yl}propyl)-3-propyl-3,7-dihydro-1H-purine-2,6-dione	17.5mg (20%)	m/z 443 $[MH]^+$ RT 3.23 min
63		8-chloro-1-[3-(5-{[2-(methyloxy)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-3-propyl-3,7-dihydro-1H-purine-2,6-dione	14.5mg (16%)	m/z 459 $[MH]^+$ RT 3.12 min
64		8-chloro-3-propyl-1-{3-[5-(2-thienylmethyl)-2H-tetrazol-2-yl]propyl}-3,7-dihydro-1H-purine-2,6-dione	17.0mg (20%)	m/z 435 $[MH]^+$ RT 3.02 min
65		8-chloro-1-(3-{5-[(2,6-difluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3-propyl-3,7-dihydro-1H-purine-2,6-dione	18.4mg (20%)	m/z 465 $[MH]^+$ RT 3.11 min
66		8-chloro-1-(3-{5-[(3,4-dichlorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3-propyl-3,7-dihydro-1H-purine-2,6-dione	19.4mg (20%)	m/z 497 $[MH]^+$ RT 3.44 min
67		8-chloro-1-(3-{5-[(2,4-difluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3-propyl-3,7-dihydro-1H-purine-2,6-dione	19.1mg (21%)	m/z 465 $[MH]^+$ RT 3.16 min

68		8-chloro-1-(3-{5-[(3,4-difluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3-propyl-3,7-dihydro-1H-purine-2,6-dione	21.5mg (23%)	m/z 465 $[MH]^+$ RT 3.19 min
69		8-chloro-1-(3-{5-[(2,5-difluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3-propyl-3,7-dihydro-1H-purine-2,6-dione	8.5mg (9%)	m/z 465 $[MH]^+$ RT 3.14 min
70		8-chloro-3-propyl-1-(3-{5-[(2,4,6-trifluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	17.4mg (18%)	m/z 483 $[MH]^+$ RT 3.09 min
71		8-chloro-1-[3-(5-{[2-fluoro-6-(trifluoromethyl)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-3-propyl-3,7-dihydro-1H-purine-2,6-dione	22.3mg (22%)	m/z 515 $[MH]^+$ RT 3.28 min
72		8-chloro-1-[3-(5-{[4-fluoro-3-(trifluoromethyl)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-3-propyl-3,7-dihydro-1H-purine-2,6-dione	17.2mg (17%)	m/z 515 $[MH]^+$ RT 3.30 min
73		8-chloro-1-[3-(5-{[2-fluoro-5-(trifluoromethyl)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-3-propyl-3,7-dihydro-1H-purine-2,6-dione	18.2mg (18%)	m/z 515 $[MH]^+$ RT 3.34 min

74		3-butyl-8-chloro-1-(3-{5-[(2,6-difluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	18.2mg (19%)	m/z 479 $[MH]^+$ RT 3.29 min
75		3-butyl-8-chloro-1-(3-{5-[(3,4-dichlorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	20.1mg (20%)	m/z 511 $[MH]^+$ RT 3.58 min
76		3-butyl-8-chloro-1-(3-{5-[(2,4-difluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	19.3mg (20%)	m/z 479 $[MH]^+$ RT 3.33 min
77		3-butyl-8-chloro-1-(3-{5-[(2-chloro-6-fluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	18.9mg (19%)	m/z 495 $[MH]^+$ RT 3.33 min
78		3-butyl-8-chloro-1-(3-{5-[(3,4-difluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	21.7mg (23%)	m/z 479 $[MH]^+$ RT 3.33 min
79		3-butyl-8-chloro-1-[3-(5-{[2-(trifluoromethyl)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione	18.1mg (18%)	m/z 511 $[MH]^+$ RT 3.32 min

80		3-butyl-8-chloro-1-(3-{5-[(2,5-difluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	24.0mg (25%)	m/z 479 $[MH]^+$ RT 3.31 min
81		3-butyl-8-chloro-1-(3-{5-[(3,5-difluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	15.9mg (17%)	m/z 479 $[MH]^+$ RT 3.38 min
82		3-butyl-8-chloro-1-{3-[5-({2-[(trifluoromethyl)oxy]phenyl}methyl)-2H-tetrazol-2-yl]propyl}-3,7-dihydro-1H-purine-2,6-dione	32.8mg (31%)	m/z 527 $[MH]^+$ RT 3.51 min
83		3-butyl-8-chloro-1-(3-{5-[(2,4,6-trifluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	20.7mg (21%)	m/z 497 $[MH]^+$ RT 3.35 min
84		3-butyl-8-chloro-1-[3-(5-{[2-fluoro-6-(trifluoromethyl)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione	23.9mg (23%)	m/z 529 $[MH]^+$ RT 3.44 min
85		3-butyl-8-chloro-1-[3-(5-{[4-fluoro-3-(trifluoromethyl)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione	13.9mg (13%)	m/z 529 $[MH]^+$ RT 3.53 min

86		3-butyl-8-chloro-1-(3-{5-[(2,4-dichlorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	17.5mg (17%)	m/z 511 $[MH]^+$ RT 3.63 min

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NMR details for selected examples from Table 3:

Example 37: 8-Chloro-1-(3-{5-[(4-fluorophenyl)methyl]-2*H*-tetrazol-2-yl}propyl)-3-propyl-3,7-dihydro-1*H*-purine-2,6-dione
^{1}H NMR ($CDCl_3$) δ: 0.99 (t, 3H, J = 7.5 Hz), 1.80 (m, 2H), 2.46 (m, 2H), 4.06 (m, 2H), 4.18 (s, 2H), 4.25 (t, 2H, J = 7Hz), 4.70 (t, 2H, J = 7.5Hz), 6.96 (m, 2H), 7.26 (m, 2H), 13.15 (br s, 1H).

Example 40 : 8-Chloro-3-(4,4,4-trifluorobutyl)-1-(3-{5-[(2,4,6-trifluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione : ^{1}H NMR ($CDCl_3$) δ: 2.07 (m, 2H), 2.21 (m, 2H), 2,44 (m, 2H), 4.18 (t, 2H, J = 7.1Hz), 4.20 (s, 2H), 4.24, (t, 2H, J = 6.8Hz), 4.68 (t, 2H, J = 7.3Hz), 6.67 (t, 2H, J = 8.1Hz), 13.04 (br s, 1H).

Example 41: ^{1}H NMR ($CDCl_3$): 2.03-2.10 (m, 2H), 2.16-2.28 (m, 2H), 2.43-2.50 (m, 2H), 4.16-4.19 (m, 2H), 4.17 (s, 2H), 4.24 (t, 2H, J=7.1Hz), 4.71(t, 2H, J=7.1Hz), 7.00-7.13 (m, 3H), 13.06 (bs, 1H).

Example 44: ^{1}H NMR ($CDCl_3$): 0.99 (t, 3H, J=7.5Hz), 1.76-1.86 (m, 2H), 2.40-2.47 (m, 2H), 4.05-4.09 (m, 2H), 4.23-4.26 (m, 2H), 4.54 (s, 2H), 4.65-4.69 (m, 2H), 7.14-7.18 (m, 1H), 7.31-7.33, (m, 2H), 13.18 (bs, 1H).

Example 45: ^{1}H NMR ($CDCl_3$): 0.97 (t, 3H, J=7.5Hz), 1.36-1.46 (m, 2H), 1.71-1.79 (m, 2H), 2.42-2.49 (m, 2H), 4.08-4.11 (m, 2H), 4.25 (s, 2H), 4.24-4.27 (m, 2H), 4.68-4.71 (m, 2H), 7.02-7.09 (m, 2H), 7.20-7.26, (m, 2H), 13.14 (bs, 1H).

Example 46: ^{1}H NMR ($CDCl_3$): 0.97 (t, 3H, J=7.5Hz), 1.36-1.45 (m, 2H), 1.71-1.79 (m, 2H), 2.42-2.49 (m, 2H), 4.09 (t, 2H, J=7.5Hz), 4.26 (t, 2H, J=7.5Hz), 4.34 (s, 2H), 4.70 (t, 2H, J=7.3Hz), 7.18-7.21 (m, 2H), 7.25-7.27, (m, 1H), 7.35-7.37, (m, 1H), 13.34 (bs, 1H).

Example 47: 3-Butyl-8-chloro-1-(3-{5-[(3-fluorophenyl)methyl]-2*H*-tetrazol-2-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione
^{1}H NMR ($CDCl_3$) δ: 0.97 (t, 3H, J = 7Hz), 1.40 (m, 2H), 1.75 (m, 2H), 2.46 (m, 2H), 4.10 (t, 2H, J = 7.5Hz), 4.21 (s, 2H), 4.26 (t, 2H , J = 6.5Hz), 4.70 (t, 2H, J = 7.5Hz), 6.90 (m, 1H), 6.99 (m, 1H), 7.07 (m, 1H), 7.25 (m, 1H), 13.25 (br s, 1H).

Example 48: ^{1}H NMR ($CDCl_3$): 0.99 (t, 3H, J=7.5Hz), 1.38-1.48 (m, 2H), 1.73-1.81 (m, 2H), 2.44-2.51 (m, 2H), 4.12 (t, 2H, J=7.5Hz), 4.20 (s, 2H), 4.27 (t, 2H, J=7.5Hz), 4.70 (t, 2H, J=7.3Hz), 6.95-7.00 (m, 2H), 7.26-7.30, (m, 2H), 13.35 (bs, 1H).

Example 49: 3-Butyl-8-chloro-1-(3-{5-[(4-fluorophenyl)methyl]-2*H*-tetrazol-2-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione

^{1}H NMR ($CDCl_3$) δ: 0.99 (t, 3H, J = 7Hz), 1.43 (m, 2H), 1.77 (m, 2H), 2.48 (m, 2H), 4.12 (t, 2H, J = 7.5Hz), 4.20 (s, 2H), 4.27 (t, 2H , J = 7Hz), 4.72 (t, 2H, J = 7.5Hz), 6.98 (m, 2H), 7.27 (m, 2H), 13.35 (br s, 1H).

Example 50: 3-Butyl-8-chloro-1-(3-{5-[(4-chlorophenyl)methyl]-2*H*-tetrazol-2-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione
^{1}H NMR ($CDCl_3$) δ: 1.02 (t, 3H, J = 7.5Hz), 1.45 (m, 2H), 1.79 (m, 2H), 2.50 (m, 2H), 4.14 (t, 2H, J = 7.5Hz), 4.22 (s, 2H), 4.29 (t, 2H , J = 7Hz), 4.75 (t, 2H, J = 7.5Hz), 7.27 (s, 4H), 13.35 (br s, 1H).

Example 55: 3-Butyl-8-chloro-1-{3-[5-(1-phenylcyclopropyl)-2H-tetrazol-2-yl]propyl}-3,7-dihydro-1H-purine-2,6-dione: ^{1}H NMR ($CDCl_3$) δ: 0.93 (t, 3H, J = 7.3Hz), 1.36 (m, 4H), 1.55 (m, 2H), 1.71 (m, 2H), 2.38 (m, 2H), 4.06 (t, 2H, J = 7.5Hz), 4.20 (t, 2H, J = 6.7Hz), 4.59 (t, 2H, J = 7.5Hz), 7.25 (m, 3H), 7.36 (m, 2H), 13.30 (br s, 1H).

Example 67: 8-Chloro-1-(3-{5-[(2,4-difluorophenyl)methyl]-2*H*-tetrazol-2-yl}propyl)-3-propyl-3,7-dihydro-1*H*-purine-2,6-dione
^{1}H NMR ($CDCl_3$) δ: 0.99 (t, 3H, J = 7.5 Hz), 1.80 (m, 2H), 2.45 (m, 2H), 4.06 (m, 2H), 4.20 (s, 2H), 4.25 (t, 2H, J = 7Hz), 4.70 (t, 2H, J = 7.5Hz), 6.80 (m, 2H), 7.23 (m, 1H).

Example 70: 8-Chloro-3-propyl-1-(3-{5-[(2,4,6-trifluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione : ^{1}H NMR ($CDCl_3$) δ: 0.99 (t, 3H, J = 7.3 Hz), 1.80 (m, 2H), 1.98 (m, 2H), 2.01 (m, 2H), 4.20 (s, 2H), 4.25 (t, 2H, J = 6.5Hz), 4.67 (t, 2H, J = 7.3Hz), 6.68 (t, 2H, J = 8.1Hz).

Example 71: ^{1}H NMR ($CDCl_3$): 0.99 (t, 3H, J=7.3Hz), 1.76-1.85 (m, 2H), 2.39-2.46 (m, 2H), 4.05-4.08 (m, 2H), 4.24 (t, 2H, J=7.1Hz), 4.39 (s, 2H), 4.64 (t, 2H, J=7.1Hz), 7.29-7.32 (m, 1H), 7.38-7.44, (m, 1H), 7.49-7.51, (m, 1H), 13.17 (bs, 1H).

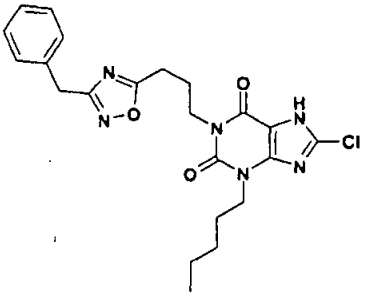
Example 78: ^{1}H NMR ($CDCl_3$): 0.99 (t, 3H, J=7.6Hz), 1.36-1.45 (m, 2H), 1.71-1.79 (m, 2H), 2.42-2.49 (m, 2H), 4.09 (t, 2H, J=7.5Hz), 4.17 (s, 2H), 4.24 (t, 2H, J=7.5Hz), 4.71 (t, 2H, J=7.3Hz), 7.00-7.14 (m, 3H), 13.07 (bs, 1H).

Example 80: ^{1}H NMR ($CDCl_3$): 0.96 (t, 3H, J=7.2Hz), 1.32-1.47 (m, 2H), 1.68-1.80 (m, 2H), 2.40-2.51 (m, 2H), 4.06-4.12 (m, 2H), 4.22 (s, 2H), 4.22-4.27 (m, 2H), 4.67-4.73 (m, 2H), 6.84-7.04 (m, 3H), 13.05 (bs, 1H).

Example 83: 3-Butyl-8-chloro-1-(3-{5-[(2,4,6-trifluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione : ^{1}H NMR ($CDCl_3$) δ: 0.97 (t, 3H, J = 7.3Hz), 1.41 (m, 2H), 1.75 (m, 2H), 2.44 (m, 2H), 4.10 (t, 2H, J = 7.5Hz), 4.20 (s, 2H), 4.25 (t, 2H , J = 6.5Hz), 4.67 (t, 2H, J = 7.4Hz), 6.67 (t, 2H, J = 8.0Hz), 13.25 (br s, 1H).

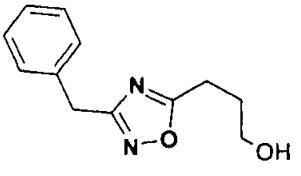
Example 87 : 8-Chloro-3-pentyl-1-{3-[3-(phenylmethyl)-1,2,4-oxadiazol-5-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione

a) 8-Chloro-3-pentyl-1-{3-[3-(phenylmethyl)-1,2,4-oxadiazol-5-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione



A solution of 3-[3-(phenylmethyl)-1,2,4-oxadiazol-5-yl]-1-propanol (88mg, 0.4mmol) in THF (4ml) was treated with 8-chloro-3-pentyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (100mg, 0.34mmol) and PPh_3 (115mg, 0.44mmol) under nitrogen. DBAD (101mg, 0.44mmol) was added in one portion and the reaction left to react for 5h. The mixture was degassed by applying a vacuum and then nitrogen was introduced. $Pd(PPh_3)_4$ (39mg, 0.034mmol) was added and the mixture degassed once more. Morpholine (294µl, 3.4mmol) was added and the mixture was stirred under nitrogen for 3h. The mixture was partitioned between 2M HCl (aq) and EtOAc. The organic layer was separated, washed with brine, dried ($MgSO_4$) and concentrated. The title compound was obtained as a white solid after purification by MDAP (64mg, 42%).
LC/MS: m/z 457 $[MH]^+$, RT 3.4min.
^1H NMR (DMSO-d_6) δ: 0.85 (t, 3H, J = 7Hz), 1.22-1.34 (m, 4H), 1.62 (m, 2H), 2.02 (m, 2H), 2.91 (t, 2H, J = 7Hz), 3.88 (t, 2H, J = 7Hz), 3.95-4.00 (m, 4H), 7.22-7.33 (m, 5H), 14.5 (br s, 1H).

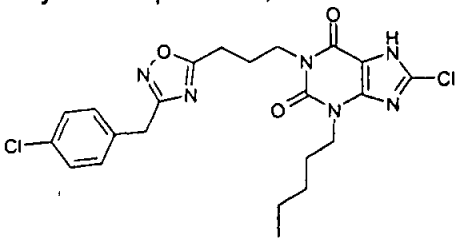
b) 3-[3-(Phenylmethyl)-1,2,4-oxadiazol-5-yl]-1-propanol



A mixture of γ-butyrolactone (223µl, 2.9mmol), benzamidine oxime (480mg, 3.2mmol), 21% solution of NaOEt in EtOH (1.3ml) and EtOH (3ml) was heated in the microwave at 140°C for 10min. The mixture was partitioned between 2M HCl (aq) and EtOAc. The organic layer was separated, washed with brine, dried ($MgSO_4$) and concentrated. The title product was purified over silica using the Companion™ system to give a pale yellow oil (143mg, 23%).
LC/MS: m/z 219 $[MH]^+$, RT 2.4min.

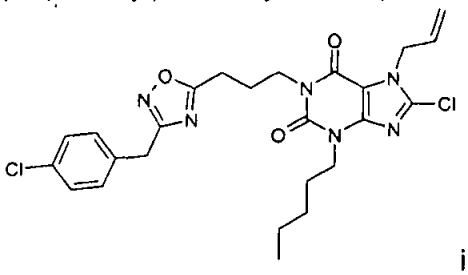
Example 88 : 8-Chloro-1-(3-{3-[(4-chlorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione

a) 8-Chloro-1-(3-{3-[(4-chlorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione



A solution of 8-chloro-1-(3-{3-[(4-chlorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3-pentyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (0.18g, 0.34mmol) in DMF (5ml) was degassed by sequential evacuation of the flask and admission of nitrogen (x3) and morpholine (0.5ml, 5.8mmol), and $Pd(PPh_3)_4$ (80mg, 0.068mmol) added. The solution was stirred for 72h then concentrated and the residues loaded onto an aminopropyl SPE (10g) with MeOH. Elution with MeOH followed by 5% AcOH/MeOH provided the title compound as a pale yellow solid, which was washed with ether to yield a white solid (0.053g, 32%).
LC/MS: m/z 491 $[MH]^+$, RT 3.69min

b) 8-Chloro-1-(3-{3-[(4-chlorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3-pentyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione



i)

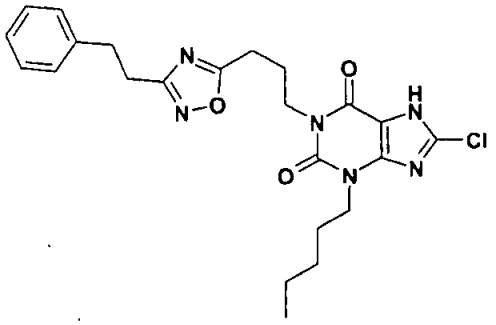
i) A mixture of γ-butyrolactone (8ml, 104mmol), 4-chlorobenzamidine oxime (3.0g, 16.25mmol), 30% solution of NaOMe in MeOH (5ml) and MeOH (80ml) was refluxed for 30h, cooled and concentrated. The residues were purified by flash chromatography over silica eluting with DCM/EtOH/0.88 aq ammonia (200:8:1) to provide a yellow oil (13g). This material was dissolved in DCM (150ml) and washed with 2M sodium hydroxide (100ml) and the organics separated, dried and concentrated to yield 3-{3-[(4-chlorophenyl)methyl]-1,2,4-oxadiazol-5-yl}-1-propanol as a viscous oil (3.95g, 96%) which was used in the next step.

ii) To a solution of 8-chloro-3-pentyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (0.10g, 0.34mmol), 3-{3-[(4-chlorophenyl)methyl]-1,2,4-oxadiazol-5-yl}-1-propanol (0.086g, 0.34mmol) and triphenylphosphine (0.186g, 0.69mmol) in THF (5ml) was added dibenzylazodicarboxylate (0.204g, 0.68mmol) and the solution stirred for 18h. The solution was then concentrated and the residues chromatographed over silica (20g, SPE) eluting with DCM initially then DCM/Et_2O mixtures to yield the title

compound contaminated with dibenzylazodicarboxylate by-products (0.18g). Material used crude in deprotection step.
LC/MS: m/z 531 $[MH]^+$, RT 3.83min.

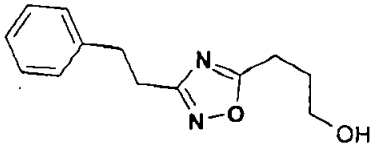
Example 89 : 8-Chloro-3-pentyl-1-{3-[3-(2-phenylethyl)-1,2,4-oxadiazol-5-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione

a) 8-Chloro-3-pentyl-1-{3-[3-(2-phenylethyl)-1,2,4-oxadiazol-5-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione



A solution of 3-[3-(2-phenylethyl)-1,2,4-oxadiazol-5-yl]-1-propanol (150mg, 0.65mmol) in THF (6ml) was treated with 8-chloro-3-pentyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (160mg, 0.54mmol) and PPh_3 (183mg, 0.70mmol) under nitrogen. DBAD (161mg, 0.70mmol) was added in one portion and the reaction left to react for 18h. The mixture was degassed by applying a vacuum and then nitrogen was introduced. $Pd(PPh_3)_4$ (39mg, 0.034mmol) was added and the mixture degassed once more. Morpholine (294µl, 3.4mmol) was added and the mixture was stirred under nitrogen for 3h. The mixture was partitioned between 2M HCl (aq) and EtOAc. The organic layer was separated, washed with brine, dried ($MgSO_4$) and concentrated. The residue was taken up into MeOH and purified by passing down an aminopropyl SPE, the product eluted with 2-5% AcOH/MeOH. The title compound was obtained as an off-white solid (185mg, 73%).
LC/MS: m/z 471 $[MH]^+$, RT 3.6min.
^{1}H NMR; (DMSO-d_6) δ: 0.85 (t, 3H, J = 7Hz), 1.23-1.34 (m, 4H), 1.63 (m, 2H), 2.06 (m, 2H), 2.87 (m, 4H), 2.93 (t, 2H, J = 7Hz), 3.89 (t, 2H, J = 7Hz), 4.00 (t, 2H, J = 6.5Hz), 7.16-7.29 (m, 5H), 14.5 (br s, 1H).

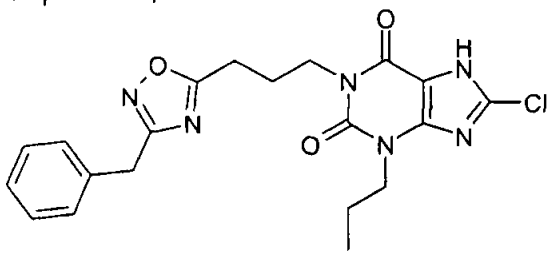
b) 3-[3-(2-Phenylethyl)-1,2,4-oxadiazol-5-yl]-1-propanol



A mixture of γ-butyrolactone (426µl, 5.5mmol), phenethylamidine oxime (1.0g, 6.1mmol), 21% solution of NaOEt in EtOH (2ml) and EtOH (3ml) was heated in the microwave at 140°C for 10min. The mixture was partitioned between 2M HCl (aq) and EtOAc. The organic layer was separated, washed with brine, dried ($MgSO_4$) and concentrated. The title product was purified by Si-SPE eluting with EtOAc/cyclohexane mixtures to give the title compound as a pale yellow oil (390mg, 31%).
LC/MS: m/z 233 $[MH]^+$, RT 2.5min.

Example 90 : 8-Chloro-1-{3-[3-(phenylmethyl)-1,2,4-oxadiazol-5-yl]propyl}-3-propyl-3,7-dihydro-1*H*-purine-2,6-dione

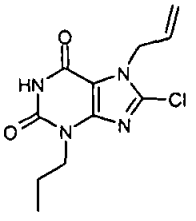
a) 8-Chloro-1-{3-[3-(phenylmethyl)-1,2,4-oxadiazol-5-yl]propyl}-3-propyl-3,7-dihydro-1*H*-purine-2,6-dione



A solution of 8-chloro-7-(2-propen-1-yl)-3-propyl-3,7-dihydro-1*H*-purine-2,6-dione (200mg, 0.74mmol) in THF (4ml) was treated with 3-[3-(phenylmethyl)-1,2,4-oxadiazol-5-yl]-1-propanol (195mg, 0.89mmol) and PPh_3 (254mg, 0.96mmol). DBAD (223mg, 0.96mmol) was added in one portion and the mixture was left to stir at rt under nitrogen for 18h. The mixture was partitioned between EtOAc and 2M HCl (aq). The organic layer was separated, washed with brine, dried ($MgSO_4$) and concentrated. The crude product was purified by a silica SPE column using a 0-70% cyclohexane/EtOAc gradient. The product fractions were combined, concentrated and further purified by a silica SPE column using a 0-60% cyclohexane/EtOAc gradient. The product fractions were combined and concentrated then dissolved in anhydrous THF (4ml). The solution was degassed by high vacuum then $Pd(PPh_3)_4$ (86mg, 0.074mmol) and morpholine (644µl, 7.4mmol) were added and the mixture left to stir at rt under nitrogen for 1 day. The mixture was partitioned between EtOAc and HCl (aq). The organic layer was separated, washed with brine, dried ($MgSO_4$) and concentrated by high vacuum. The crude product was purified by an aminopropyl SPE using MeOH to load the compound onto the column and wash through the impurities then a 2-4% AcOH/MeOH gradient to elute the product. The product fractions were combined and concentrated by high vacuum to leave the title compound as a white solid (74mg, 23%).
LC/MS: m/z 429 $[MH]^+$, RT 3.14min.

^{1}H NMR; (DMSO-d_6) δ: 0.87 (t, 3H, J = 7.5 Hz), 1.65 (m, 2H), 2.02 (m, 2H), 2.91 (t, 2H, J = 7.5Hz), 3.86 (t, 2H, J = 7Hz), 3.97 (s,t overlapping, 4H), 7.27 (m, 5H) 14.46 (s, 1H).

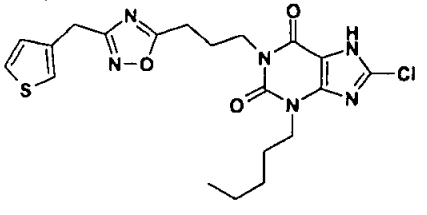
b) 8-Chloro-7-(2-propen-1-yl)-3-propyl-3,7-dihydro-1*H*-purine-2,6-dione



A mixture of 8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (1.5g, 6.6mmol), 1-iodopropane (1.2g, 6.9mmol) and sodium carbonate (0.9g, 8.5mmol) in DMF (40ml) was heated at 50°C for 18h. The reaction mixture was concentrated *in vacuo* and the residue treated with water (60ml) and extracted with EtOAc (3x 80ml). The combined organic extracts were dried ($MgSO_4$) filtered and evaporated. The residue was triturated with ether/cyclohexane, the solid was filtered off and dried to afford the title compound (0.82g, 46%).
LC/MS: m/z 269 $[MH]^+$.

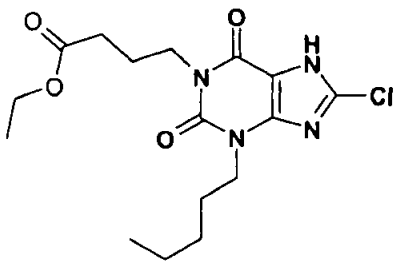
Example 91: 8-Chloro-3-pentyl-1-{3-[3-(3-thienylmethyl)-1,2,4-oxadiazol-5-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione

a) 8-Chloro-3-pentyl-1-{3-[3-(3-thienylmethyl)-1,2,4-oxadiazol-5-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione



A mixture of ethyl 4-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)butanoate (70mg, 0.19mmol), *N*-hydroxy-2-(3-thienyl)ethanimidamide (36mg, 0.23mmol), 21% solution of NaOEt in EtOH (78μL, 0.21mmol) and EtOH (1.5ml) was heated in the microwave at 140°C for 10min. After cooling the reaction was partitioned between 2M HCl (aq) and EtOAc. The organic layer was separated and the aqueous layer extracted again with EtOAc. The combined extracts were concentrated and purified by MDAP. The title compound was freeze dried from 1,4-dioxane to give a white solid (27mg, 31%).
LC/MS: m/z 463 $[MH]^+$, RT 3.4min.

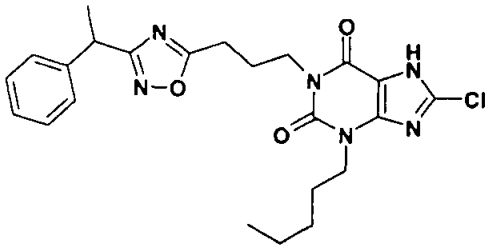
b) Ethyl 4-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)butanoate



A solution of 8-chloro-3-pentyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (3.0g, 10.1mmol) in anhydrous DMF (35ml) was treated with Cs_2CO_3 (3.6g, 11.1mmol) and ethyl 4-bromobutyrate (1.6ml, 11.1mmol). The mixture was stirred at rt for 18h then degassed under a gentle vacuum, then nitrogen introduced. This was repeated twice. $Pd(PPh_3)_4$ (1.17g, 1.0mmol) was added and the mixture degassed once more. Morpholine (8.8ml, 101mmol) was added and left to stir for 3 h at rt. The mixture was partitioned between 2M HCl (aq) and EtOAc. The organic layer was separated, washed with brine, dried ($MgSO_4$) and concentrated, giving a yellow solid (5.16g). The residue was taken up in MeOH and divided into two equal portions, and then each passed down an aminopropyl SPE (20g), eluting with MeOH followed by 5% AcOH/MeOH. The product fractions were combined and concentrated giving the title compound as a near white solid (3.01g, 80%).

LC/MS: m/z 371 $[MH]^+$, RT 3.2min.

Example 92 : 8-Chloro-3-pentyl-1-{3-[3-(1-phenylethyl)-1,2,4-oxadiazol-5-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione

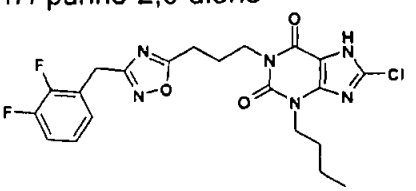


A mixture of ethyl 4-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)butanoate (70mg, 0.19mmol), *N*-hydroxy-2-phenylpropanimidamide (38mg, 0.23mmol), 21% solution of NaOEt in EtOH (78µl, 0.21mmol) and EtOH (1.5ml) was heated in the microwave at 140°C for 10min. After cooling the reaction was partitioned between 2M HCl (aq) and EtOAc. The organic layer was separated and the aqueous layer extracted again with EtOAc. The combined extracts were concentrated and purified by the MDAP. The title compound was freeze dried from 1,4-dioxane to give a white solid (44mg, 49%).

LC/MS: m/z 471 $[MH]^+$, RT 3.6min.

Example 93 : 3-Butyl-8-chloro-1-{3-[3-(2,3-difluorobenzyl)-1,2,4-oxadiazol-5-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione

a) 3-Butyl-8-chloro-1-{3-[3-(2,3-difluorobenzyl)-1,2,4-oxadiazol-5-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione

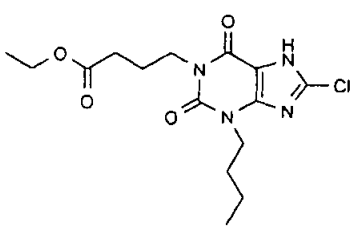


2,3-Difluorophenylacetonitrile (23mg, 0.15mmol) was dissolved in EtOH (1ml). Hydroxylamine hydrochloride (14mg, 0.20mmol) was added, followed by water (0.5ml) and potassium carbonate (41mg, 0.3mmol). The mixture was heated at reflux overnight and then cooled and partitioned between EtOAc and brine. The organic phase was evaporated and the crude amidoxime thus obtained was dissolved in EtOH (1ml). Ethyl 4-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)butanoate (43mg, 0.12mmol) and 21% by wt. ethanolic sodium ethoxide ((0.067ml, 0.18mmol) was added and the mixture heated in the microwave reactor at 140°C for 10min. The mixture was partitioned between EtOAc and 2M HCl, the organic phase evaporated and the product purified by MDAP to provide the title compound as a solid (13mg).

LC/MS: m/z 479 $[MH]^+$, RT 3.52min.

^{1}H NMR (MeOH-d_4) δ: 0.96 (t, 3H, J = 7Hz), 1.34-1.45 (m, 2H), 1.65-1.75 (m, 2H), 2.13-2.22 (m, 2H), 2.97 (t, 2H, J = 7Hz), 4.00 (t, 2H, J = 7Hz), 4.05 (s, 2H), 4.12 (t, 2H, J = 7Hz), 7.03-7.25 (m, 3H).

b) Ethyl 4-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)butanoate



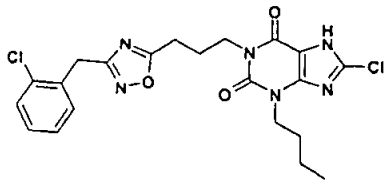
To 3-butyl-8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (6.0g, 21.24mmol) in dry DMF (100ml) was added Cs_2CO_3 (7.62g, 23.36mmol) followed by ethyl 4-bromobutyrate (4.556g, 23.36mmol). The mixture was heated at 55°C for 18h and allowed to cool then degassed by repeatedly evacuating and readmitting nitrogen. Morpholine (14.9g, 171mmol) was added followed by tetrakis(triphenylphosphine)palladium(0) (4.0g, 3.46mmol) and the mixture was stirred for 4h. EtOAc (300ml) and 2M HCl (150ml) and water (100ml) were added and the organic phase separated, washed with brine (3 x 100ml) and filtered. The filtrate was dried (Na_2SO_4) and evaporated. The crude product (10g) was purified by aminopropyl SPE (3 x 20g), loading in THF/MeOH (1:1), washing with THF/MeOH (1:1) and neat

MeOH and eluting the product with DCM/MeOH (1:1) containing 5% added AcOH to afford the title compound (5.08g).

LC/MS: m/z 357 $[MH]^+$, RT 3.06min.

^1H NMR (d^4 MeOH) 0.96 (3H, t, J = 7Hz), 1.33-1.42 (2H, m), 1.64-1.74 (2H, m), 2.12-2.21 (2H, m), 2.95 (2H, t, J = 8Hz), 3.99 (2H, t, J = 7Hz), 4.03 (2H, s), 4.11 (2H, t, J = 7Hz), 7.03-7.21 (3H, m).

Example 94 : 3-Butyl-8-chloro-1-{3-[3-(2-chlorobenzyl)-1,2,4-oxadiazol-5-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione

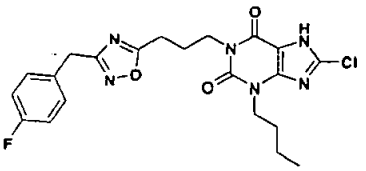


Ethyl 4-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)butanoate (53mg, 0.15mmol) and (1*Z*)-2-(2-chlorophenyl)-*N*-hydroxyethanimidamide (30mg, 0.18mmol; Entry **1**, table 7) were heated in EtOH (0.75ml) with 21% ethanolic sodium ethoxide (0.083ml, 0.22mmol) at 140°C for 10min. The mixture was then partitioned between EtOAc and 2M HCl and the organic phase evaporated. The product was purified by MDAP to yield the title compound as a solid (34.8mg).

LC/MS: m/z 477 $[MH]^+$, RT 3.59min.

^1H NMR (d^6 DMSO) 0.89 (3H, t, J = 8Hz), 1.24-1.34 (2H, m), 1.56-1.65 (2H, m), 1.98-2.07 (2H, m), 2.92 (2H, t, J = 7Hz), 3.89 (2H, t, J = 7Hz), 3.98 (2H, t, J = 7Hz), 4.09 (2H, s), 7.28-7.48 (4H, m).

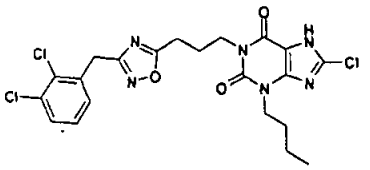
Example 95 : 3-Butyl-8-chloro-1-{3-[3-(4-fluorobenzyl)-1,2,4-oxadiazol-5-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione



Starting from (1*Z*)-2-(4-fluorophenyl)-*N*-hydroxyethanimidamide (28mg, 0.18mmol; Entry **2**, Table 7) was similarly obtained the title compound as a solid (10.0mg).

LC/MS: m/z 461 $[MH]^+$, RT 3.49min.

Example 96 : 3-Butyl-8-chloro-1-{3-[3-(2,3-dichlorobenzyl)-1,2,4-oxadiazol-5-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione

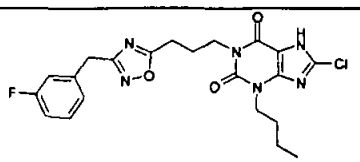
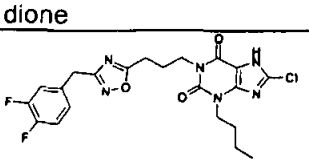


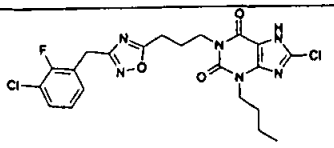
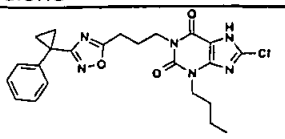
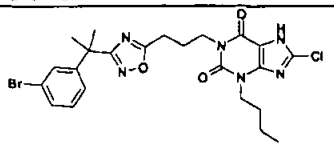
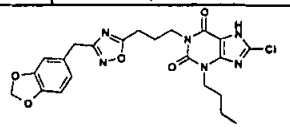
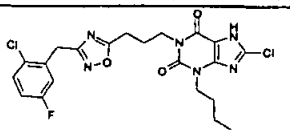
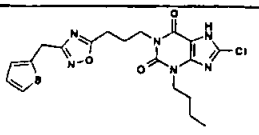
Ethyl 4-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)butanoate (53mg, 0.15mmol) and (1*Z*)-2-(2,3-dichlorophenyl)-*N*-hydroxyethanimidamide (36mg, 0.165mmol; Entry **3**, Table 7) and 21% ethanolic sodium ethoxide (0.083ml, 0.22mmol) were heated together in EtOH (0.75ml) in the microwave reactor at 140°C for 10min. The mixture was then partitioned between EtOAc and 2M HCl, the organic phase separated, evaporated and the product purified by MDAP to give the title compound as a solid (42.1mg).

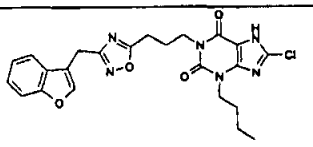
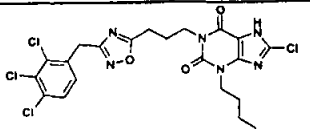
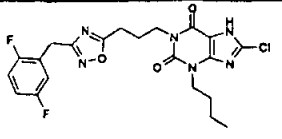
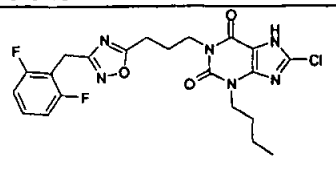
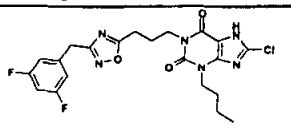
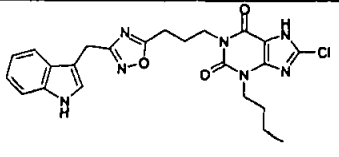
LC/MS: m/z 511, 513, 515 (isotopes) $[MH]^+$, RT 3.66min.

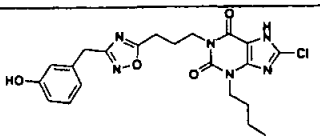
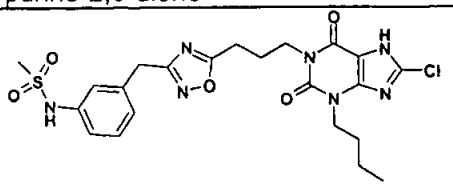
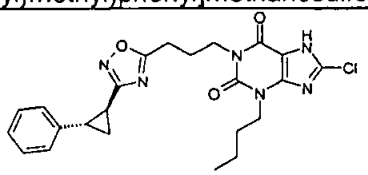
The following compounds (Table 4) were prepared using a method analogous to that for Example 96, using the appropriate amidoxime, (with the exceptions that for Example **110** (Table 4) during workup the pH was adjusted to 5 prior to extraction with EtOAc; and in the case of Example **111** (Table 4) the crude product was stirred for 18h with EtOH (1ml) and 2M NaOH (0.5ml) and Example **112** (Table 4) was stirred for 18h with EtOH (0.75ml) and 2M NaOH (0.5ml) prior to repeat workup and purification by MDAP).

Table 4

Example	Structure	Amidoxime (see table 7)	Wt of amidoxime Mg	Yield mg	LC/MS :
97	 3-butyl-8-chloro-1-{3-[3-(3-fluorobenzyl)-1,2,4-oxadiazol-5-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione	**4**	28	32.4	m/z 461 $[MH]^+$ RT 3.41 *min*
98	 3-butyl-8-chloro-1-{3-[3-(3,4-difluorobenzyl)-1,2,4-oxadiazol-5-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione	**5**	31	28.3	m/z 479 $[MH]^+$ RT 3.46 min

99	 3-butyl-8-chloro-1-{3-[3-(3-chloro-2-fluorobenzyl)-1,2,4-oxadiazol-5-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione	**6**	33	32.3	m/z 495 $[MH]^+$ RT 3.55 min
100	 3-butyl-8-chloro-1-{3-[3-(1-phenylcyclopropyl)-1,2,4-oxadiazol-5-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione	**8**	29	3.5	m/z 469 $[MH]^+$ RT 3.43 min
101	 1-(3-{3-[1-(3-bromophenyl)-1-methylethyl]-1,2,4-oxadiazol-5-yl}propyl)-3-butyl-8-chloro-3,7-dihydro-1*H*-purine-2,6-dione	**9**	42	2.6	m/z 551 $[MH]^+$ RT 3.71 min
102	 1-{3-[3-(1,3-benzodioxol-5-ylmethyl)-1,2,4-oxadiazol-5-yl]propyl}-3-butyl-8-chloro-3,7-dihydro-1*H*-purine-2,6-dione	**10**	32	30.5	m/z 487 $[MH]^+$ RT 3.27 min
103	 3-butyl-8-chloro-1-(3-{3-[(2-chloro-5-fluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione	**19**	33	26.2	m/z 495 $[MH]^+$ RT 3.47 min
104	 3-butyl-8-chloro-1-{3-[3-(2-thienylmethyl)-1,2,4-oxadiazol-5-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione	**21**	26	33.4	m/z 449 $[MH]^+$ RT 3.23 min

105	 1-{3-[3-(1-benzofuran-3-ylmethyl)-1,2,4-oxadiazol-5-yl]propyl}-3-butyl-8-chloro-3,7-dihydro-1*H*-purine-2,6-dione	**22**	31	27.3	m/z 483 $[MH]^+$ RT 3.47 min
106	 3-butyl-8-chloro-1-(3-{3-[(2,3,4-trichlorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione	**15**	42	29.8	m/z 545 $[MH]^+$ RT 3.79 min
107	 3-butyl-8-chloro-1-(3-{3-[(2,5-difluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione	**16**	31	34.8	m/z 479 $[MH]^+$ RT 3.35 min
108	 3-butyl-8-chloro-1-(3-{3-[(2,6-difluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione	**17**	31	38.2	m/z 479 $[MH]^+$ RT 3.31 min
109	 3-butyl-8-chloro-1-(3-{3-[(3,5-difluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione	**18**	31	35.4	m/z 479 $[MH]^+$ RT 3.39 min
110	 3-butyl-8-chloro-1-{3-[3-(1*H*-indol-3-ylmethyl)-1,2,4-oxadiazol-5-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione	**20**	31	16.1	m/z 482 $[MH]^+$ RT 3.31 min

111	 3-butyl-8-chloro-1-(3-{3-[(3-hydroxyphenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione	**7**	28	10	m/z 459 $[MH]^+$ RT 3.07 min
112	 *N*-[3-({5-[3-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)propyl]-1,2,4-oxadiazol-3-yl}methyl)phenyl]methanesulfonamide	**25**	40	28.4	m/z 536 $[MH]^+$ RT 3.03 min
113	 3-butyl-8-chloro-1-(3-{3-[(1*S*,2*S*)-2-phenylcyclopropyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione	(1*S*,2*S*)-*N*-hydroxy-2-phenylcyclopropanecarboximidamide	29	29.6	m/z 469 $[MH]^+$ RT 3.51 min

NMR details for selected examples from Table 4:

Example 97: 3-butyl-8-chloro-1-{3-[3-(3-fluorobenzyl)-1,2,4-oxadiazol-5-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione

^{1}H NMR (DMSO-d_6) δ: 0.90 (t, 3H, J = 7Hz), 1.25-1.36 (m, 2H), 1.56-1.67 (m, 2H), 2.0-2.1 (m, 2H), 2.94 (t, 2H, J = 7Hz), 3.90 (t, 2H, J = 7 Hz), 3.98 (t, 2H, J = 7Hz), 4.02 (s, 2H), 7.05-7.15 (m, 3H), 7.32-7.40 (m, 1H).

Example 98: 3-Butyl-8-chloro-1-{3-[3-(3,4-difluorobenzyl)-1,2,4-oxadiazol-5-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione

^{1}H NMR (DMSO-d_6) δ: 0.89 (t, 3H, J = 7.5Hz), 1.25-1.34 (m, 2H), 1.56-1.65 (m, 2H), 1.99-2.07 (m, 2H), 2.92 (t, 2H, J = 7Hz), 3.89 (t, 2H, J = 7 Hz), 3.98 (t, 2H, J = 7Hz), 4.02 (s, 2H), 7.10-7.15 (m, 1H), 7.32-7.39 (m, 2H), 14.45 (br s, 1H).

Example 100: 3-butyl-8-chloro-1-{3-[3-(1-phenylcyclopropyl)-1,2,4-oxadiazol-5-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione

^{1}H NMR (MeOH-d_4) δ: 0.95 (t, 3H, J = 7Hz), 1.25-1.30 (m, 2H), 1.30-1.45 (m, 4H), 1.64-1.75 (m, 2H), 2.15-2.25 (m, 2H), 2.94 (t, 2H, J = 7Hz), 3.98 (t, 2H, J = 7Hz), 4.10 (t, 2H, J = 7Hz), 7.20-7.37 (m, 5H).

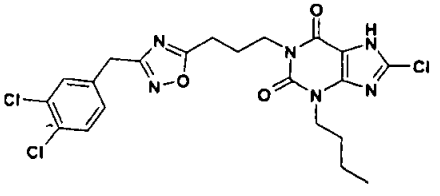
Example 102: 1-{3-[3-(1,3-benzodioxol-5-ylmethyl)-1,2,4-oxadiazol-5-yl]propyl}-3-butyl-8-chloro-3,7-dihydro-1*H*-purine-2,6-dione
^{1}H NMR (DMSO-d_6) δ: 0.90 (t, 3H, J = 7Hz), 1.25-1.36 (m, 2H), 1.58-1.68 (m, 2H), 1.98-2.09 (m, 2H), 2.92 (t, 2H, J = 7Hz), 3.88-3.95 (m, 4H), 3.99 (t, 2H, J = 7Hz), 5.98 (s, 2H), 6.70-6.86 (m, 3H).

Example 110: 3-butyl-8-chloro-1-{3-[3-(1*H*-indol-3-ylmethyl)-1,2,4-oxadiazol-5-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione
^{1}H NMR (DMSO-d_6) δ: 0.89 (t, 3H, J = 7Hz), 1.23-1.36 (m, 2H), 1.56-1.67 (m, 2H), 1.96-2.08 (m, 2H), 2.90 (t, 2H, J = 7Hz), 3.90 (t, 2H, J = 7 Hz), 3.99 (t, 2H, J = 7Hz), 4.04 (s, 2H), 6.92-7.50 (m, 5H), 10.95 (s, 1H).

Example 111: 3-butyl-8-chloro-1-(3-{3-[(3-hydroxyphenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione
^{1}H NMR (DMSO-d_6) δ: 0.90 (t, 3H, J = 7Hz), 1.25-1.38 (m, 2H), 1.57-1.68 (m, 2H), 1.96-2.07 (m, 2H), 2.92 (t, 2H, J = 7Hz), 3.86 (s, 2H), 3.89 (t, 2H, J = 7Hz), 3.99 (t, 2H, J = 7Hz), 6.58-6.68 (m, 3H), 7.08 (m, 1H), 9.40 (s,1H).

Example 112: *N*-[3-({5-[3-(3-Butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)propyl]-1,2,4-oxadiazol-3-yl}methyl)phenyl]methanesulfonamide
^{1}H NMR (DMSO-d_6) δ: 0.89 (t, 3H, J = 7.5Hz), 1.24-1.34 (m, 2H), 1.56-1.65 (m, 2H), 1.97-2.06 (m, 2H), 2.91 (t, 2H, J = 7.5Hz), 2.97 (s, 3H), 3.90 (t, 2H, J = 7.5Hz), 3.96 (s, 2H), 3.97 (t, 2H, J = 7Hz), 6.96-6.99 (m, 1H), 7.06-7.13 (m, 2H), 7.26 (t, 1H, J = 8Hz), 9.75 (s, 1H), 14.45 (br s, 1H).

Example 114: 3-Butyl-8-chloro-1-(3-{3-[(3,4-dichlorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione

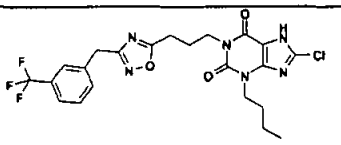
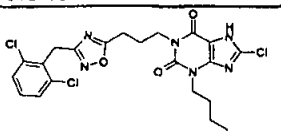
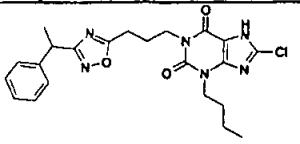
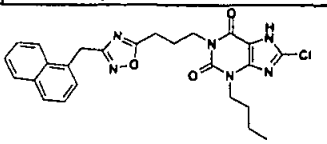


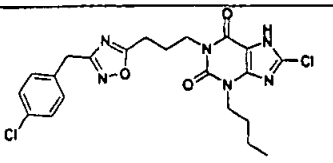
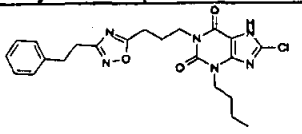
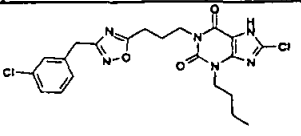
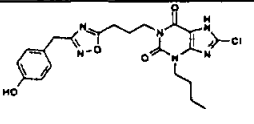
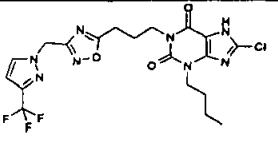
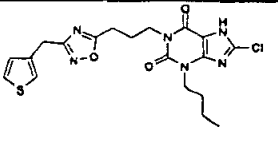
Ethyl 4-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)butanoate (71mg, 0.2mmol), (1*Z*)-2-(3,4-dichlorophenyl)-*N*-hydroxyethanimidamide (48mg, 0.22mmol) and 21% by wt. ethanolic sodium ethoxide (0.111ml, 0.3mmol) were heated together in EtOH (1ml) in the microwave reactor at 140°C for 10min. The mixture was then partitioned between EtOAc and 2M HCl, the organic phase separated and evaporated, and the crude product was purified by MDAP to give the title compound as a solid (48.8mg).

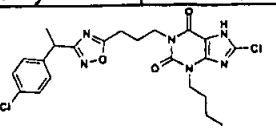
LC/MS: m/z 511, 513 $[MH]^+$, RT 3.65min.

The following compounds (Table 5) were prepared using a method analogous to that for Example 114, using the appropriate amidoxime (with the exception that for Example **115** and Example **125**, 0.185ml, (0.5mmol) of 21% sodium ethoxide was added in order to allow for the amidoximes being the hydrochloride salts).

Table 5

Example	Structure	Amidoxime	Wt of amidoxime mg	Yield mg	LC/MS:
115	 3-butyl-8-chloro-1-[3-(3-{[3-(trifluoromethyl)phenyl]methyl}-1,2,4-oxadiazol-5-yl)propyl]-3,7-dihydro-1*H*-purine-2,6-dione	(1*Z*)-*N*-hydroxy-2-[3-(trifluoromethyl)phenyl]ethanimidamide hydrochloride	56	46.5	m/z 511 $[MH]^+$ RT 3.63 min
116	 3-butyl-8-chloro-1-(3-{3-[(2,6-dichlorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione	(1*Z*)-2-(2,6-dichlorophenyl)-*N*-hydroxyethanimidamide	48	53.8	m/z 511 $[MH]^+$ RT 3.64 min
117	 3-butyl-8-chloro-1-{3-[3-(1-phenylethyl)-1,2,4-oxadiazol-5-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione	(1*Z*)-*N*-hydroxy-2-phenylpropanimidamide	36	45.4	m/z 457 $[MH]^+$ RT 3.51 min
118	 3-butyl-8-chloro-1-{3-[3-(1-naphthalenylmethyl)-1,2,4-oxadiazol-5-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione	(1*Z*)-*N*-hydroxy-2-(1-naphthalenyl)ethanimidamide	44	48.6	m/z 493 $[MH]^+$ RT 3.67 min

119	 3-butyl-8-chloro-1-(3-{3-[(4-chlorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione	(1Z)-2-(4-chlorophenyl)-*N*-hydroxyethanimidamide	41	35.6	m/z 477 $[MH]^+$ RT 3.60 min
120	 3-butyl-8-chloro-1-{3-[3-(2-phenylethyl)-1,2,4-oxadiazol-5-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione	(1Z)-*N*-hydroxy-3-phenylpropanimidamide	36	29.6	m/z 457 $[MH]^+$ RT 3.55 min
121	 3-butyl-8-chloro-1-(3-{3-[(3-chlorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione	(1Z)-2-(3-chlorophenyl)-*N*-hydroxyethanimidamide	41	39.4	m/z 477 $[MH]^+$ RT 3.64 min
122	 3-butyl-8-chloro-1-(3-{3-[(4-hydroxyphenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione	(1Z)-*N*-hydroxy-2-(4-hydroxyphenyl)ethanimidamide	36	53.5	m/z 459 $[MH]^+$ RT 3.08 min
123	 3-butyl-8-chloro-1-[3-(3-{[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]methyl}-1,2,4-oxadiazol-5-yl)propyl]-3,7-dihydro-1*H*-purine-2,6-dione	(1Z)-*N*-hydroxy-2-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]ethanimidamide	46	58.1	m/z 501 $[MH]^+$ RT 3.33 min
124	 3-butyl-8-chloro-1-{3-[3-(3-thienylmethyl)-1,2,4-	(1Z)-*N*-hydroxy-2-(3-thienyl)ethanimidamide	34	32.6	m/z 449 $[MH]^+$ RT 3.31 min

	oxadiazol-5-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione				
125	 3-butyl-8-chloro-1-(3-{3-[1-(4-chlorophenyl)ethyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione	(1Z)-2-(4-chlorophenyl)-*N*-hydroxypropanimidamide hydrochloride	52	30.3	m/z 491 $[MH]^+$ RT 3.67 min

NMR details for selected examples from Table 5

Example 115: ^{1}H NMR (d^6 DMSO) 0.88 (3H, t, J = 7Hz), 1.24-1.33 (2H, m), 1.56-1.65 (2H, m), 1.98-2.06 (2H, m), 2.92 (2H, t, J = 7Hz), 3.89 (2H, t, J = 7Hz), 3.97 (2H, t, J = 7Hz), 4.14 (2H, s), 7.52-7.70 (4H, m).

Example 117: 3-butyl-8-chloro-1-{3-[3-(1-phenylethyl)-1,2,4-oxadiazol-5-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione
^{1}H NMR (DMSO-d_6) δ: 0.89 (t, 3H, J = 7Hz), 1.22-1.35 (m, 2H), 1.52 (d, 3H, J = 8Hz), 1.56-1.68 (m, 2H), 1.95-2.08 (m, 2H), 2.91 (t, 2H, J = 7Hz), 3.89 (t, 2H, J = 7Hz), 3.95 (t, 2H, J = 7Hz), 4.18 (q, 1H, J = 8Hz), 7.17-7.32 (m, 5H).

Example 119: 3-butyl-8-chloro-1-(3-{3-[(4-chlorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione
^{1}H NMR (DMSO-d_6) δ: 0.89 (t, 3H, J = 7Hz), 1.23-1.37 (m, 2H), 1.55-1.67 (m, 2H), 1.97-2.09 (m, 2H), 2.90 (t, 2H, J = 7Hz), 3.88 (t, 2H, J = 7Hz), 3.97 (t, 2H, J = 7Hz), 4.00 (s, 2H), 7.27-7.40 (m, 4H).

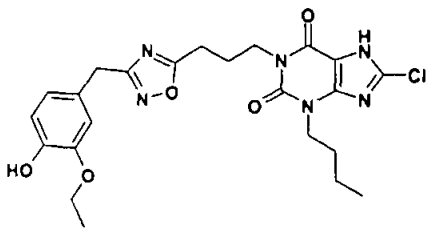
Example 122: 3-butyl-8-chloro-1-(3-{3-[(4-hydroxyphenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione
^{1}H NMR (DMSO-d_6) δ: 0.90 (t, 3H, J = 7Hz), 1.23-1.37 (m, 2H), 1.57-1.68 (m, 2H), 1.96-2.08 (m, 2H), 2.90 (t, 2H, J = 7Hz), 3.82 (s, 2H), 3.90 (t, 2H, J = 7Hz), 3.98 (t, 2H, J = 7Hz), 6.68 (d, 2H, J = 9Hz), 7.04 (d, 2H, J = 9Hz), 9.32 (s, 1H).

Example 123: 3-butyl-8-chloro-1-[3-(3-{[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]methyl}-1,2,4-oxadiazol-5-yl)propyl]-3,7-dihydro-1*H*-purine-2,6-dione
^{1}H NMR (DMSO-d_6) δ: 0.90 (t, 3H, J = 7Hz), 1.23-1.36 (m, 2H), 1.57-1.69 (m, 2H), 1.95-2.08 (m, 2H), 2.95 (t, 2H, J = 7Hz), 3.91 (t, 2H, J = 7Hz), 3.97 (t, 2H, J = 7Hz), 5.62 (s, 2H), 6.79 (s, 1H), 8.10 (s, 1H).

Example 125: 3-butyl-8-chloro-1-(3-{3-[1-(4-chlorophenyl)ethyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione

^{1}H NMR (DMSO-d_6) δ: 0.90 (t, 3H, J = 7Hz), 1.23-1.38 (m, 2H), 1.51 (d, 3H, J = 6Hz), 1.55-1.69 (m, 2H), 1.96-2.10 (m, 2H), 2.92 (t, 2H, J = 7Hz), 3.89 (t, 2H, J = 7Hz), 3.98 (t, 2H, J = 7Hz), 4.24 (q, 1H, J = 6Hz), 7.27-7.40 (m, 4H).

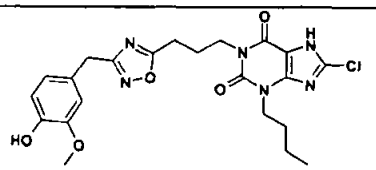
Example 126 : 3-Butyl-8-chloro-1-[3-(3-{[3-(ethyloxy)-4-hydroxyphenyl]methyl}-1,2,4-oxadiazol-5-yl)propyl]-3,7-dihydro-1*H*-purine-2,6-dione

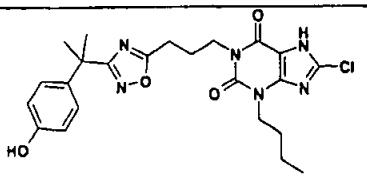
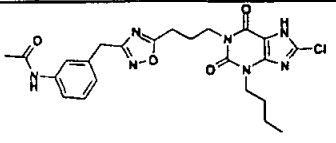


Ethyl 4-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)butanoate (53mg, 0.15mmol) and (1*Z*)-2-[3-(ethyloxy)-4-hydroxyphenyl]-*N*-hydroxyethanimidamide (35mg, 0.165mmol; entry 11, Table 7) were mixed in EtOH (0.75ml). Ethanolic sodium ethoxide (21% by wt., 0.083ml, 0.22mmol) was added and the mixture was heated in the microwave at 140°C for 10min. A further 0.055ml (0.15mmol) of NaOEt solution was then added and the mixture heated for a further 10min period at 140°C. The mixture was partitioned between EtOAc and 2M HCl and the organic phase evaporated and purified by MDAP to give the title compound as a solid (29.6mg).
LC/MS: m/z 503 $[MH]^+$, RT 3.15min.

The following compounds (Table 6) were prepared using a method analogous to that for Example 126, using the appropriate amidoxime (with the exception that for Example **127** (Table 6), the crude product after workup was stirred with EtOH (1ml) and 2M NaOH (0.5ml) overnight in order to hydrolyse residual starting ester, prior to repeat HCl workup and purification by MDAP).

Table 6

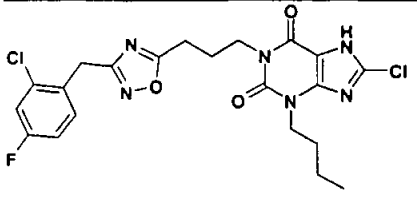
Example	Structure	Amidoxime (see table 7)	Wt of aldoxime mg	Yield mg	LC/MS:
127	 3-butyl-8-chloro-1-[3-(3-{[4-hydroxy-3-(methyloxy)phenyl]methyl}-1,2,4-oxadiazol-5-yl)propyl]-3,7-dihydro-1*H*-purine-2,6-dione	**12**	32	19.3	m/z 489 $[MH]^+$ RT 2.98 min

128	 3-butyl-8-chloro-1-(3-{3-[1-(4-hydroxyphenyl)-1-methylethyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione	13	32	37.2	m/z 487 $[MH]^+$ RT 3.23 min
129	 *N*-[3-({5-[3-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)propyl]-1,2,4-oxadiazol-3-yl}methyl)phenyl]acetamide	14	34	23.6	m/z 500 $[MH]^+$ RT 2.94 min

NMR details for selected examples from Table 6

Example 129: *N*-[3-({5-[3-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)propyl]-1,2,4-oxadiazol-3-yl}methyl)phenyl]acetamide
^{1}H NMR (DMSO-d_6) δ: 0.90 (t, 3H, J = 7Hz), 1.25-1.38 (m, 2H), 1.57-1.68 (m, 2H), 1.95-2.07 (m, 5H), 2.92 (t, 2H, J = 7Hz), 3.91 (t, 2H, J = 7Hz), 3.94 (s, 2H), 3.98 (m, 2H), 6.88-7.50 (m, 4H), 9.90 (s, 1H).

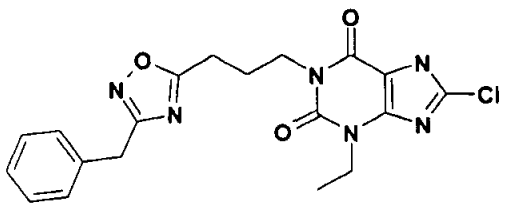
Example 130: 3-Butyl-8-chloro-1-(3-{3-[(2-chloro-4-fluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione



Ethyl 4-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)butanoate (100mg, 0.28mmol) and (1*Z*)-2-(2-chloro-4-fluorophenyl)-*N*-hydroxyethanimidamide (62.4mg, 0.308mmol) and 21% by wt. ethanolic sodium ethoxide (0.157ml, 0.42mmol) were heated together in a microwave reactor in EtOH (1.5ml) at 140°C for 10min. The mixture was worked up by partitioning between EtOAc and 2M HCl. The organic phase was evaporated and purified by MDAP to afford the title compound as a solid (73mg).
LC/MS: m/z 495 $[MH]^+$, RT 3.55min.

Example 131 : 8-Chloro-3-ethyl-1-{3-[3-(phenylmethyl)-1,2,4-oxadiazol-5-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione

a) 8-Chloro-3-ethyl-1-{3-[3-(phenylmethyl)-1,2,4-oxadiazol-5-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione

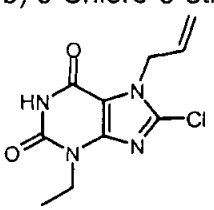


A solution of 8-chloro-3-ethyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (150mg, 0.59mmol) in anhydrous THF (4ml) was treated with 3-[3-(phenylmethyl)-1,2,4-oxadiazol-5-yl]-1-propanol (154mg, 0.71mmol) and triphenylphosphine (200mg, 0.76mmol). DBAD (162mg, 0.71mmol) was added in one portion and the mixture was left to stir at rt, under nitrogen for 18h. The mixture was degassed by high vacuum then $Pd(PPh_3)_4$ (68mg, 0.059mmol) and morpholine (515µl, 5.9mmol) were added. The mixture was left to stir at rt, under nitrogen, for 3h. The mixture was partitioned between EtOAc and 2M HCl (aq). The organic layer was separated, washed with brine, dried ($MgSO_4$) and concentrated by high vacuum. The crude material was purified by an aminopropyl SPE using MeOH to load the compound onto the column and wash through the impurities, then with 2% AcOH/MeOH to elute the compound. The UV active fractions were combined and concentrated by high vacuum. The product was further purified by MDAP. The product fractions were combined and concentrated to give the title compound as a white solid (61mg, 25%).

LC/MS: m/z 415 $[MH]^+$, RT 3.01min

^1H NMR; (DMSO-d_6) δ: 1.19 (t, 3H, J = 7Hz), 2.93 (m, 2H), 2.91 (t, 2H, J = 7.5Hz), 3.96 (m, 6H), 7.27 (m, 5H) 14.46 (s, 1H).

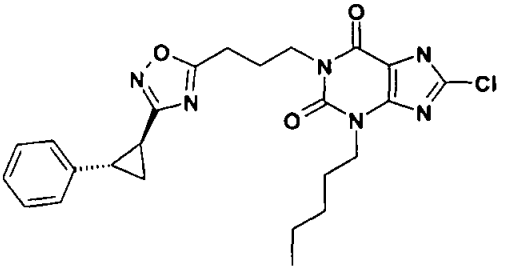
b) 8-Chloro-3-ethyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione



A solution of 8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (10g, 0.044mol) in anhydrous DMF (100ml) was treated with iodoethane (5.4ml, 0.068mol) and Na_2CO_3 (4.9g, 0.046mol). The reaction mixture was left to stir at rt under nitrogen for 2 days. Iodoethane (0.35ml, 0.0044mol) was added and the mixture was left to stir at rt for 1 day. The mixture was partitioned between EtOAc and 2M HCl. The organic layer was separated, washed sequentially with saturated sodium sulphite solution and

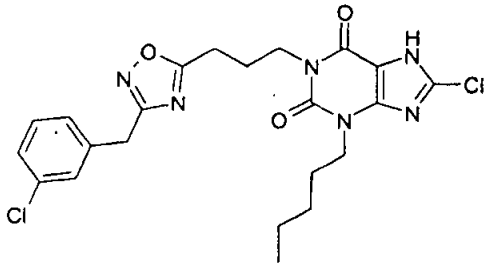
brine, dried ($MgSO_4$) and concentrated. The crude solid was washed with Et_2O to give the title compound as a white solid (8.37g, 75%).
LC/MS: m/z 255 $[MH]^+$, RT 2.35min.

Example 132 : 8-Chloro-3-pentyl-1-(3-{3-[(1*S*,2*S*)-2-phenylcyclopropyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione



Ethyl 5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)pentanoate (70mg, 0.19mmol) was dissolved in EtOH (1.5ml). The solution was treated with a 21% solution of NaOEt in EtOH (78µl, 0.21mmol) and (1*S*,2*S*)-*N*-hydroxy-2-phenylcyclopropanecarboximidamide (37mg, 0.21mmol). The reaction was heated in the microwave at 140°C for 10min. The mixture was partitioned between EtOH and 2M HCl (aq). The organic layer was separated and concentrated, the resulting crude product was purified by MDAP. The product fractions were combined and concentrated to give the title compound as a white solid (35mg, 38%).
LC/MS: m/z 483 $[MH]^+$, RT 3.67min.

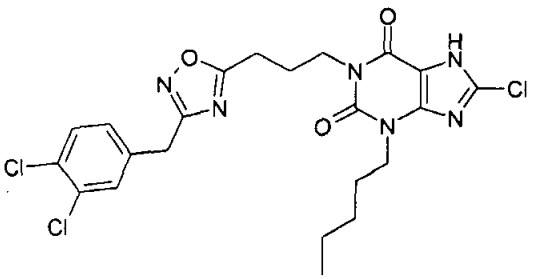
Example 133 : 8-Chloro-1-(3-{3-[(3-chlorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione



Ethyl 5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)pentanoate (70mg, 0.19mmol) was dissolved in EtOH. The solution was treated with a 21% solution of NaOEt in EtOH (78µl, 0.21mmol) and (1*Z*)-2-(3-chlorophenyl)-*N*-hydroxyethanimidamide (38mg, 0.21mmol). The reaction was heated in the microwave at 140°C for 10min. The mixture was partitioned between EtOH and 2M HCl (aq). The organic layer was decanted off and concentrated. The crude product was purified on the MDAP. The product fractions were combined and concentrated to give the title compound as a white solid (46mg, 49%).

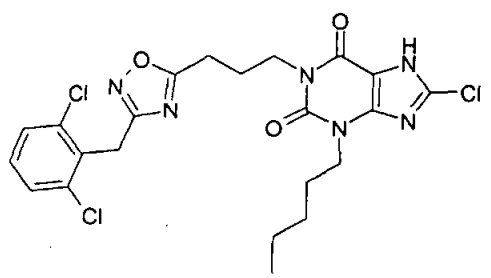
LC/MS: m/z 491 $[MH]^+$, RT 3.64min.
^{1}H NMR (DMSO-d_6) δ: 0.85 (t, 3H, J = 7Hz), 1.27 (m, 4H), 1.62 (m, 2H), 2.02 (m, 2H), 2.92 (t, 2H, J = 7.5Hz), 3.88 (t, 2H, J=7 Hz), 3.97 (t, 2H, J = 6.5Hz), 4.02 (s, 2H), 7.23 (d, 1H, J = 7Hz), 7.34 (m, 3H).

Example 134: 8-Chloro-1-(3-{3-[(3,4-dichlorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione



Ethyl 5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)pentanoate (70mg, 0.19mmol) was dissolved in EtOH. The solution was treated with a 21% solution of NaOEt in EtOH (78µl, 0.21mmol) and (1Z)-2-(3,4-dichlorophenyl)-*N*-hydroxyethanimidamide (46mg, 0.21mmol). The reaction was heated in the microwave at 140°C for 10min. The mixture was partitioned between EtOH and 2M HCl (aq). The organic layer was decanted off and concentrated. The crude product was purified on the MDAP. The product fractions were combined and concentrated to give the title compound as a white solid (66mg, 66%).
LC/MS: m/z 527 $[MH]^+$, RT 3.80min.

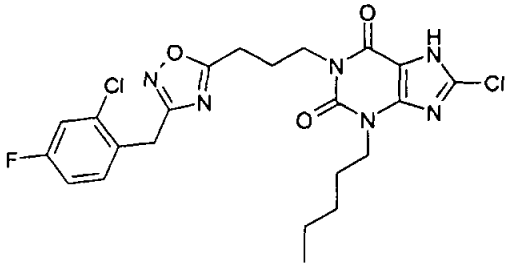
Example 135 : 8-Chloro-1-(3-{3-[(2,6-dichlorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione



Ethyl 5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)pentanoate (70mg, 0.19mmol) was dissolved in EtOH. The solution was treated with a 21% solution of NaOEt in EtOH (78µl, 0.21mmol) and (1Z)-2-(2,6-dichlorophenyl)-*N*-hydroxyethanimidamide (46mg, 0.21mmol). The reaction was heated in the microwave at 140°C for 10min. The mixture was partitioned between EtOH and 2M HCl (aq). The organic layer was decanted off and concentrated by nitrogen blowdown. The crude

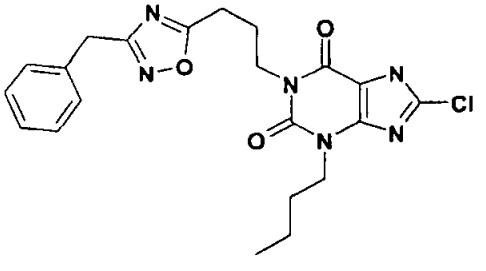
product was purified on the MDAP. The product fractions were combined and concentrated to give the title compound as a white solid (80mg, 80%).
LC/MS: m/z 526 $[MH]^+$, RT 3.6 min.

Example 136 : 8-Chloro-1-(3-{3-[(2-chloro-4-fluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione



Ethyl 5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)pentanoate (70mg, 0.19mmol) was dissolved in EtOH. The solution was treated with a 21% solution of NaOEt in EtOH (78µl, 0.21mmol) and (1Z)-2-(2-chloro-4-fluorophenyl)-*N*-hydroxyethanimidamide (42mg, 0.21mmol). The reaction was heated in the microwave at 140°C for 10min. The mixture was partitioned between EtOH and 2M HCl (aq). The organic layer was decanted off and concentrated. The crude product was purified on the MDAP. The product fractions were combined and concentrated to give the title compound as a white solid (65mg, 67%).
LC/MS: m/z 509 $[MH]^+$, RT 3.63min.

Example 137 : 3-Butyl-8-chloro-1-{3-[3-(phenylmethyl)-1,2,4-oxadiazol-5-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione



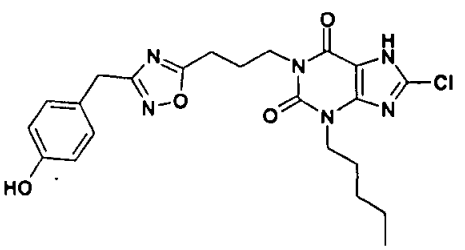
A solution of 3-butyl-8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (205mg, 0.73mmol) in anhydrous THF (4ml) was treated with 3-[3-(phenylmethyl)-1,2,4-oxadiazol-5-yl]-1-propanol (190mg, 0.87mmol) and PPh_3 (247mg, 0.94mmol). DBAD (217mg, 0.94mmol) was added in one portion and the mixture was stirred at rt under nitrogen for 18h. The mixture was degassed by high vacuum then $Pd(PPh_3)_4$ (84mg, 0.073mmol) and morpholine (636µl, 7.3mmol) were added. The mixture was stirred at rt under nitrogen for 3h. The mixture was partitioned between EtOAc and 2M HCl (aq) and the organic layer separated, washed with brine, dried ($MgSO_4$) and

concentrated. The crude material was purified by an aminopropyl column using MeOH to load the compound onto the column and wash through the impurities, then with 2-4% AcOH/MeOH gradient to remove the compound from the column. Further purification was effected by MDAP to give the title compound as a white solid (75mg, 23%).

LC/MS: m/z 443 $[MH]^+$, RT 3.37min.

^{1}H NMR; (DMSO-d_6) δ: 0.89 (t, 3H, J = 7.5 Hz), 1.29 (m, 2H), 1.61 (m, 2H), 2.02 (m, 2H), 2.91 (t, 2H, J = 7.5Hz), 3.89 (t, 2H, J = 7Hz), 3.97 (m, 4H), 7.27 (m, 5H) 14.46 (s, 1H).

Example 138: 8-Chloro-1-(3-{3-[(4-hydroxyphenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione

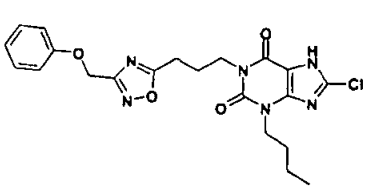


Ethyl 5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)pentanoate (29mg, 0.078mmol) and (1*Z*)-*N*-hydroxy-2-(4-hydroxyphenyl)ethanimidamide (14mg, 0.084mmol) were heated in EtOH (1ml) with 21% ethanolic sodium ethoxide (0.043ml, 0.117mmol) under microwave irradiation at 140°C for 10min. The mixture was partitioned between EtOAc and 2M HCl and the organic phase evaporated. This material was stirred with EtOH (1ml) and 2M NaOH (0.5ml) for 18h, before being worked up again by partition between EtOAc and 2M HCl. Purification by MDAP afforded the title compound (6.5mg).

LC/MS: m/z 473 $[MH]^+$, RT 3.34min.

^{1}H NMR (MeOH-d_4) δ: 0.92 (t, 3H, J = 7Hz), 1.25-1.45 (m, 4H), 1.68-1.78 (m, 2H), 2.11-2.21 (m, 2H), 2.93 (t, 2H, J = 7Hz), 3.82 (s, 2H), 3.98 (t, 2H, J = 7Hz), 4.10 (t, 2H, J = 7Hz), 6.70 (d, 2H, J = 10Hz), 7.02 (d, 2H, J = 10Hz).

Example 139: 3-Butyl-8-chloro-1-(3-{3-[(phenyloxy)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione



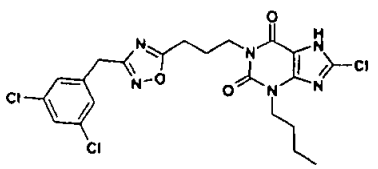
To ethyl 4-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)butanoate (26mg, 0.073mmol) and (1*Z*)-*N*-hydroxy-2-(phenyloxy)ethanimidamide hydrochloride (16mg, 0.079mmol) in EtOH (1ml) was added 21%wt. ethanolic sodium ethoxide solution (0.068 ml, 0.183mmol) and the mixture was heated under microwave

irradiation at 140°C for 10min. The mixture was partitioned between EtOAc and 2M HCl, the organic phase dried (Na_2SO_4) evaporated and purified by MDAP to give title compound as a gum which solidified upon trituration with ether (5.9mg).

LC/MS: m/z 459 $[MH]^+$, RT 3.39min.

^1H NMR (DMSO-d_6) δ: 0.90 (t, 3H, J = 8Hz), 1.22-1.36 (m, 2H), 1.57-1.68 (m, 2H), 2.02-2.14 (m, 2H), 3.00 (t, 2H, J = 8Hz), 3.90 (t, 2H, J = 7Hz), 4.00 (t, 2H, J = 7Hz), 5.18 (s, 2H), 6.95-7.35 (m, 5H).

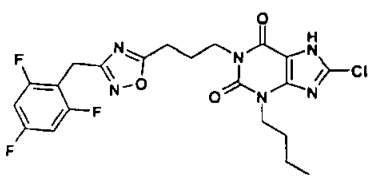
Example 140: 3-Butyl-8-chloro-1-{3-{3-[(3,5-dichlorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione



To ethyl 4-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)butanoate (185mg, 0.52mmol) and (1*Z*)-2-(3,5-dichlorophenyl)-*N*-hydroxyethanimidamide (126mg, 0.58mmol; Entry 23, Table 7) in dry EtOH (2ml) was added 21%wt. ethanolic sodium ethoxide solution (0.29ml, 0.78mmol) and the mixture was heated by microwaves at 140°C for 10min. The reaction was worked up by partition between EtOAc and 2M HCl and evaporating the organic phase. Purification by MDAP afforded the title compound as a solid (135mg).

LC/MS: m/z 511 $[MH]^+$, RT 3.71min.

Example 141: 3-Butyl-8-chloro-1-{3-{3-[(2,4,6-trifluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione



Similarly prepared starting from (1*Z*)-*N*-hydroxy-2-(2,4,6-trifluorophenyl)ethanimidamide (119mg, 0.58mmol; Entry 24, Table 7) in a yield of 135mg.

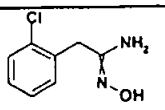
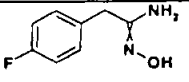
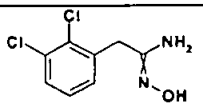
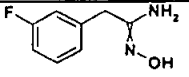
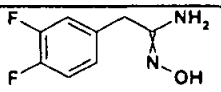
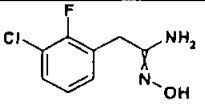
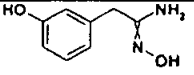
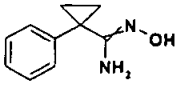
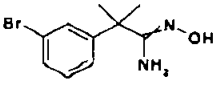
LC/MS: m/z 497 $[MH]^+$, RT 3.39min.

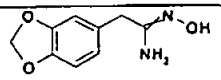
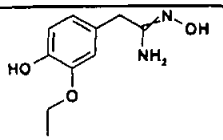
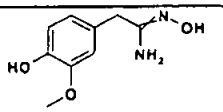
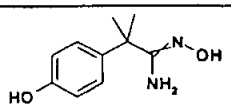
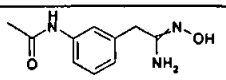
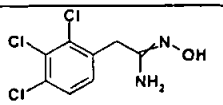
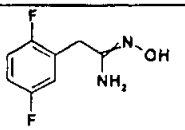
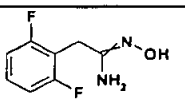
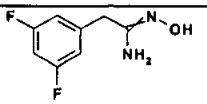
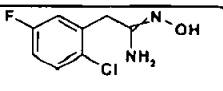
^1H NMR (DMSO-d_6) δ: 0.90 (t, 3H, J = 7Hz), 1.24-1.36 (m, 2H), 1.55-1.66 (m, 2H), 1.96-2.06 (m, 2H), 2.91 (t, 2H, J = 8Hz), 3.91 (t, 2H, J = 8 Hz), 3.94 – 4.02 (m, 4H), 7.18-7.28 (m, 2H).

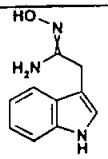
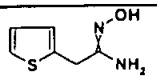
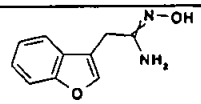
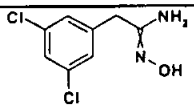
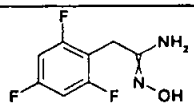
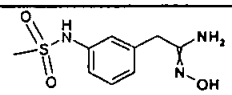
Amidoximes:

These are available by the methods detailed below and exemplified by analogues in Table 7.

Table 7 (Intermediates)

Entry	Structure	Name	Method	Yield mg	LC/MS:
1		**(1*Z*)-2-(2-chlorophenyl)-*N*-hydroxyethanimidamide**	G	38	m/z 185 $[MH]^+$ RT 1.04 min
2		**(1*Z*)-2-(4-fluorophenyl)-*N*-hydroxyethanimidamide**	G	42	m/z 169 $[MH]^+$ RT 0.72 min
3		**(1*Z*)-2-(2,3-dichlorophenyl)-*N*-hydroxyethanimidamide**	B	64	m/z 219 $[MH]^+$ RT 1.83 min
4		**(1*Z*)-2-(3-fluorophenyl)-*N*-hydroxyethanimidamide**	A	78	m/z 169 $[MH]^+$ RT 0.62 min
5		**(1*Z*)-2-(3,4-difluorophenyl)-*N*-hydroxyethanimidamide**	A	88	m/z 187 $[MH]^+$ RT 0.74min
6		**(1*Z*)-2-(3-chloro-2-fluorophenyl)-*N*-hydroxyethanimidamide**	A	92	m/z 203 $[MH]^+$ RT 1.40 min
7		**(1*Z*)-*N*-hydroxy-2-(3-hydroxyphenyl)ethanimidamide**	A	67	m/z 167 $[MH]^+$ RT 0.46 min
8		***N*-hydroxy-1-phenylcyclopropanecarboximidamide**	C	75	m/z 177 $[MH]^+$ RT 1.06 min
9		**(1*Z*)-2-(3-bromophenyl)-*N*-hydroxy-2-methylpropanimidamide**	D	74	m/z 257 $[MH]^+$ RT 2.04 min

10		**(1*Z*)-2-(1,3-benzodioxol-5-yl)-*N*-hydroxyethanimidamide**	C	98	m/z 195 $[MH]^+$ RT 0.73 min
11		**(1*Z*)-2-[3-(ethyloxy)-4-hydroxyphenyl]-*N*-hydroxyethanimidamide**	C	109	m/z 211 $[MH]^+$ RT 0.76 min
12		**(1*Z*)-*N*-hydroxy-2-[4-hydroxy-3-(methyloxy)phenyl]ethanimidamide**	C	98	m/z 197 $[MH]^+$ RT 0.50 min
13		**(1*Z*)-*N*-hydroxy-2-(4-hydroxyphenyl)-2-methylpropanimidamide**	D	66	m/z 195 $[MH]^+$ RT 0.85 min
14		***N*-{3-[(2*Z*)-2-(hydroxyamino)-2-iminoethyl]phenyl}acetamide**	C	91	m/z 208 $[MH]^+$ RT 0.73 min
15		**(1*Z*)-*N*-hydroxy-2-(2,3,4-trichlorophenyl)ethanimidamide**	C	124	m/z 253 $[MH]^+$ RT 2.29 min
16		**(1*Z*)-2-(2,5-difluorophenyl)-*N*-hydroxyethanimidamide**	C	89	m/z 187 $[MH]^+$ RT 0.66 min
17		**(1*Z*)-2-(2,6-difluorophenyl)-*N*-hydroxyethanimidamide**	C	86	m/z 187 $[MH]^+$ RT 0.62 min
18		**(1*Z*)-2-(3,5-difluorophenyl)-*N*-hydroxyethanimidamide**	C	96	m/z 187 $[MH]^+$ RT 0.80 min
19		**(1*Z*)-2-(2-chloro-5-fluorophenyl)-*N*-hydroxyethanimidamide**	C	97	m/z 203 $[MH]^+$ RT 0.90 min

20		**(1Z)-*N*-hydroxy-2-(1*H*-indol-3-yl)ethanimidamide**	C	95	m/z 190 $[MH]^+$ RT 0.90 min
21		**(1Z)-*N*-hydroxy-2-(2-thienyl)ethanimidamide**	C	74	m/z 157 $[MH]^+$ RT 0.38 min
22		**(1Z)-2-(1-benzofuran-3-yl)-*N*-hydroxyethanimidamide**	C	87	m/z 191 $[MH]^+$ RT 1.46 min
23		**(1Z)-2-(3,5-dichlorophenyl)-*N*-hydroxyethanimidamide**	E	165	m/z 219 $[MH]^+$ RT 2.03 min
24		**(1Z)-*N*-hydroxy-2-(2,4,6-trifluorophenyl)ethanimidamide**	F	297	m/z 205 $[MH]^+$ RT 0.66 min
25		**(1Z)-*N*-hydroxy-2-{3-[(methylsulfonyl)amino]phenyl}ethanimidamide**	C	125	m/z 244 $[MH]^+$ RT 0.63 min

Method A

The corresponding nitrile (0.5mmol) was stirred in EtOH (1.5ml) with 50% aqueous hydroxylamine solution (0.08ml, 1.3mmol) and heated at 65°C for 4.5h. After cooling the crude reaction mixture was loaded onto an SCX SPE cartridge (2g) and washed with MeOH, then the amidoxime product was eluted with 2M ammonia in MeOH.

Method B

Similar to Method A except that the product crystallised out from the crude reaction mixture and was isolated by filtration instead of by SCX.

Method C

Similar to Method A except that the product was purified on a 5g SCX cartridge.

Method D

Similar to Method C except that the heating period was 18h.

Method E
Similar to Method C except that the scale was 0.753mmol of nitrile.

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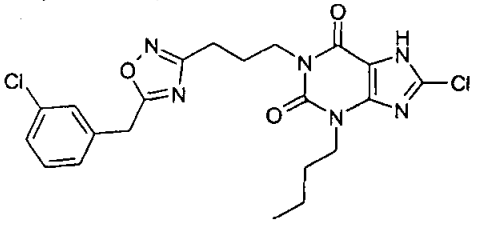
Method F
Similar to Method A except that the scale was 1.5mmol of nitrile and purification was on a 10g SCX cartridge.

Method G
Similar to Method A except that the heating time was 2.75h and the scale was 0.25mmol of nitrile.

It should be noted that the above assignment of (Z)-stereochemistry has not been confirmed by experimental data. The person skilled in the art will also recognise that there can be interconversion between E & Z isomers. (Dondoni, Alessandro; Lunazzi, Lodovico; Giorgianni, Patrizia; Macciantelli, Dante. Carbon-nitrogen rotational barrier as a stereochemical probe of benzamidoximes. Journal of Organic Chemistry (1975), 40(20), 2979-80)

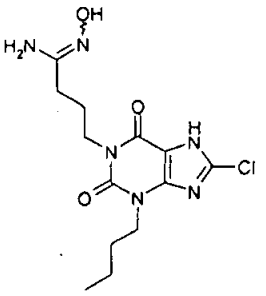
Example 142: 3-Butyl-8-chloro-1-(3-{5-[(3-chlorophenyl)methyl]-1,2,4-oxadiazol-3-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione

a) 3-Butyl-8-chloro-1-(3-{5-[(3-chlorophenyl)methyl]-1,2,4-oxadiazol-3-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione



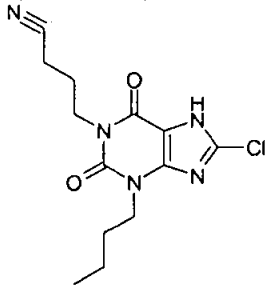
(3-Chlorophenyl)acetic acid (0.1mmol), *N*-[3-(dimethylamino)propyl]-*N'*-ethylcarbodiimide hydrochloride (21mg, 0.11mmol) and 1*H*-1,2,3-benzotriazol-1-ol (15mg, 0.11mmol) were stirred in 1-methyl-2-pyrrolidinone (1ml). To this was added (1Z)-4-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)-*N*-hydroxybutanimidamide (34mg, 0.1mmol) and the mixture stirred at rt for 17h and then at 80°C for 24h. The reaction mixture was purified, without further modification, by preparative HPLC (auto prep) to give the title compound (13mg, 27%).
LC/MS: m/z 477, 479 $[MH]^+$, RT 3.5min.
^{1}H NMR ($CDCl_3$) δ: 0.96 (t, 3H, J = 7Hz), 1.32-1.47 (m, 2H), 1.68-1.80 (m, 2H), 2.12-2.24 (m, 2H), 2.83 (t, 2H, J = 7.5Hz), 4.05-4.24 (m, 6H), 7.16-7.30 (m, 4H).

b) (1Z)-4-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)-*N*-hydroxybutanimidamide



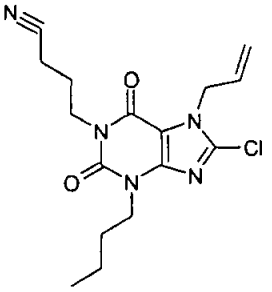
4-(3-Butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)butanenitrile (1g, 0.0032mol) was stirred in EtOH (3.5ml) and water (1.8ml). Hydroxylamine hydrochloride (344mg, 0.0049mol) and potassium carbonate (652mg, 0.0049mol) were added and the mixture heated at 80°C for 3 days. After cooling the crude reaction mixture was evaporated. The crude product was dissolved in water, neutralised to pH7 with HCl, and loaded onto an Oasis™ cartridge (2g). This was eluted with water to remove the salts and then with MeOH, to give the title compound (957mg, 86%).
LC/MS: m/z 343, 345 $[MH]^+$, RT 2.04min.

c) 4-(3-Butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)butanenitrile



4-[3-Butyl-8-chloro-2,6-dioxo-7-(2-propen-1-yl)-2,3,6,7-tetrahydro-1H-purin-1-yl]butanenitrile (2.1g, 6mmol) was stirred in a mixture of nitrogen degassed DCM (20ml) and AcOH (2ml). Tetrakis(triphenylphosphine)palladium (675mg, 0.6mmol) and phenyl silane (7.4ml, 60mmol) were added and the mixture stirred at rt for 2d. This was then evaporated and the residue triturated with a mixture of diethylether:cyclohexane (1:1) to afford the title compound (1.47g, 60%) as a white solid.
LC/MS: m/z 310 $[MH]^+$, RT 2.66min.

d) 4-[3-Butyl-8-chloro-2,6-dioxo-7-(2-propen-1-yl)-2,3,6,7-tetrahydro-1*H*-purin-1-yl]butanenitrile



3-butyl-8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (2.0g, 0.0072mol) in dry MeCN (20ml) was added Cs_2CO_3 (4.68g, 0.0144mol) followed by bromobutyronitrile (1.38g, 0.0094mol). The mixture was heated at 80°C for 18h and then allowed to cool. The reaction mixture was evaporated and the crude product partitioned between EtOAc and HCl (2N). The organic phase was separated and washed with brine, dried ($MgSO_4$) and evaporated to give the crude product. This was purified by silica SPE (50g), eluting with cyclohexane:ethylacetate (2:1 to 1:1) to afford the title compound as a clear oil (2.1g, 85%).

LC/MS: m/z 350 $[MH]^+$, RT 3.10min.

The following compounds (Table 8) were prepared using a method analogous to that for Example 142, from the corresponding acids and (1Z)-4-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)-*N*-hydroxybutanimidamide.

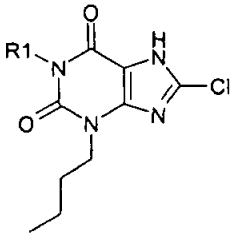
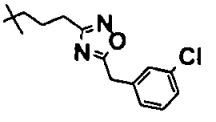
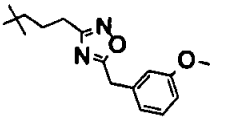
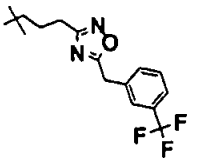
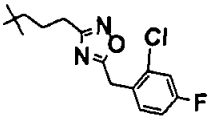
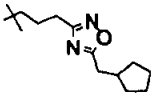
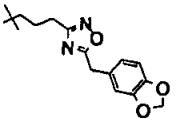
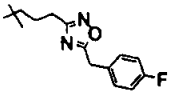
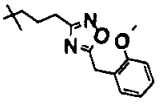
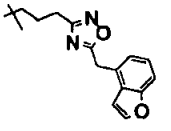


Table 8

Example		Compound: R1 =	Yield %	LC/MS:
143	3-butyl-8-chloro-1-(3-{5-[(3-chlorophenyl)methyl]-1,2,4-oxadiazol-3-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione		27	m/z 477 $[MH]^+$ RT 3.5 min
144	3-butyl-8-chloro-1-[3-(5-{[3-(methyloxy)phenyl]methyl}-1,2,4-oxadiazol-3-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione		22	m/z 473 $[MH]^+$ RT 3.3 min

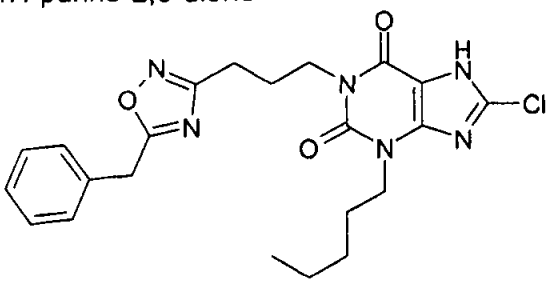
Example		Compound: R1 =	Yield %	LC/MS:
145	3-butyl-8-chloro-1-[3-(5-{[3-(trifluoromethyl)phenyl]methyl}-1,2,4-oxadiazol-3-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione		23	m/z 511 $[MH]^+$ RT 3.5 min
146	3-butyl-8-chloro-1-(3-{5-[(2-chloro-4-fluorophenyl)methyl]-1,2,4-oxadiazol-3-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione		28	m/z 495 $[MH]^+$ RT 3.5 min
147	3-butyl-8-chloro-1-{3-[5-(cyclopentylmethyl)-1,2,4-oxadiazol-3-yl]propyl}-3,7-dihydro-1H-purine-2,6-dione		15	m/z 435 $[MH]^+$ RT 3.5 min
148	1-{3-[5-(1,3-benzodioxol-5-ylmethyl)-1,2,4-oxadiazol-3-yl]propyl}-3-butyl-8-chloro-3,7-dihydro-1H-purine-2,6-dione		27	m/z 487 $[MH]^+$ RT 3.3 min
149	3-butyl-8-chloro-1-(3-{5-[(4-fluorophenyl)methyl]-1,2,4-oxadiazol-3-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione		28	m/z 461 $[MH]^+$ RT 3.3 min
150	3-butyl-8-chloro-1-[3-(5-{[2-(methyloxy)phenyl]methyl}-1,2,4-oxadiazol-3-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione		21	m/z 473 $[MH]^+$ RT 3.3 min
151	1-{3-[5-(1-benzofuran-4-ylmethyl)-1,2,4-oxadiazol-3-yl]propyl}-3-butyl-8-chloro-3,7-dihydro-1H-purine-2,6-dione		24	m/z 483 $[MH]^+$ RT 3.4 min

NMR details for selected examples from Table 8

Example 145: ^{1}H NMR ($CDCl_3$) 0.96 (3H, t, J = 7.5Hz), 1.32-1.47 (2H, m), 1.65-1.81 (2H, m), 2.12-2.25 (2H, m), 2.84 (2H, t, J = 7.5 Hz), 4.02 (2H, t, 7.5Hz), 4.22 (2H, t, 7Hz), 4.24 (2H, s), 7.40-7.62 (4H, m).

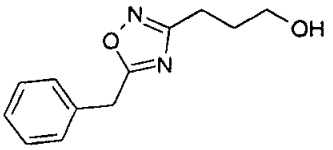
Example 152: 8-Chloro-3-pentyl-1-{3-[5-(phenylmethyl)-1,2,4-oxadiazol-3-yl]propyl}-3,7-dihydr -1*H*-purine-2,6-dione

a) 8-Chloro-3-pentyl-1-{3-[5-(phenylmethyl)-1,2,4-oxadiazol-3-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione



To a stirred solution of 8-chloro-3-pentyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (0.20, 0.67mmol) in THF (5ml) was added 3-[5-(phenylmethyl)-1,2,4-oxadiazol-3-yl]-1-propanol (0.162g, 0.74mmol), DBAD (0.186g, 0.81mmol) and triphenylphosphine (0.212g, 0.81mmol) and the solution stirred for 18h. To the solution was added $Pd(PPh_3)_4$ (75mg, 0.067mmol) and morpholine (600µl, 6.7mmol) were added and stirred for at rt under nitrogen for a further 3h. 75mg of $Pd(PPh_3)_4$ was added and the mixture left to stir for another 3h. The mixture was partitioned between EtOAc and 2M HCl (aq). The organic layer was separated, washed with brine, dried ($MgSO_4$) and concentrated. The crude material was purified by an aminopropyl SPE using MeOH to load the compound onto the column and wash through the impurities, then with 2-4% AcOH/MeOH to elute the compound. The product fractions were combined and concentrated then further purified by MDAP. The product fractions were combined and concentrated give the title compound as a white solid (51mg, 20%).
LC/MS: m/z 457 $[MH]^+$, RT 3.54min.

b) 3-[5-(Phenylmethyl)-1,2,4-oxadiazol-3-yl]-1-propanol



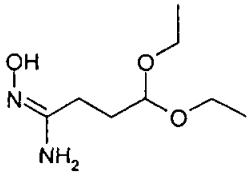
A mixture of (1*E*)-4,4-bis(ethyloxy)-*N*-hydroxybutanimidamide (3.2g, 16.8mmol), ethyl phenylacetate (2.3ml, 14.4mmol) and sodium ethoxide (21% solution in EtOH, 6.4ml) was heated in a microwave at 140°C for 10min. The material was combined with that from a second reaction (using 1.2g of (1*E*)-4,4-bis(ethyloxy)-*N*-hydroxybutanimidamide and conducted as above) and partitioned between 1M HCl solution and EtOAc. The organic layer was separated, washed with brine, dried and concentrated to provide 5-[3,3-bis(ethyloxy)propyl]-5-(phenylmethyl)-1,2,4-oxadiazole which was used without purification in the next stage.
Crude 3-[3,3-bis(ethyloxy)propyl]-5-(phenylmethyl)-1,2,4-oxadiazole (5.63g, 19.4mmol) in EtOH (75ml) was stirred with p-toluenesulphonic acid (0.738g, 3.9mmol) for 21h and the mixture partitioned between EtOAc and water. The organics were isolated washed

with water and brine, dried and concentrated to a red oil. This material contained significant amounts of acetal, therefore the oil was dissolved in THF (15ml) and treated with 2M HCl solution for 2h then partitioned between EtOAc and water. The organics were isolated washed with brine, dried and concentrated to yield 3-[5-(phenylmethyl)-1,2,4-oxadiazol-3-yl]propanal as a red/brown oil (3.77g) which was used crude in the next stage.

A solution of crude 3-[5-(phenylmethyl)-1,2,4-oxadiazol-3-yl]propanal (3.76g, 17.4mmol) in MeOH (60ml) was cooled to 0°C and sodium borohydride (0.724g, 19.1mmol) added portionwise over 30min. The cooling bath was removed and the solution stirred for a further 1h then partitioned between 1M HCl and EtOAc. The organic layer was separated and the aqueous extracted with EtOAc. The combined extracts were washed with brine, dried and concentrated to an orange liquid. This was purified on a 50g silica SPE eluting with cyclohexane/EtOAc (20% to 80% gradient elution) to provide the title compound as a yellow oil (2.24g).

LC/MS: m/z 210 $[MH]^+$.

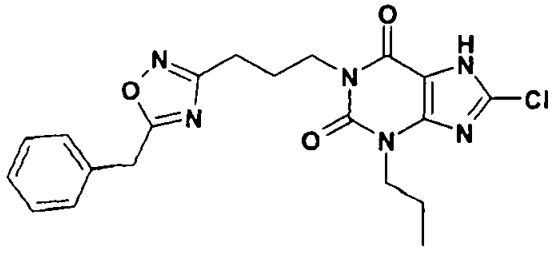
c) (1*E*)-4,4-bis(ethyloxy)-*N*-hydroxybutanimidamide



A mixture of 3-cynopropionaldehyde diethylacetal (6.12g, 39mmol), hydroxylamine hydrochloride (4.06g, 58.4mmol), potassium carbonate (10.76g, 77.9mmol) in water (20ml) and EtOH (40ml) was refluxed for 24h. The mixture was allowed to cool and then partitioned between water and EtOAc. The organic layer was separated and the aqueous extracted with EtOAc. The combined organic fractions were washed with brine, dried and concentrated to provide the title compound as a colourless oil contaminated with ~20% starting nitrile (6.03g, 81%).

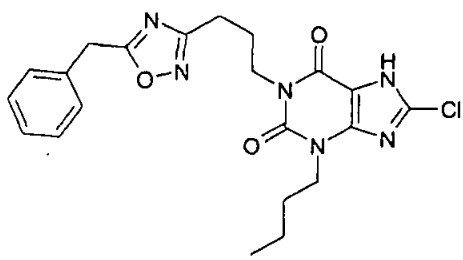
LC/MS: m/z 191 $[MH]^+$.

Example 153 : 8-Chloro-1-{3-[5-(phenylmethyl)-1,2,4-oxadiazol-3-yl]propyl}-3-propyl-3,7-dihydro-1*H*-purine-2,6-dione



A solution of 8-chloro-7-(2-propen-1-yl)-3-propyl-3,7-dihydro-1*H*-purine-2,6-dione (200mg, 0.74mmol) in THF (4ml) was treated with 3-[5-(phenylmethyl)-1,2,4-oxadiazol-3-yl]-1-propanol (195mg, 0.89mmol) and PPh_3 (254mg, 0.96mmol). DBAD (223mg, 0.96mmol) was added in one portion and the mixture was left to stir at rt under nitrogen for 18h. The mixture was partitioned between EtOAc and 2M HCl (aq). The organic layer was separated, washed with brine, dried ($MgSO_4$) and concentrated by high vacuum. The crude product was purified on a silica SPE column using a 0-70% cyclohexane/EtOAc gradient. The product fractions were combined, concentrated by high vacuum and purified on a silica SPE column using a 0-60% cyclohexane/EtOAc gradient. The product fractions were combined and concentrated then dissolved in anhydrous THF (4ml). The solution was degassed by high vacuum then $Pd(PPh_3)_4$ (61mg, 0.053mmol) and morpholine (460µl, 5.3mmol) were added and the mixture left to stir at rt under nitrogen for 1 day. The mixture was partitioned between EtOAc and 2M HCl (aq). The organic layer was separated, washed with brine, dried ($MgSO_4$) and concentrated by high vacuum. The crude product was purified by an aminopropyl SPE using MeOH to load the compound onto the column and wash through the impurities then a 2-4% AcOH/MeOH gradient to elute the product. The product fractions were combined and concentrated to leave the title compound as a white solid (36mg, 11%).
LC/MS: m/z 429 $[MH]^+$, RT 3.14min.
^1H NMR (DMSO-d_6) δ: 0.86 (t, 3H, J = 7.5Hz), 1.65 (m, 2H), 1.93 (m, 2H), 2.70 (t, 2H, J = 7.5Hz), 3.86 (t, 2H, J = 7Hz), 3.96 (t, 2H, J = 7Hz), 4.28 (s, 2H), 7.32 (m, 5H).

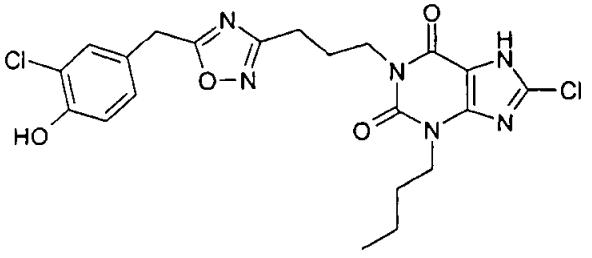
Example 154 : 3-Butyl-8-chloro-1-{3-[5-(phenylmethyl)-1,2,4-oxadiazol-3-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione



A solution of 3-[5-(phenylmethyl)-1,2,4-oxadiazol-3-yl]-1-propanol (594mg, 2.7mmol) in THF (25ml) was treated with 3-butyl-8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (700mg, 2.48mmol) and PPh_3 (779mg, 2.97mmol) under nitrogen. DBAD (684mg, 2.97mmol) was added in one portion and the reaction left to react for 60h. The mixture was partitioned between 2M HCl (aq) and EtOAc. The organic layer was separated, washed with brine, dried ($MgSO_4$) and concentrated. MeOH was added to the residue and then passed down an aminopropyl column with the product eluting with 2-4% AcOH/MeOH. Product fractions were combined and concentrated. The off-white residue was recrystallised from EtOAc:cyclohexane (1:1), giving the title compound as a white solid (696mg, 63%).
LC/MS: m/z 443 $[MH]^+$, RT 3.4min.

^{1}H NMR (DMSO-d_6) δ: 0.89 (t, 3H, J = 7Hz), 1.29 (m, 2H), 1.61 (m, 2H), 1.93 (m, 2H), 2.70 (t, 2H, J = 7.5Hz), 3.90 (t, 2H, J = 7Hz), 3.96 (t, 2H, J = 7Hz), 4.28 (2H, s), 7.31 (m, 5H), 14.4 (br s, 1H).

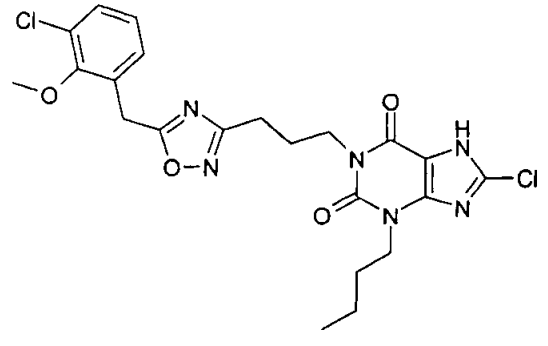
Example 155 : 3-Butyl-8-chloro-1-(3-{5-[(3-chloro-4-hydroxyphenyl)methyl]-1,2,4-oxadiazol-3-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione



A solution of 3-chloro-4-hydroxyphenylacetic acid (24mg, 0.13mmol) in DMSO (1ml) was treated with CDI (21mg, 0.13mmol) and left to react for 30min. (1*Z*)-4-(3-Butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)-*N*-hydroxybutanimidamide (50mg, 0.15mmol) was added and the mixture heated in the microwave at 120°C for 15min. The solution was directly purified by MDAP to obtain the title compound as a white solid (12mg, 17%).

LC/MS: m/z 493 $[MH]^+$, RT 3.2min.

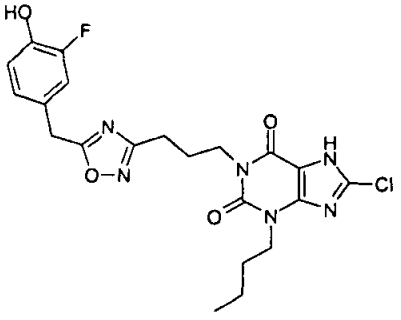
Example 156 : 3-Butyl-8-chloro-1-[3-(5-{[3-chloro-2-(methyloxy)phenyl]methyl}-1,2,4-oxadiazol-3-yl)propyl]-3,7-dihydro-1*H*-purine-2,6-dione



A mixture of [3-chloro-2-(methyloxy)phenyl]acetic acid (32mg, 0.16mmol) in DMF (1.5ml) was treated with CDI (26mg, 0.16mmol) and left to react for 45min. (1*Z*)-4-(3-Butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)-*N*-hydroxybutanimidamide (60mg, 0.18mmol) was added and the mixture heated in the microwave at 140°C for 15min. After cooling, the reaction was partitioned between 2M HCl (aq) and EtOAc. The organic layer was separated then concentrated and purified by the MDAP. The title compound was obtained as a white solid (25mg, 28%).

LC/MS: m/z 507 $[MH]^+$, RT 3.5min.

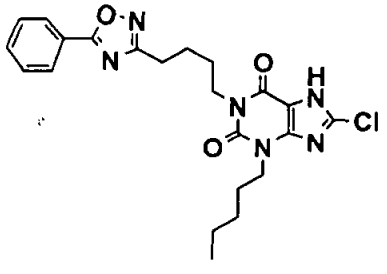
Example 157 : 3-Butyl-8-chloro-1-(3-{5-[(3-fluoro-4-hydroxyphenyl)methyl]-1,2,4-oxadiazol-3-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione



A mixture of (3-fluoro-4-hydroxyphenyl)acetic acid (27mg, 0.16mmol) in DMF (1.5ml) was treated with CDI (26mg, 0.16mmol) and left to react for 45min. (1*Z*)-4-(3-Butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)-*N*-hydroxybutanimidamide (60mg, 0.18mmol) was added and the mixture heated in the microwave at 140°C for 15min. After cooling, the reaction was partitioned between 2M HCl (aq) and EtOAc. The organic layer was separated then concentrated and purified by MDAP. The title compound was obtained as a white solid (10mg, 12%).
LC/MS: m/z 477 $[MH]^+$, RT 3.2min.

Example 158 : 8-chloro-3-pentyl-1-[4-(5-phenyl-1,2,4-oxadiazol-3-yl)butyl]-3,7-dihydro-1H-purine-2,6-dione

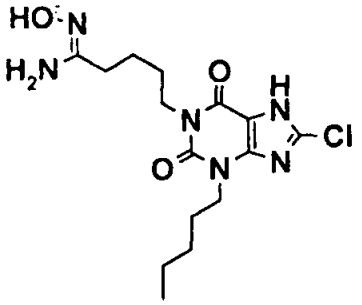
a) Preparation of 8-chloro-3-pentyl-1-[4-(5-phenyl-1,2,4-oxadiazol-3-yl)butyl]-3,7-dihydro-1H-purine-2,6-dione



Benzoic acid (18mg, 0.15mmol) was treated with a solution of 1H-1,2,3-benzotriazol-1-ol hydrate (25mg, 0.19mmol) in DMSO (0.3ml). To this was added a solution/suspension of N-[3-(dimethylamino)propyl]-N'-ethylcarbodiimide hydrochloride (29mg, 0.15mmol) in DMSO (0.3ml) followed by a solution of 5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-hydroxypentanimidamide (55mg, 0.15mmol) in DMSO (0.3ml). The mixture was heated at 40°C for 1h, then at 80°C for 5h and then cooled. The mixture was subjected to purification by MDAP. Product-containing fractions were blown to dryness by a stream of nitrogen to yield the title compound as a white solid (17.2mg, 25%).
LC/MS: m/z 457 $[MH]^+$, RT 3.67min.

^{1}H NMR ($CDCl_3$) δ: 0.90 (t, 3H, J = 6.8Hz), 1.35 (m, 4H), 1.76 (m, 2H), 1.89 (m, 4H), 2.88 (t, 2H, J = 7.2Hz), 4.08 (t, 2H, J = 7.5Hz), 4.17 (t, 2H, J = 6.7Hz), 7.50 (m, 2H), 7.57 (m, 1H), 8.08, (d, 2H, J = 7.3Hz).

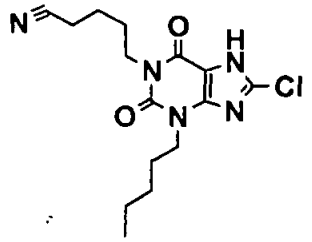
b) 5-(8-Chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-hydroxypentanimidamide



A solution of 5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)pentanenitrile (3.0g, 8.9mmol) in EtOH (30ml) was treated with water (15ml), potassium carbonate (1.48g, 10.7mmol) and hydroxylamine hydrochloride (0.74g, 10.7mmol)and then heated at 70°C overnight. A further potassium carbonate (1.5g, 10.9mmol) and hydroxylamine hydrochloride (1.0g, 14.5mmol) were cautiously added to the mixture which was then heated to 90°C for 24h. The mixture was cooled and concentrated *in vacuo* to remove most of the EtOH. The residual mixture was treated with water (30ml) and acidified to pH 7 by the cautious addition of 2M aqueous hydrochloric acid. The precipitated solid was filtered off, washed with water, then with diethyl ether and thoroughly dried to yield the title compound as a white solid (2.80g, 85%).

LC/MS: m/z 371 $[MH]^+$, RT 2.27min.

c) 5-(8-Chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)pentanenitrile

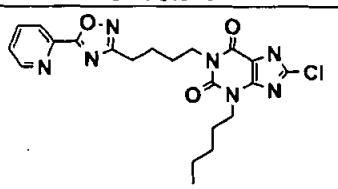
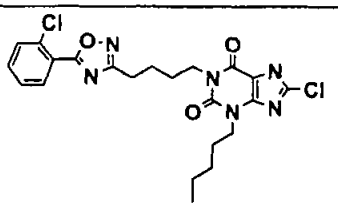
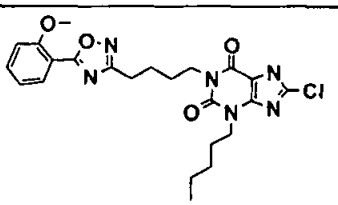
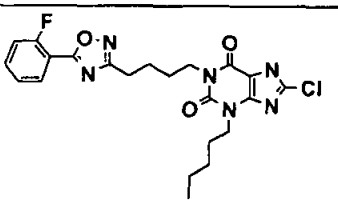


A solution of 8-chloro-3-pentyl-7-(2-propen-1-yl)-3,7-dihydro-1H-purine-2,6-dione (4.0g, 13.5mmol) in DMF (100ml) was treated with caesium carbonate (4.83g, 14.8mmol) and 5-bromopentanenitrile (1.73ml, 14.8mmol). The mixture was heated at 50°C in a nitrogen atmosphere for 19h and then cooled. The mixture was then degassed by the repeated successive application of a vacuum and then nitrogen pressure. The mixture was then treated with tetrakis(triphenylphosphine)palladium(0) (1.1g, 0.94mmol) and morpholine (11.8ml, 136mmol). The mixture was stirred in a nitrogen atmosphere for

3h and then partitioned between EtOAc and 2M aqueous hydrochloric acid. The organic layer was separated, washed with brine, dried ($MgSO_4$) and concentrated to reveal a yellow, oily residue. This was dissolved in MeOH, divided equally into four portions and each portion applied to a 20g aminopropyl SPE which was then washed through with MeOH. The desired product was eluted from the cartridge with a 5% v/v solution of AcOH in MeOH. The product-containing fractions were combined and concentrated to yield the title compound as a pale yellow solid (4.03g, 88%).
LC/MS: m/z 338 $[MH]^+$, RT 3.05min.

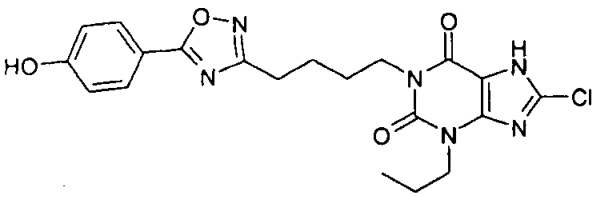
The following compounds were prepared using a method analogous to that for Example 158 (8-chloro-3-pentyl-1-[4-(5-phenyl-1,2,4-oxadiazol-3-yl)butyl]-3,7-dihydro-1H-purine-2,6-dione) from the corresponding acids:

Table 9

#	Structure	Name	Yield	LC/MS:
159		8-chloro-3-pentyl-1-{4-[5-(2-pyridinyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione	7.3mg (11%)	m/z 458 $[MH]^+$ RT 3.21 min
160		8-chloro-1-{4-[5-(2-chlorophenyl)-1,2,4-oxadiazol-3-yl]butyl}-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	12.8mg (17%)	m/z 491 $[MH]^+$ RT 3.77 min
161		8-chloro-1-(4-{5-[2-(methyloxy)phenyl]-1,2,4-oxadiazol-3-yl}butyl)-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	21.7mg (30%)	m/z 487 $[MH]^+$ RT 3.54 min
162		8-chloro-1-{4-[5-(2-fluorophenyl)-1,2,4-oxadiazol-3-yl]butyl}-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	16.6mg (23%)	m/z 475 $[MH]^+$ RT 3.62 min

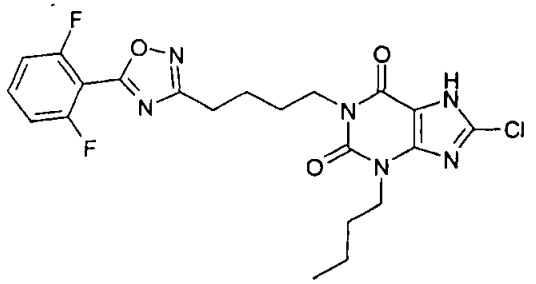
In addition Example **159**, 8-chloro-3-pentyl-1-{4-[5-(2-pyridinyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione has the following spectral data: ^1H NMR ($CDCl_3$) δ: 0.89 (t, 3H, J = 6.9Hz), 1.75 (m, 4H), 1.89 (m, 6H), 2.92 (t, 2H, J = 7.1Hz), 4.07 (t, 2H, J = 7.4Hz), 4.16 (t, 2H, J = 6.9Hz), 7.52 (m, 1H), 7.92 (m, 1H), 8.18 (m, 1H), 8.83 (m, 1H), 13.40 (br s, 1H).

Example 163: 8-Chloro-1-{4-[5-(4-hydroxyphenyl)-1,2,4-oxadiazol-3-yl]butyl}-3-propyl-3,7-dihydro-1*H*-purine-2,6-dione



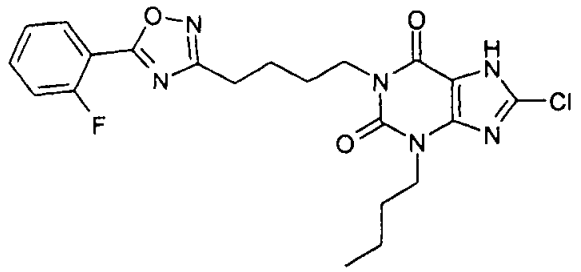
4-Hydroxybenzoic acid (18mg, 0.13mmol) and CDI (24mg, 0.15mmol) were stirred in anhydrous DMSO (0.9ml) at rt for 1h. (1*Z*)-5-(8-Chloro-2,6-dioxo-3-propyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)-*N*-hydroxypentanimidamide (50mg, 0.15mmol; prepared in a manner similar to (1*Z*)-5-(8-Chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)-*N*-hydroxypentanimidamide as described in Example 158(b)) was added and the mixture was stirred at 90°C for 2h. The reaction mixture was purified by MDAP. The product fraction was combined and concentrated under high vacuum to give the title compound as a white solid (7mg, 11%).
LC/MS: m/z 443 $[MH]^+$, RT 3.28min.

Example 164 : 3-Butyl-8-chloro-1-{4-[5-(2,6-difluorophenyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione



2,6-Difluorobenzoic acid (40mg, 0.25mmol) and CDI (45mg, 0.28mmol) were stirred in anhydrous DMSO (0.9ml) at rt for 1h. (1*Z*)-5-(3-Butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)-*N*-hydroxypentanimidamide (100mg, 0.28mmol) was added and the mixture was stirred at 90°C for 16h. The reaction mixture was purified by MDAP. The product fraction was combined and concentrated to give the title compound as a white solid (18mg, 15%).
LC/MS: m/z 479 $[MH]^+$, RT 3.40min.

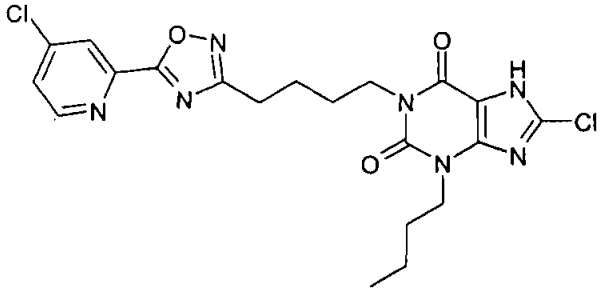
Example 165 : 3-Butyl-8-chloro-1-{4-[5-(2-fluorophenyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione



2-Fluorobenzoic acid (36mg, 0.25mmol) and CDI (45mg, 0.28mmol) were stirred in anhydrous DMSO (0.9ml) at rt for 1h. (1Z)-5-(3-Butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)-*N*-hydroxypentanimidamide (100mg, 0.28mmol) was added and the mixture was stirred at 90°C for 16h. The mixture was purified by MDAP. The product fraction was combined and concentrated to give the title compound as a white solid (33mg, 29%).

LC/MS: m/z 461 $[MH]^+$, RT 3.44min.

Example 166 : 3-Butyl-8-chloro-1-{4-[5-(4-chloro-2-pyridinyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione

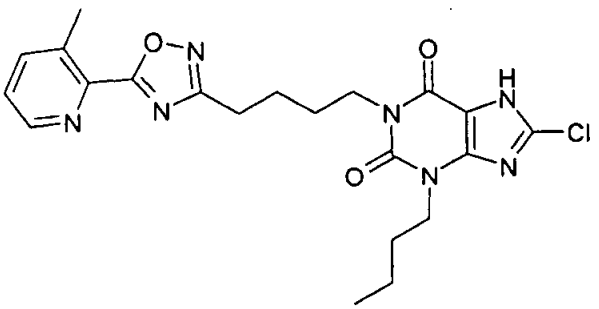


4-Chloro-2-pyridinecarboxylic acid (40mg, 0.25mmol) and CDI (45mg, 0.28mmol) were stirred in anhydrous DMSO (0.9ml) at rt for 1h. (1Z)-5-(3-Butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)-*N*-hydroxypentanimidamide (100mg, 0.28mmol) was added and the mixture was stirred at 90°C for 16h. The reaction mixture was purified by MDAP. The product fraction was combined and concentrated to give the title compound as a white solid (13mg, 11%).

LC/MS: m/z 478 $[MH]^+$, RT 3.31min.

^1H NMR (DMSO-d_6) δ_H 14.4 (br. s, 1H), 8.79 (d, 1H, J=6Hz), 8.24 (d, 1H, J=2Hz), 7.88 (dd, 1H, J=6Hz & 2Hz), 3.91 (m, 4H), 2.85 (t, 2H, J=7.5Hz), 1.56-1.76 (m, 6H), 1.28 (m, 2H), 0.87 (t, 3H, J=7.5Hz) ppm.

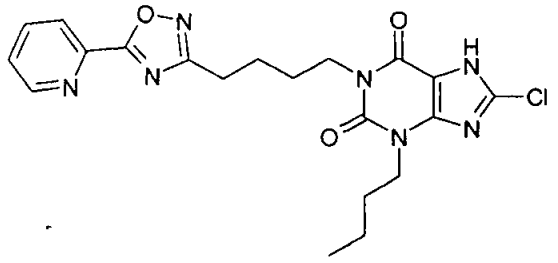
Example 167 : 3-Butyl-8-chloro-1-{4-[5-(3-methyl-2-pyridinyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione



3-Methyl-2-pyridinecarboxylic acid (35mg, 0.25mmol) and CDI (45mg, 0.28mmol) were stirred in anhydrous DMSO (0.9ml) at rt for 1h. (1Z)-5-(3-Butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)-*N*-hydroxypentanimidamide (100mg, 0.28mmol) was added and the mixture was stirred at 90°C for 16h. The reaction mixture was purified by MDAP. The product fraction was combined and concentrated to give the title compound as a white solid 14mg, 12%).
LC/MS: m/z 458 $[MH]^+$, RT 3.13min.

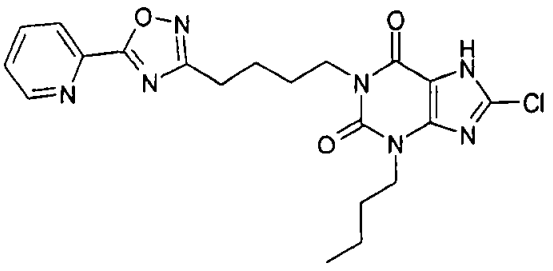
Example 168 : 3-Butyl-8-chloro-1-{4-[5-(2-pyridinyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione

Method A



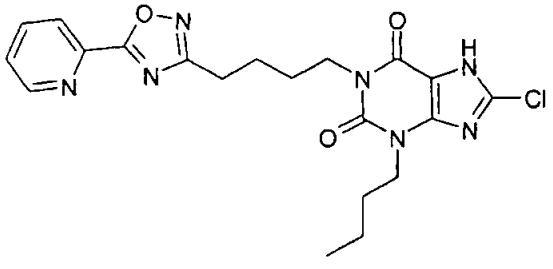
2-Pyridinecarboxylic acid (31mg, 0.25mmol) and CDI (45mg, 0.28mmol) were stirred in anhydrous DMSO (0.5ml) at rt for 1h. A solution of (1Z)-5-(3-Butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)-*N*-hydroxypentanimidamide (100mg, 0.28mmol) in DMSO (0.4ml) was added and the mixture was stirred at 90°C for 16h. The reaction mixture was purified directly by MDAP. The product fractions were combined and concentrated to give the title compound as a white solid (14mg, 12%).
LC/MS: m/z 444 $[MH]^+$, RT 3.01min.
^{1}H NMR (DMSO-d_6) δ: 0.87 (t, 3H, J = 7 Hz), 1.27 (m, 2H), 1.65 (m, 6H), 2.84 (t, 2H, J = 7 Hz), 3.91 (m, 4H), 7.70 (dd 1H, J = 5 & 7Hz), 8.07 (m, 1H), 8.19 (d, 1H, J = 8Hz), 8.81 (d, 1H, J = 5Hz), 14.5 (br. s, 1H).

Method B



2-Pyridinecarboxylic acid (675mg, 5.3mmol) and CDI (909mg, 5.6mmol) were stirred in anhydrous DMF (30ml) at rt under nitrogen for 90mins. (1*Z*)-5-(3-Butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)-*N*-hydroxypentanimidamide (2.0g, 5.6mmol) and DMF (10ml) were added and the mixture was stirred at 100°C for 20h. The reaction mixture was cooled to rt then partitioned between sat. NH_4Cl(aq) solution and EtOAc. The organic layer was separated, and the aqueous solution extracted with EtOAc. The combined extracts were washed with brine, dried $MgSO_4$ and concentrated giving an orange liquid. This was purified using the Companion™ system giving two identical white solids (649mg; 240mg).
LC/MS: m/z 444 $[MH]^+$, RT 3.04min.

Method C



A 12-L, round-bottom flask was equipped with an overhead, mechanical stirrer, a temperature probe with a J-KEM temperature controller, a condenser and a nitrogen inlet adapter. The flask was charged with picolinic acid (0.180 kg, 1.46 mol), MIBK (4.0 L), 1,1'-carbonyldiimidazole (0.23 kg, 1.42 mol,) and more MIBK (0.66 L). The mixture was stirred and warmed to 50 °C over approximately 1 hour, and the temperature overshot to 56 °C. The solids dissolved during the heat up to 50 °C and carbon dioxide was generated. After 1 hour at 50 °C, (1*Z*)-5-(3-Butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)-*N*-hydroxypentanimidamide (0.467 kg, 1.31 mol) was added to the reaction. The mixture was then warmed to 90 °C over 1 hour. HPLC analysis of the reaction after heating at 90 °C for 5.5 hours indicated that the reaction was complete. The heat was turned off, and 1.0 N hydrochloric acid solution (2.33 L) was added. The temperature dropped to 61 °C. After stirring overnight, the product precipitated and was filtered. The filtercake was washed with water (1 x 2.23 L, 1 x 2.43 L) and heptanes (1.40 L). The wet cake was dried in a vacuum oven at 50 °C for 22 hours to give 396 g of product (68%) HPLC analysis 97.7% (AUC) t_R = 18.6 min.

Method D

Formation of 3-Butyl-8-chloro-1-{4-[5-(2-pyridinyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione Form 1

The reaction vessel was charged with 3-Butyl-8-chloro-1-{4-[5-(2-pyridinyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione (1wt), acetone (20vol) and water (0.6vol). The mixture was stirred and warmed to 50-60 °C and agitated for a minimum of 1 hour. A solution was formed which is clarified at this temperature by filtration through a 1micron filter into a 2nd reaction vessel. The solution was cooled over approximately 3 hours to 33-38°C and seeded at this temperature with 3-Butyl-8-chloro-1-{4-[5-(2-pyridinyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione (Form 1, 0.01wt). The thin suspension was agitated at this temperature for a minimum of 1hour then cooled to 20-25°C and held at this temperature for a minimum of 12hours. The suspension thus formed was cooled to 13-17°C and held at this temperature for a minimum of 1hour. The suspension was then sampled*, and the solid collected by filtration in the laboratory. The solid was dried and analysed by xrpd/DSC to check form. If the form is as required (Form 1) the batch is filtered, washed (2x3vol acetone) and dried in a vacuum oven at 50°C. The batch is offloaded once analysis shows solvent levels (acetone, water) to be at acceptable.

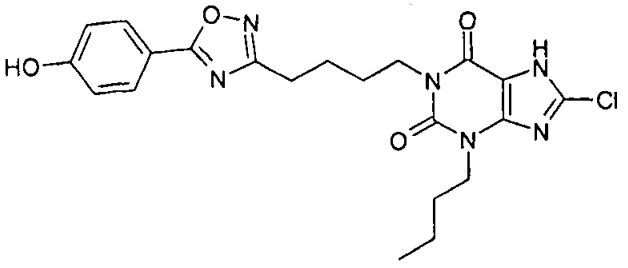
Expected yield (75-80%w/w).

If the form of the sample taken at * is shown to be other than pure Form 1, then **the batch is reheated to 35-45°C and agitated at this temperature for a minimum of 1hour. The thin suspension is then cooled to 20-25°C and held at this temperature for a minimum of 12hours. The suspension thus formed is then cooled to 13-17°C and held at this temperature for a minimum of 1hour. The suspension is then sampled, and the solid collected by filtration in the laboratory. The solid is dried and analysed by xrpd/DSC to check form. If the form is as required (Form 1) the batch is filtered, washed and dried as described previously. If the form is not pure Form 1, then the cycle from ** is repeated until a satisfactory result is obtained.

X-Ray Powder Diffraction (XRPD)

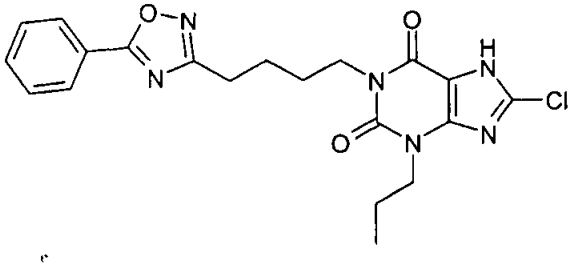
X-ray powder diffraction (XRPD) data are shown in Figures 1-3. The data were acquired on a PANalytical X'Pert Pro powder diffractometer, model PW3040/60, serial number DY1850 using an X'Celerator detector. The acquisition conditions were: radiation: Cu Kα, generator tension: 40 kV, generator current: 45 mA, start angle: 2.0°2θ, end angle: 40.0°2 θ, step size: 0.0167 °2 θ, time per step: 31.75 seconds. The samples were prepared by mounting a few milligrams of sample on a Si wafer (zero background) plates, resulting in a thin layer of powder.

Example 169: 3-Butyl-8-chloro-1-{4-[5-(4-hydroxyphenyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione



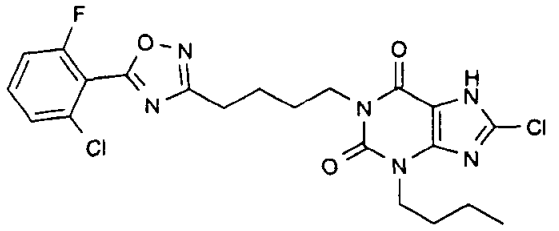
4-Hydroxybenzoic acid (35mg, 0.25mmol) and CDI (45mg, 0.28mmol) were stirred in anhydrous DMSO (0.9ml) at rt for 1h. (1*Z*)-5-(3-Butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)-*N*-hydroxypentanimidamide (100mg, 0.28mmol) was added and the mixture was stirred at 90°C for 16h. The mixture was purified by MDAP to give the title compound as a white solid (5mg, 4%).
LC/MS: m/z 459 $[MH]^+$, RT 3.24min.

Example 170 : 8-Chloro-1-[4-(5-phenyl-1,2,4-oxadiazol-3-yl)butyl]-3-propyl-3,7-dihydro-1*H*-purine-2,6-dione



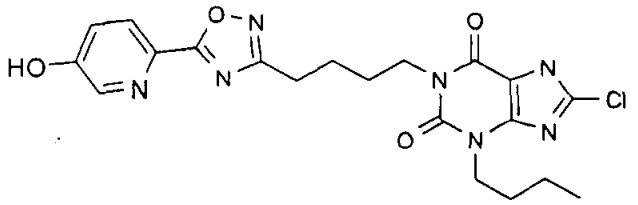
Benzoic acid (9mg, 0.074mmol) and CDI (13mg, 0.081mmol) were stirred in anhydrous DMSO (0.9ml) at rt for 1h. (1*Z*)-5-(8-Chloro-2,6-dioxo-3-propyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)-*N*-hydroxypentanimidamide (28mg, 0.081mmol) was added and the mixture was stirred at 80°C for 4h. The mixture was purified by MDAP to give the title compound as a white solid (0.6mg, 2%).
LC/MS: m/z 429 $[MH]^+$, RT 3.21min.
^{1}H NMR (MeOH-d_4) δ: 0.93 (t, 3H, J = 7.5Hz), 1.74 (m, 4H), 1.84 (m, 2H), 2.84 (t, 2H, J = 7Hz), 3.97 (t, 2H, J = 7.5Hz), 4.08 (t, 2H, J = 7Hz), 7.57 (dd, 2H, J = 7 & 7.5Hz), 7.65 (dd, 1H, J = 7 & 7.5Hz), 8.08 (d, 2H, J = 7.5Hz).

Example 171: 3-Butyl-8-chloro-1-{4-[5-(2-chloro-6-fluorophenyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione



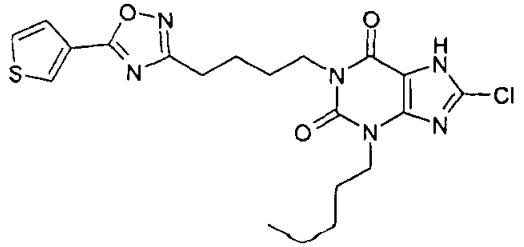
2-Chloro-6-fluorobenzoic acid (44mg, 0.25mmol) and CDI (45mg, 0.28mmol) were stirred in anhydrous DMSO (0.9ml) at rt for 1h. (1*Z*)-5-(3-Butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)-*N*-hydroxypentanimidamide (100mg, 0.28mmol) was added and the mixture was stirred at 90°C for 16h. The mixture was purified by MDAP. The product fraction was combined and concentrated to give the title compound as a white solid (6.4mg, 5%).
LC/MS: m/z 495 $[MH]^+$, RT 3.58min.

Example 172: 3-Butyl-8-chloro-1-{4-[5-(5-hydroxy-2-pyridinyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione



5-Hydroxy-2-pyridinecarboxylic acid (24mg, 0.17mmol) and CDI (31mg, 0.19mmol) were stirred in anhydrous DMSO (0.9ml) at rt for 1h. (1*Z*)-5-(3-Butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)-*N*-hydroxypentanimidamide (68mg, 0.19mmol) was added and the mixture was stirred at 90°C for 16h. The mixture was purified by MDAP and the product fractions concentrated to give the title compound as a white solid (19mg, 24%).
LC/MS: m/z 459 $[MH]^+$, RT 3.03min.

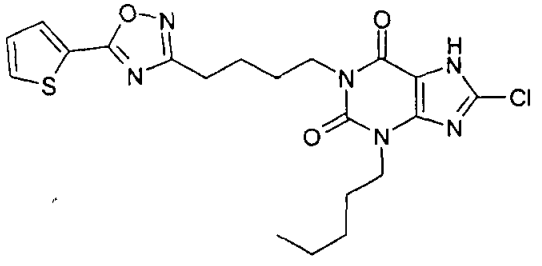
Example 173: 8-Chloro-3-pentyl-1-{4-[5-(3-thienyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione



A solution of (1*Z*)-5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)-*N*-hydroxypentanimidamide (50mg, 0.13mmol) in EtOH (1ml) was treated with a 21%

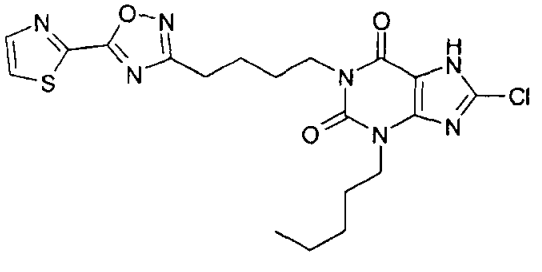
solution of NaOEt in EtOH (55µl, 0.21mmol) and ethyl 3-thiophenecarboxylate (18µl, 0.13mmol). The mixture was heated in the microwave at 150°C for 10min. After cooling, the reaction was partitioned between 2M HCl (aq) and EtOAc. The organic layer was separated and the aqueous extracted again with EtOAc. The combined extracts were concentrated and purified by the MDAP. The title compound was obtained as an off-white solid (20mg, 32%).
LC/MS: m/z 463 $[MH]^+$, RT 3.6min.

Example 174 : 8-Chloro-3-pentyl-1-{4-[5-(2-thienyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione



2-Thiophenecarboxylic acid (14mg, 0.11mmol) was dissolved in NMP (0.9ml) and treated with CDI (18mg, 0.11mmol). After 1h, (1*Z*)-5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)-*N*-hydroxypentanimidamide (50mg, 0.13mmol) was added and the mixture heated in the microwave at 150°C for 15min. The solution was directly purified by MDAP to obtain the title compound which was then freeze dried from 1,4-dioxane to give the title compound as a white solid (19mg, 31%).
LC/MS: m/z 463 $[MH]^+$, RT 3.5min.

Example 175: 8-Chloro-3-pentyl-1-{4-[5-(1,3-thiazol-2-yl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione

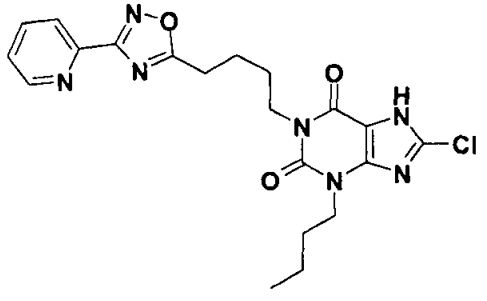


A solution of (1*Z*)-5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)-*N*-hydroxypentanimidamide (50mg, 0.13mmol) in EtOH (1.5ml) was treated with a 21% solution of NaOEt in EtOH (50µl, 0.13mmol) and ethyl 1,3-thiazole-2-carboxylate (18mg, 0.11mmol). The mixture was heated in the microwave at 170°C for 10min. After cooling, the reaction was partitioned between 2M HCl (aq) and EtOAc. The organic layer was separated then concentrated and purified by the MDAP. The title compound was obtained as a white solid (13mg, 21%).

LC/MS: m/z 464 $[MH]^+$, RT 3.3min.
^{1}H NMR (DMSO-d_6) δ: 0.83 (t, 3H, J = 7Hz), 1.21-1.32 (m, 4H), 1.60-1.77 (m, 6H), 2.84 (t, 2H, J = 7Hz), 3.91 (m, 4H), 8.23 (d, 1H, J = 3Hz), 8.27 (d, 1H, J = 3Hz),14.4 (br s, 1H).

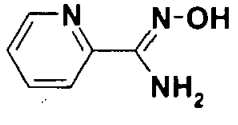
Example 176: 3-butyl-8-chloro-1-{4-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione

a) Preparation of 3-butyl-8-chloro-1-{4-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione



To a mixture of ethyl 5-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)pentanoate (120mg, 0.32mmol) and of N-hydroxy-2-pyridinecarboximidamide (50mg, 0.36mmol) in EtOH (2ml) was added a 21% (w/v) solution of sodium ethoxide in EtOH (0.225ml, 0.62mmol) and then heated in a sealed vial in a microwave oven at 140°C for 10min. The cooled mixture was evaporated to dryness and the residue partitioned between chloroform (5ml) and saturated aqueous ammonium chloride (5ml). The organic phase was evaporated to dryness and the crude product subjected to purification by MDAP. Product containing fractions were combined and evaporated to dryness. The product was triturated to a solid in a small amount of diethyl ether then dried to reveal the title compound as a white solid (44mg, 31%).
LC/MS: m/z 444 $[MH]^+$, RT 3.03min.
^{1}H NMR ($CDCl_3$) δ: 0.96 (t, 3H, J = 7.3Hz), 1.40 (m, 2H), 1,74 (m, 2H), 1.88 (m, 2H), 1.99 (m, 2H), 3.07 (t, 2H, J = 7.5Hz), 4.09 (t, 2H, J = 7.5Hz), 4.17 (t, 2H, J = 7.0Hz), 7.43 (m, 1H), 7.64 (m, 1H), 8.10 (m, 1H), 8.79 (m, 1H).

b) Preparation of N-hydroxy-2-pyridinecarboximidamide



To a mixture of 2-pyridinecarbonitrile (3g, 29mmol) and potassium carbonate (4.1g, 30mmol)in EtOH (30ml) was added water (15ml) and, cautiously, hydroxylamine hydrochloride (2.9g, 42mmol) and then heated at reflux for 6h, cooled and evaporated

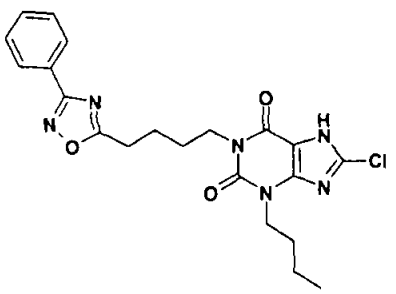
to dryness. The residue was treated with water (100ml) and the suspended solid product filtered off, washed with water and dried to yield the title compound as a white solid (2.28g, 57%).

^{1}H NMR (DMSO-d_6) δ: 5.85 (br s, 2H), 7.40 (m, 1H), 7.79 (m, 1H), 7.86 (m, 1H), 8.55 (m, 1H), 9.92 (s, 1H)

Example 177: 3-Butyl-8-chloro-1-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)butyl]-3,7-dihydro-1*H*-purine-2,6-dione

Method A

a) 3-Butyl-8-chloro-1-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)butyl]-3,7-dihydro-1*H*-purine-2,6-dione

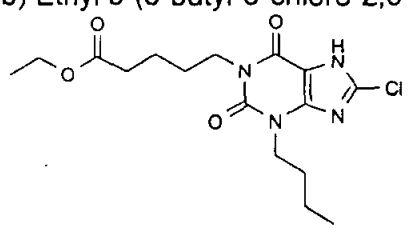


Ethyl 5-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)pentanoate (74mg, 0.2mmol) and benzamidoxime (30mg, 0.22mmol) were suspended in dry EtOH (1ml) and ethanolic sodium ethoxide (21% by wt., 0.111ml, 0.3mmol) was added. The mixture was gently warmed until solids were dissolved and then heated in the microwave reactor at 140°C for 10min. The mixture was then partitioned between EtOAc and 2M HCl and the organic phase dried (Na_2SO_4) and evaporated. MDAP afforded the pure title compound (40.7mg).

LC/MS: m/z 443 $[MH]^+$, RT 3.67min.

^{1}H NMR (DMSO-d_6) δ: 0.89 (t, 3H, J = 7Hz), 1.22-1.34 (m, 2H), 1.57-1.75 (m, 4H), 1.75-1.86 (m, 2H), 3.05 (t, 2H, J = 7 Hz), 3.88-3.98 (m, 4H), 7.52-7.63 (m, 3H), 7.95-8.0 (m, 2H).

b) Ethyl 5-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)pentanoate



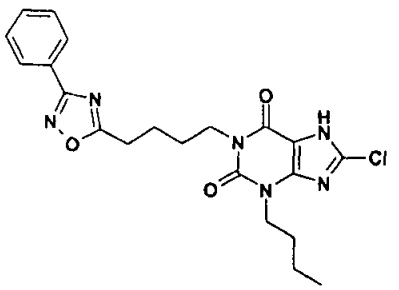
To 3-butyl-8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (1.5g, 5.31mmol) in dry DMF (25ml) was added Cs_2CO_3 (1.905g, 5.84mmol), followed by ethyl 5-bromovalerate (1.46g, 6.99mmol). The mixture was heated at 55°C for 18h then allowed to cool. It was degassed by repeatedly evacuating and readmitting nitrogen,

then morpholine (3.70ml, 42.5mmol) and tetrakis(triphenylphosphine)palladium(0) (1.0g, 0.865mmol) were added and the mixture stirred for 5h. EtOAc (75ml), 2M HCl (40ml) and water (20ml) were added and the organic phase was separated, washed with brine (3 x 25ml), filtered to remove some insoluble yellow solid, dried (Na_2SO_4) and evaporated. The residue (2.5g) was purified by aminopropyl SPE (20g), loading in THF-MeOH (1:1), washing with MeOH and eluting the product with DCM-MeOH (1:1) containing 5% added AcOH to afford the title compound (1.53g).
LC/MS:, m/z 371 MH^+, RT 3.18min

140

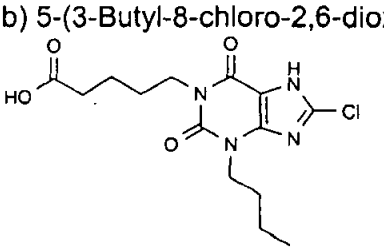
Method B

a) 3-Butyl-8-chloro-1-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)butyl]-3,7-dihydro-1*H*-purine-2,6-dione



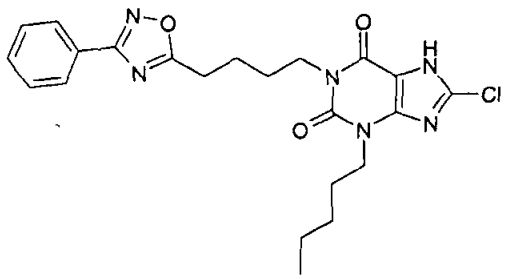
CDI (0.98g, 6.1mmol) was added to a solution of 5-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)pentanoic acid (1.89g, 5.5mmol) in DMF (15ml) and stirred under nitrogen for 1.5h. Benzamidoxime (0.91g, 6.1mmol) was added and the mixture stirred at 110°C overnight. The reaction mixture was partitioned between EtOAc and 2M HCl. The organic layer was separated, washed with brine, dried ($MgSO_4$) and evaporated. The crude product was crystallised from methanol and then further purified using the Companion™ system and a gradient elution from cyclohexane to EtOAc. Product containing fractions were combined and evaporated to give the title compound as a white solid (850mg).
LC/MS: m/z 443 $[MH]^+$, RT 3.52min.
^{1}H NMR (MeOH-d_4) δ: 0.94 (t, 3H, J = 7.5Hz), 1.31-1.41 (m, 2H), 1.65-1.73 (m, 2H), 1.75-1.83 (m, 2H), 1.87-1.96 (m, 2H), 3.04 (t, 2H, J = 7.5Hz), 4.01 (t, 2H, J = 7.5Hz), 4.06 (t, 2H, J = 7Hz), 7.46-7.55 (m, 3H), 7.98-8.02 (m, 2H).

b) 5-(3-Butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)pentanoic acid



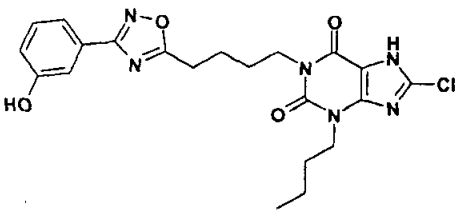
A mixture of ethyl 5-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)pentanoate (2.8g, 7.55mmol), LiOH (542mg, 22.7mmol), water (2.5ml) and methanol (50ml) was stirred at rt for for 60h. The mixture was portioned between water and EtOAc and the pH of the aqueous phase adjusted to pH 4-5. The organic layer was separated, washed with brine, dried ($MgSO_4$) and evaporated to give the title compound as a white solid (2.18g).
LC/MS: m/z 343 $[MH]^+$, RT 2.69min.

Example 178 : 8-Chloro-3-pentyl-1-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)butyl]-3,7-dihydro-1*H*-purine-2,6-dione



A mixture of methyl 5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)pentanoate (50mg, 0.13mmol), benzamidine oxime (20mg, 0.15mmol) and a 21% solution of NaOEt in EtOH (76µl, 0.20mmol) in EtOH (1.5ml) was heated in the microwave at 140°C for 10min. After cooling the reaction was partitioned between 2M HCl (aq) and EtOAc. The organic layer was separated, dried ($MgSO_4$) and concentrated. Purification by the MDAP gave the title compound as a white solid (25mg, 41%).
LC/MS: m/z 457 $[MH]^+$, RT 3.7min.
^{1}H NMR (DMSO-d_6) δ: 0.82 (t, 3H, J = 7 Hz), 1.25 (m, 4H), 1.66 (m, 4H), 1.79 (m, 2H), 3.04 (t, 2H, J = 7Hz), 3.92 (4H,m), 7.57 (m, 3H), 7.97 (m, 2H), 14.5 (br s, 1H).

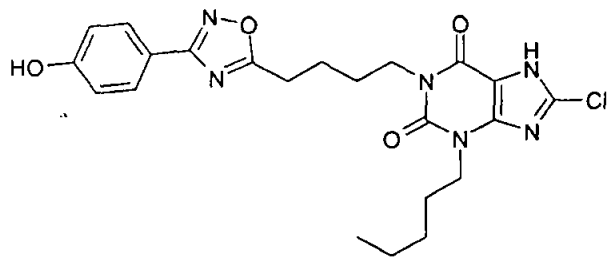
Example 179: 3-Butyl-8-chloro-1-{4-[3-(3-hydroxyphenyl)-1,2,4-oxadiazol-5-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione



A mixture of ethyl 5-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)pentanoate (50mg, 0.13mmol), *N*,3-dihydroxybenzenecarboximidamide (25mg, 0.16mmol), 21% solution of NaOEt in EtOH (55µl, 0.15mmol) and EtOH (1.5ml) was heated in the microwave at 180°C for 10min. Another aliquot of 21% solution of NaOEt in EtOH (55µl, 0.21mmol) was added and the mixture heated in the microwave at

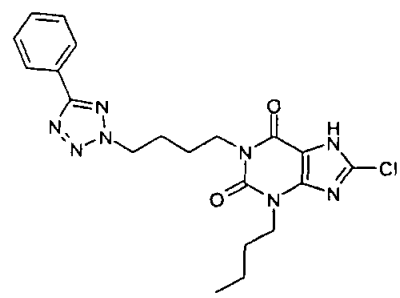
175°C for 30min. After cooling the reaction was partitioned between 2M HCl (aq) and EtOAc. The organic layer was separated, concentrated and purified by the MDAP. The title compound was obtained as an off-white solid (20mg, 32%).
LC/MS: m/z 459 $[MH]^+$, RT 3.3min.

Example 180 : 8-Chloro-1-{4-[3-(4-hydroxyphenyl)-1,2,4-oxadiazol-5-yl]butyl}-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione



A solution of 5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)pentanoic acid (50mg, 0.14mmol) in DMF (2ml) was treated with CDI (23mg, 0.14mmol) and stirred at rt for 30min. *N*,4-dihydroxybenzenecarboximidamide (26mg, 0.17mmol) was added and the mixture heated in the microwave at 120°C for 15min. After cooling the reaction was partitioned between 2M HCl (aq) and EtOAc. The organic layer was separated, concentrated and purified by the MDAP. The title compound was obtained as an off-white solid (17mg, 26%).
LC/MS: m/z 473 $[MH]^+$,RT 3.5min.

Example 181: 3-Butyl-8-chloro-1-[4-(5-phenyl-2*H*-tetrazol-2-yl)butyl]-3,7-dihydro-1*H*-purine-2,6-dione



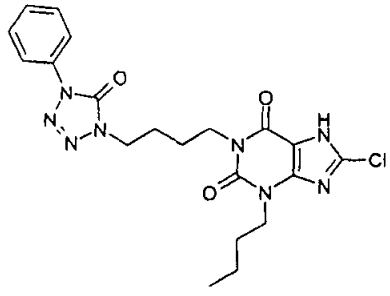
A mixture of 4-[3-butyl-8-chloro-2,6-dioxo-7-(2-propen-1-yl)-2,3,6,7-tetrahydro-1*H*-purin-1-yl]butyl methanesulfonate (50mg, 0.12mmol), Cs_2CO_3 (45mg, 0.14mmol) and DMF (3ml) was treated with 5-phenyl-1*H*-tetrazole (20mg, 0.14mmol) and stirred for 60h at 50°C. After cooling, the mixture was degassed by applying a vacuum and then nitrogen was introduced. $Pd(PPh_3)_4$ (20mg, 0.017mmol) was added and the mixture degassed once more. Morpholine (150µl, 1.7mmol) was added and the mixture was stirred under nitrogen for 18h, then partitioned between 2M HCl (aq) and EtOAc. The organic layer was separated and the aqueous layer extracted again with EtOAc. The

combined extracts were concentrated, giving a yellow residue. MeOH was added and then passed down an NH_2-propyl column with the product eluting with 2% AcOH/MeOH. Further purification by MDAP gave the title compound as an off-white solid (15mg, 29%).

LC/MS: m/z 443 $[MH]^+$, RT 3.4min.

^{1}H NMR (DMSO-d_6) δ: 0.86 (t, 3H, J = 7Hz), 1.26 (m, 2H), 1.59 (m, 4H), 1.97 (m, 2H), 3.90 (m, 4H), 4.76 (t, 2H, J = 7Hz), 7.54 (m, 3H), 8.02 (m, 2H), 14.4 (br s, 1H).

Example 182 : 3-Butyl-8-chloro-1-[4-(5-oxo-4-phenyl-4,5-dihydro-1H-tetrazol-1-yl)butyl]-3,7-dihydro-1H-purine-2,6-dione



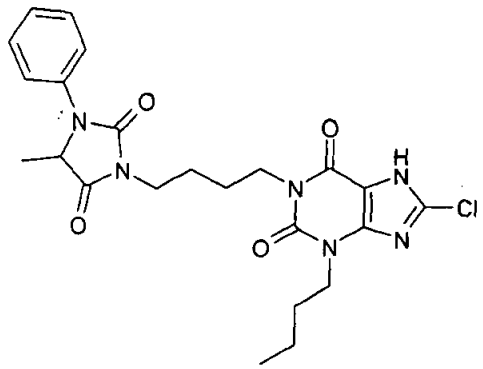
A mixture of 4-[3-butyl-8-chloro-2,6-dioxo-7-(2-propen-1-yl)-2,3,6,7-tetrahydro-1*H*-purin-1-yl]butyl methanesulfonate (50mg, 0.12mmol), Cs_2CO_3 (45mg, 0.14mmol) and DMF (3ml) was treated with 1-phenyl-1,2-dihydro-5*H*-tetrazol-5-one (23mg, 0.14mmol) and stirred for 60h at 50°C. After cooling, the mixture was degassed by applying a vacuum and then nitrogen was introduced. $Pd(PPh_3)_4$ (20mg, 0.017mmol) was added and the mixture degassed once more. Morpholine (150µl, 1.7mmol) was added and the mixture was stirred under nitrogen for 18h, then partitioned between 2M HCl (aq) and EtOAc. The organic layer was separated and the aqueous layer extracted again with EtOAc. The combined extracts were concentrated, giving a yellow residue. MeOH was added and then passed down an aminopropyl column with the product eluting with 2% AcOH/MeOH. Further purification by MDAP gave the title compound as an off-white solid (27mg, 51%). NB. ca. 10% O-alkylated material present.

LC/MS: m/z 459 $[MH]^+$, RT 3.1min.

^{1}H NMR (DMSO-d_6) δ: 0.88 (t, 3H, J = 7Hz), 1.28 (m, 2H), 1.62 (m, 4H), 1.79 (m, 2H), 3.91 (m, 4H), 4.03 (m, 2H), 7.44 (m, 1H), 7.57 (m, 2H), 7.85 (m, 2H), 14.5 (br s, 1H).

Example 183 : 3-Butyl-8-chloro-1-[4-(4-methyl-2,5-dioxo-3-phenyl-1-imidazolidinyl)butyl]-3,7-dihydro-1*H*-purine-2,6-dione

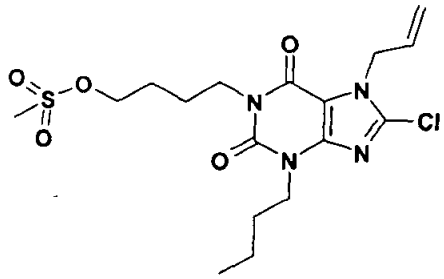
a)3-Butyl-8-chloro-1-[4-(4-methyl-2,5-dioxo-3-phenyl-1-imidazolidinyl)butyl]-3,7-dihydro-1*H*-purine-2,6-dione



A mixture of 4-[3-butyl-8-chloro-2,6-dioxo-7-(2-propen-1-yl)-2,3,6,7-tetrahydro-1*H*-purin-1-yl]butyl methanesulfonate (88mg, 0.20mmol), Cs_2CO_3 (80mg, 0.24mmol) and DMF (2ml) was treated with 5-methyl-1-phenyl-2,4-imidazolidinedione (46mg, 0.24mmol) and stirred for 18h at 70°C. After cooling, the mixture was degassed by applying a vacuum and then nitrogen was introduced. $Pd(PPh_3)_4$ (25mg, 0.022mmol) was added and the mixture degassed once more. Morpholine (174μL, 2.0mmol) was added and the mixture was stirred under nitrogen for 5h, then partitioned between 2M HCl (aq) and EtOAc. The organic layer was separated and the aqueous layer extracted again with EtOAc. The combined extracts were concentrated, giving a yellow residue. MeOH was added and then passed down an aminopropyl SPE with the product eluting with 2% AcOH/MeOH. Further purification by MDAP gave the title compound as a solid (70mg, 71%).

LC/MS: m/z 487 $[MH]^+$, RT 3.2min.

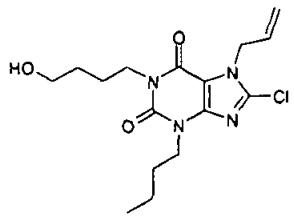
b) 4-[3-Butyl-8-chloro-2,6-dioxo-7-(2-propen-1-yl)-2,3,6,7-tetrahydro-1*H*-purin-1-yl]butyl methanesulfonate



A solution of 3-butyl-8-chloro-1-(4-hydroxybutyl)-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (1.30g, 3.66mmol) in DCM (10ml) was treated with triethylamine (0.77ml, 5.50mmol) followed by portionwise addition of methanesulfonic anhydride (702mg, 4.03mmol). CARE, effervescence. The reaction mixture was stirred at rt for 10min then partitioned between sat. $NaHCO_3$ (aq) solution and DCM. The organic layer was separated and washed with 1M HCl (aq) and then brine. It was dried ($MgSO_4$) and concentrated, giving the title compound as a viscous oil (1.60g, quant.).

LC/MS: m/z 433 $[MH]^+$, RT 3.3min.

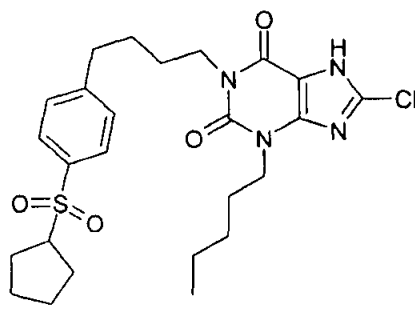
c) 3-Butyl-8-chloro-1-(4-hydroxybutyl)-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione



A stirred solution of 3-butyl-8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (5.0g, 17.7mmol) in DMF (100ml) was treated with Cs_2CO_3 (6.3g, 19.5mmol) and 4-bromo-1-butanol (3.0ml, 21.2mmol). The mixture was heated at 50°C for 5h then partitioned between 2M HCl (aq) and EtOAc. The organic layer was separated, washed with brine, dried ($MgSO_4$) and concentrated, giving a yellow solid. Purification by silica SPE (EtOAc/cyclohexane mixtures as the eluent) and then by the Companion™ system (IPA/DCM mixtures as the eluent) gave the title compound as a colourless oil (1.35g, 21%).

LC/MS: m/z 355 $[MH]^+$, RT 2.9min.

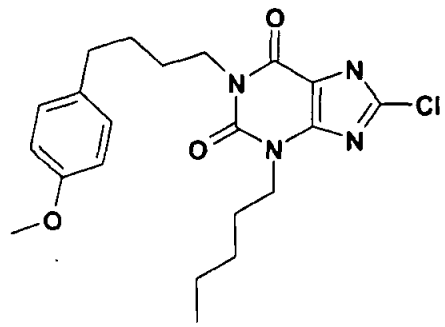
Example 184 : 8-Chloro-1-{4-[4-(cyclopentylsulfonyl)phenyl]butyl}-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione



8-Chloro-3-pentyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (100mg, 0.34mmol) was dissolved in DMF (1ml) and sequentially treated with 4-[4-(cyclopentylsulfonyl)phenyl]-1-butanol (105mg, 0.37mmol), PPh_3 (404µl of a 1M solution in DMF) and DBAD (404µl of a 1M solution in DMF). After stirring for 24h under nitrogen, the mixture was degassed by applying a vacuum and then nitrogen was introduced. $Pd(PPh_3)_4$ (39mg, 0.034mmol) was added and the mixture degassed once more. Morpholine (297µl, 3.4mmol) was added and the mixture was stirred under nitrogen for 63h, then partitioned between 2M HCl (aq) and EtOAc. The organic layer was separated, washed with brine, dried ($MgSO_4$) and concentrated, giving a yellow residue. MeOH was added and then passed down an aminopropyl SPE with the product eluting with 2% AcOH/MeOH. The product was further purified by MDAP giving the title compound as a beige solid (5mg, 3%).

LC/MS: m/z 521 $[MH]^+$, RT 3.7min.

Example 185 : 8-Chloro-1-{4-[4-(methyloxy)phenyl]butyl}-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione



A solution of 4-(4-bromobutyl)phenyl methyl ether (88mg, 0.36mmol) in DMF (3ml) was reacted with 8-chloro-3-pentyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (90mg, 0.30mmol) and Cs_2CO_3 (109mg, 0.33mmol) for 5h at 50°C. The mixture was degassed by applying a vacuum and then nitrogen was introduced. $Pd(PPh_3)_4$ (35mg, 0.030mmol) was added and the mixture degassed once more. Morpholine (0.26ml, 3.0mmol) was added and the mixture was stirred under nitrogen for 3h. Another aliquot of $Pd(PPh_3)_4$ (35mg, 0.030mmol) was added and left for a further 3h. The mixture was partitioned between 2M HCl (aq) and EtOAc. The organic layer was separated and the aqueous layer extracted again with EtOAc. The combined extracts were concentrated, giving a yellow residue. MeOH was added and then passed down an aminopropyl SPE with the product eluting with 3% AcOH/MeOH. The product was further purified by MDAP giving the title compound as a solid (2mg, 1.5%).

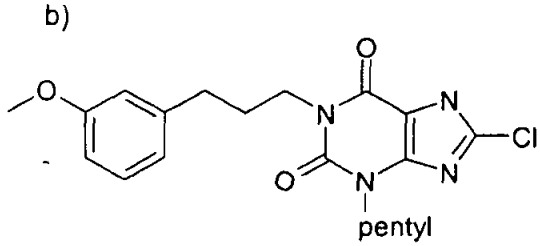
LC/MS: m/z 419 $[MH]^+$, RT 3.7min.

^1H NMR; (MeOH-d_4) δ: 0.90 (t, 3H, J = 7Hz), 1.28-1.40 (m, 4H), 1.57-1.75 (m, 6H), 2.57 (t, 2H, J = 7Hz), 3.73 (s, 3H), 3.97-4.02 (4H, m), 6.77 (m, 2H), 7.06 (m, 2H).

Example 186: 8-Chloro-3-pentyl-1-{3-[3-(methyloxy)phenyl]propyl}-3,7-dihydro-1H-purine-2,6-dione

a) 8-Chloro-3-pentyl-1-{3-[3-(methyloxy)phenyl]propyl}-3,7-dihydro-1H-purine-2,6-dione

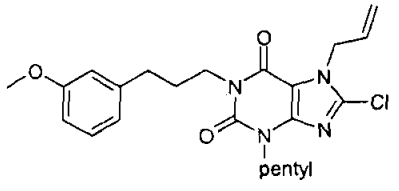
b)



8-Chloro-3-pentyl-1-{3-[3-(methyloxy)phenyl]propyl}-7-(2-propen-1-yl)-3,7-dihydro-1H-purine-2,6-dione (2.94g) was dissolved in anhydrous THF (40ml). The solution was

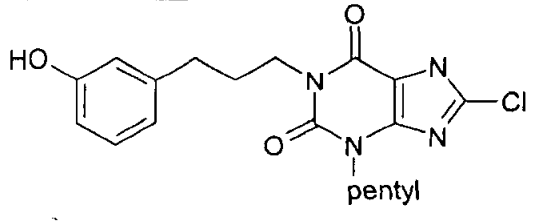
degassed using a nitrogen/vacuum purge 6 times. Tetrakis(triphenylphosphine) palladium (0.66g) was added followed by morpholine (5ml). After stirring for 18hr, the reaction mixture was diluted with EtOAc and was washed with 1N HCl and brine (x2), dried ($MgSO_4$) and evaporated *in vacuo*. This crude material was purified on an aminopropyl SPE (70g) eluting with MeOH then MeOH containing 3% AcOH to give the title compound as a pale yellow solid (1.56g).
LC/MS: m/z 405 $[MH]^+$, RT 3.51min.

b) 8-Chloro-3-pentyl-1-{3-[3-(methyloxy)phenyl]propyl}-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione



8-Chloro-3-pentyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (1.76g, 5.94mmol) and 3-[3-(methyloxy)phenyl]-1-propanol (1.00g, 6.04mmol) were dissolved in anhydrous THF (50ml) under an atmosphere of nitrogen. After 5min triphenylphosphine (1.87g, 7.12mmol) was added. After a further 5min di-tert-butyl azodicarboxylate (1.64g, 7.1mmol) was added. The solution was stirred for 20h at rt. The cloudy solution was concentrated *in vacuo* and purified on a 50g Silica II SPE (IST) using a Biotage FlashMaster™ Personal, eluting with cyclohexane /EtOAc 5:1 the appropriate fractions were concentrated *in vacuo* to give the title compound as a pale cream oil containing minor impurities(2.94g).
LC/MS:, m/z 445 $[MH]^+$, RT 3.88min.

Example 187 : 8-Chloro-1-[3-(3-hydroxyphenyl)propyl]-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione



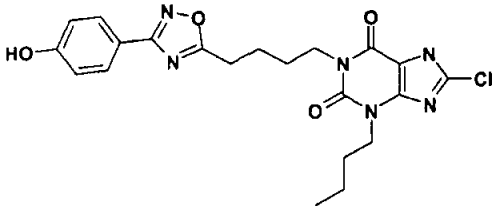
To a suspension of 8-chloro-3-pentyl-1-{3-[3-(methyloxy)phenyl]propyl}-3,7-dihydro-1H-purine-2,6-dione (1.52g, 3.86mmol) in anhydrous DCM (40ml) at -73°C was slowly added 1N borontribromide in DCM (4.6ml). The reaction mixture was stirred at -70°C for 2hours and then at rt for 96h. The reaction mixture was cooled in ice, and water (6.8ml) was added slowly. The reaction mixture was then diluted with EtOAc and water, and the organic phase was washed with saturated, sodium hydrogen carbonate (x3) and brine then dried ($MgSO_4$) and evaporated *in vacuo*. A portion of this crude material

(90mg) was purified by MDAP to give the title compound after freeze drying as a white solid (40mg).

LC/MS:, m/z 391 $[MH]^+$, RT 3.43min.

^1H NMR (DMSO-d_6) δ: 0.85 (t, 3H, J = 7Hz); 1.27 (m, 4H); 1.63 (m, 2H); 1.80 (m, 2H); 2.50 (m, 2H); 3.89 (m, 4H); 6.57 (m, 3H); 7.02 (t, 1H, J = 8Hz); 9.22 (s, 1H); 14.39 (s, 1H)

Example 188: 3-butyl-8-chloro-1-{4-[3-(4-hydroxyphenyl)-1,2,4-oxadiazol-5-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione

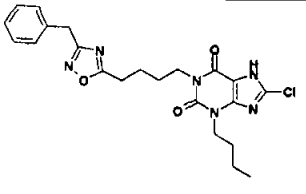


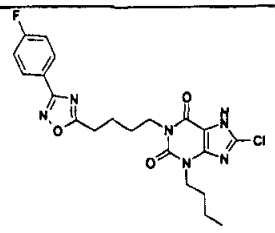
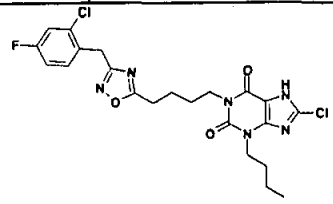
A stirred solution of 5-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)pentanoic acid (100mg, 0.29mmol) in DMF (4ml) was treated with CDI (52mg, 0.32mmol). After 1h, *N*,4-dihydroxybenzenecarboximidamide was added and the mixture heated at 100°C for 6h. On cooling, the reaction mixture was partitioned between 2M HCl (aq) and EtOAc. The organic layer was separated, washed with brine, dried (MgSO4) and concentrated. Purification by MDAP afforded the title compound as a pale grey solid (72mg).

LC/MS: m/z 459 $[MH]^+$, RT 3.27min.

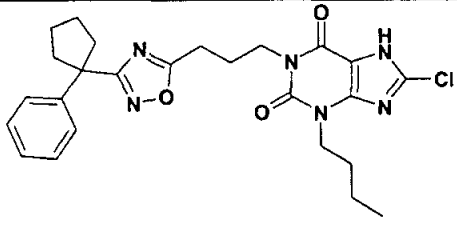
The following compounds (**Table 10**) were prepared using a method analogous to that for **Example 177**, using the appropriate amidoxime.

Table 10

Example	Structure	Yield (mg)	LC/MS
189	 3-butyl-8-chloro-1-{4-[3-(phenylmethyl)-1,2,4-oxadiazol-5-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	48.4	m/z 457 $[MH]^+$ RT 3.56min

190	 3-butyl-8-chloro-1-{4-[3-(4-fluorophenyl)-1,2,4-oxadiazol-5-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	35.8	m/z 461 $[MH]^+$ RT 3.74min
191	 3-butyl-8-chloro-1-(4-{3-[(2-chloro-4-fluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}butyl)-3,7-dihydro-1*H*-purine-2,6-dione	48.2	m/z 509 $[MH]^+$ RT 3.74min

Example 192: 3-Butyl-8-chloro-1-{3-[3-(1-phenylcyclopentyl)-1,2,4-oxadiazol-5-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione

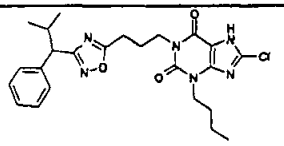
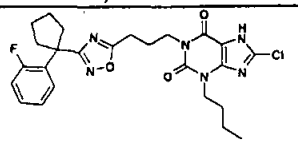
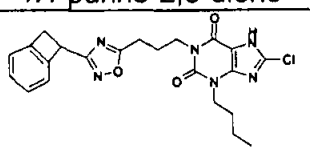
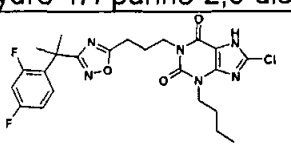
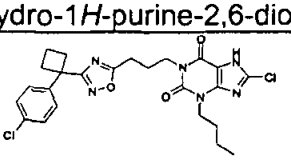
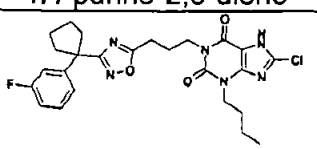


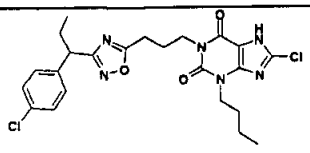
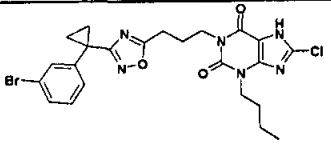
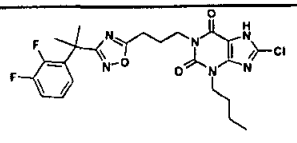
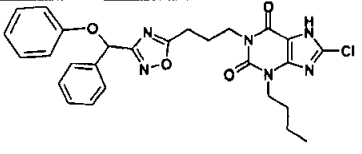
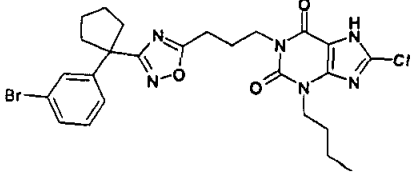
Ethyl 4-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)butanoate (53mg, 0.15mmol), *N*-hydroxy-1-phenylcyclopentanecarboximidamide (34mg, 0.165mmol) and sodium methoxide (20mg, 0.37mmol) in dry MeOH (0.75ml) were heated at 140°C in the microwave reactor for 10min. The mixture was then partitioned between ethyl acetate and 2M HCl, the organic phase evaporated and the product purified by MDAP to give the title compound as a solid (29.1mg).
LC/MS: m/z 497 $[MH]^+$, RT 3.76min.

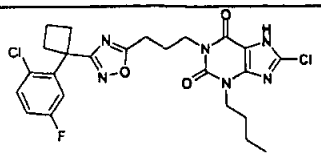
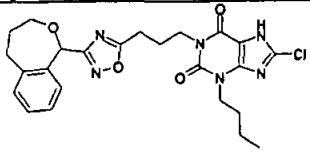
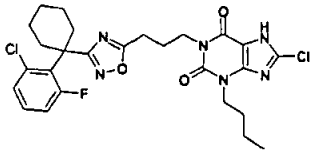
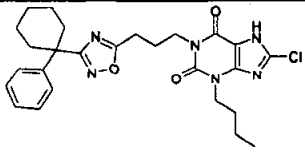
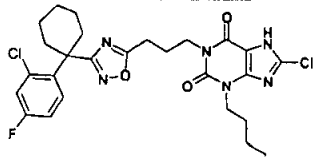
The following compounds (**Table 11**) were prepared using a method analogous to that for **Example 192**, using the appropriate amidoxime [with the exception that for **Examples 210**, **211** and **212** EtOH was used as reaction solvent; for **Examples 210**, **211** and **212** the reactions were worked up by adding 2M HCl until neutral and evaporating the solvent; for **Example 206** the scale was 32mg of starting ethyl ester; **Example 208** the scale was 42mg of starting ethyl ester].

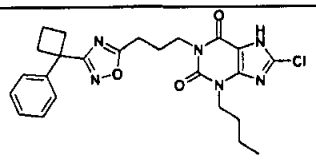
Table 11

Example	Structure	Yield	LC/MS

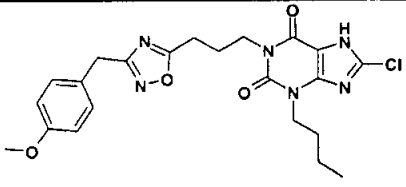
		(mg)	
193	 3-butyl-8-chloro-1-{3-[3-(2-methyl-1-phenylpropyl)-1,2,4-oxadiazol-5-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione	17.4	m/z 485 $[MH]^+$ RT 3.74min
194	 3-butyl-8-chloro-1-(3-{3-[1-(2-fluorophenyl)cyclopentyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione	33.7	m/z 515 $[MH]^+$ RT 3.73min
195	 1-[3-(3-bicyclo[4.2.0]octa-1,3,5-trien-7-yl-1,2,4-oxadiazol-5-yl)propyl]-3-butyl-8-chloro-3,7-dihydro-1*H*-purine-2,6-dione	28.8	m/z 455 $[MH]^+$ RT 3.43min
196	 3-butyl-8-chloro-1-(3-{3-[1-(2,4-difluorophenyl)-1-methylethyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione	33.4	m/z 507 $[MH]^+$ RT 3.59min
197	 3-butyl-8-chloro-1-(3-{3-[1-(4-chlorophenyl)cyclobutyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione	33.8	m/z 517 $[MH]^+$ RT 3.85min
198	 3-butyl-8-chloro-1-(3-{3-[1-(3-	34.2	m/z 515 $[MH]^+$ RT 3.80min

	fluorophenyl)cyclopentyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione		
199	 3-butyl-8-chloro-1-(3-{3-[1-(4-chlorophenyl)propyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione	16.3	m/z 505 $[MH]^+$ RT 3.80min
200	 1-(3-{3-[1-(3-bromophenyl)cyclopropyl]-1,2,4-oxadiazol-5-yl}propyl)-3-butyl-8-chloro-3,7-dihydro-1*H*-purine-2,6-dione	34.9	m/z 549 $[MH]^+$ RT 3.72min
201	 3-butyl-8-chloro-1-(3-{3-[1-(2,3-difluorophenyl)-1-methylethyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione	30.4	m/z 507 $[MH]^+$ RT 3.59min
202	 3-butyl-8-chloro-1-(3-{3-[phenoxy(phenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	3	m/z 535$[MH]^+$ RT 3.69min.
203	 1-(3-{3-[1-(3-bromophenyl)cyclopentyl]-1,2,4-oxadiazol-5-yl}propyl)-3-butyl-8-	38.8	m/z 577$[MH]^+$ RT 3.99 min.

	chloro-3,7-dihydro-1H-purine-2,6-dione		
204	 3-butyl-8-chloro-1-(3-{3-[1-(2-chloro-5-fluorophenyl)cyclobutyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	41.4	m/z 535[MH]$^+$ RT 3.79 min.
205	 3-butyl-8-chloro-1-{3-[3-(1,3,4,5-tetrahydro-2-benzoxepin-1-yl)-1,2,4-oxadiazol-5-yl]propyl}-3,7-dihydro-1H-purine-2,6-dione	27.4	m/z 499[MH]$^+$ RT 3.42 min.
206	 3-butyl-8-chloro-1-(3-{3-[1-(2-chloro-6-fluorophenyl)cyclohexyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	12.9	m/z 563[MH]$^+$ RT 4.02min.
207	 3-butyl-8-chloro-1-{3-[3-(1-phenylcyclohexyl)-1,2,4-oxadiazol-5-yl]propyl}-3,7-dihydro-1H-purine-2,6-dione	34.8	m/z 511[MH]$^+$ RT 3.88min.
208	 3-butyl-8-chloro-1-(3-{3-[1-(2-chloro-4-fluorophenyl)cyclohexyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-	19	m/z 563[MH]$^+$ RT 4.00min.

	dihydro-1H-purine-2,6-dione		
209	 3-butyl-8-chloro-1-{3-[3-(1-phenylcyclobutyl)-1,2,4-oxadiazol-5-yl]propyl}-3,7-dihydro-1H-purine-2,6-dione	30.5	m/z 483[MH]$^+$ RT 3.64min.

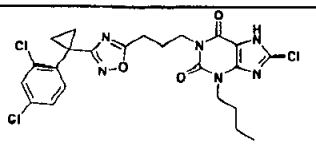
Example 210: 3-Butyl-8-chloro-1-[3-(3-{[4-(methyloxy)phenyl]methyl}-1,2,4-oxadiazol-5-yl)propyl]-3,7-dihydro-1*H*-purine-2,6-dione

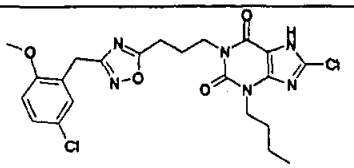
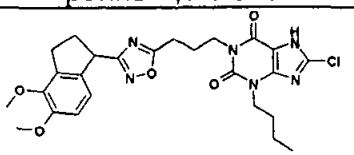
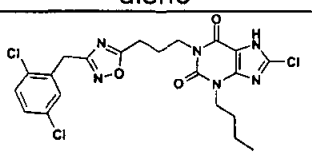
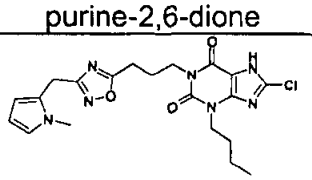
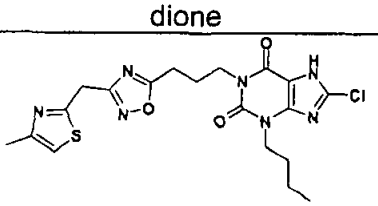


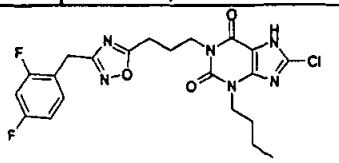
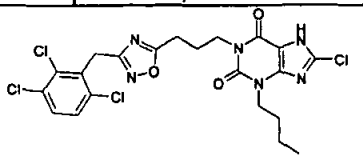
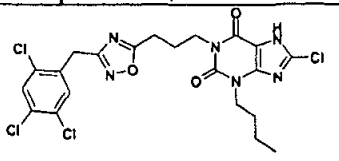
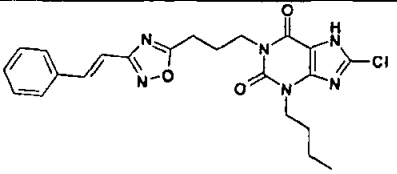
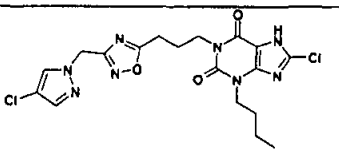
Prepared using a method analogous to that used for **Example 93**, except an additional final purification step using HPLC was employed. Yield 6.0mg.
LC/MS: m/z 473 [MH]$^+$, RT 3.27min.

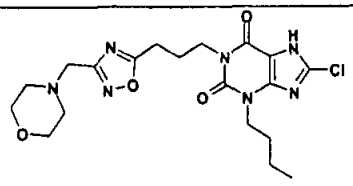
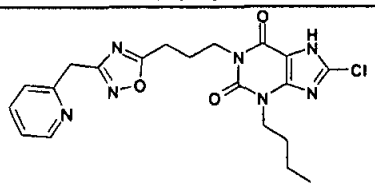
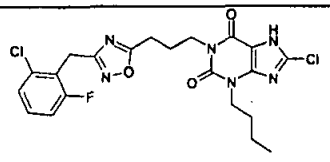
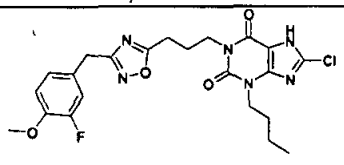
The following compounds (**Table 12**) were prepared using a method analogous to that for **Example 96**, using the appropriate amidoxime [with the exception that for **Example 211** the scale was 0.12mmol instead of 0.15mmol; for **Example 216** the crude product was stirred in EtOH (0.75ml) with 2M NaOH (0.5ml) overnight prior to the usual EtOAc/HCl workup and MDAP; **Example 218** was isolated as an impurity from the preparation of **Example 219** and was separated from it by HPLC; for **Examples 221, 222** and **223** the pH during aqueous workup was adjusted to approximately 5 prior to extraction; additionally **Example 223** was further purified by silica SPE (2g, DCM-MeOH 40:1then 20:1) after MDAP].

Table 12

Example	Structure	Yield (mg)	LC/MS
211	 3-butyl-8-chloro-1-(3-{3-[1-(2,4-	23.8	m/z 537 [MH]$^+$ RT 3.83min

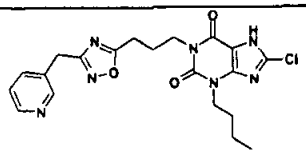
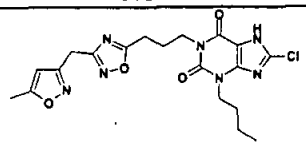
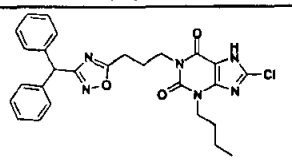
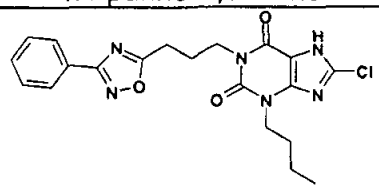
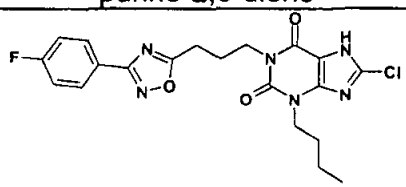
	dichlorophenyl)cyclopropyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione		
212	 3-butyl-8-chloro-1-[3-(3-{[5-chloro-2-(methyloxy)phenyl]methyl}-1,2,4-oxadiazol-5-yl)propyl]-3,7-dihydro-1*H*-purine-2,6-dione	39.5	m/z 507 $[MH]^+$ RT 3.58min
213	 1-(3-{3-[4,5-bis(methyloxy)-2,3-dihydro-1*H*-inden-1-yl]-1,2,4-oxadiazol-5-yl}propyl)-3-butyl-8-chloro-3,7-dihydro-1*H*-purine-2,6-dione	35.8	m/z 529 $[MH]^+$ RT 3.41min
214	 3-butyl-8-chloro-1-(3-{3-[(2,5-dichlorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione	9.7	m/z 511 $[MH]^+$ RT 3.63min
215	 3-butyl-8-chloro-1-(3-{3-[(1-methyl-1*H*-pyrrol-2-yl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione	18.0	m/z 446 $[MH]^+$ RT 3.15min
216	 3-butyl-8-chloro-1-(3-{3-[(4-methyl-1,3-thiazol-2-yl)methyl]-1,2,4-	15.5	m/z 464 $[MH]^+$ RT 2.94min

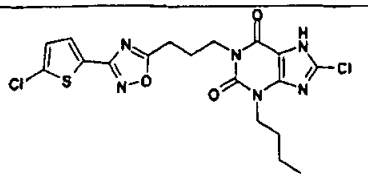
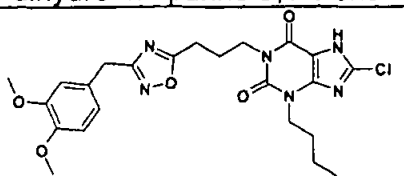
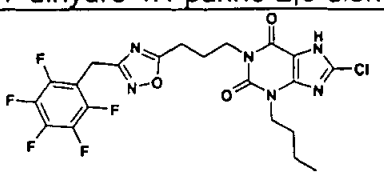
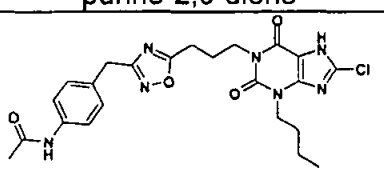
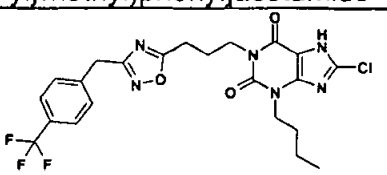
	oxadiazol-5-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione		
217	 3-butyl-8-chloro-1-(3-{3-[(2,4-difluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione	33.5	m/z 479 $[MH]^+$ RT 3.35min
218	 3-butyl-8-chloro-1-(3-{3-[(2,3,6-trichlorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione	4.6	m/z 545 $[MH]^+$ RT 3.71min
219	 3-butyl-8-chloro-1-(3-{3-[(2,4,5-trichlorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione	17.7	m/z 545 $[MH]^+$ RT 3.79min
220	 3-butyl-8-chloro-1-(3-{3-[(*E*)-2-phenylethenyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione	17.8	m/z 455 $[MH]^+$ RT 3.49min
221	 3-butyl-8-chloro-1-(3-{3-[(4-chloro-1*H*-pyrazol-1-yl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione	39.2	m/z 467 $[MH]^+$ RT 3.24min

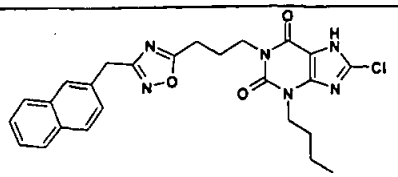
222	 3-butyl-8-chloro-1-{3-[3-(4-morpholinylmethyl)-1,2,4-oxadiazol-5-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione	27.0	m/z 452 $[MH]^+$ RT 2.56min
223	 3-butyl-8-chloro-1-{3-[3-(2-pyridinylmethyl)-1,2,4-oxadiazol-5-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione	23.6	m/z 444 $[MH]^+$ RT 2.92min
224	 3-butyl-8-chloro-1-(3-{3-[(2-chloro-6-fluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	38.8	m/z 495$[MH]^+$ RT 3.43min
225	 3-butyl-8-chloro-1-[3-(3-{[3-fluoro-4-(methyloxy)phenyl]methyl}-1,2,4-oxadiazol-5-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione	27	m/z 491$[MH]^+$ RT 3.31min

The following compounds (**Table 13**) were prepared using a method analogous to that for **Example 114**, using the appropriate amidoxime [with the exception that **Example 226** was conducted on half the scale of **Example 114** and during workup the aqueous phase was neutralised prior to extraction; **Example 227** was conducted on half the scale of **Example 114** and the crude product stirred with 2M NaOH (0.5ml) in EtOH (1ml) for 5h prior to workup and MDAP; for **Example 232** 0.185ml (0.5mmol) of 21% NaOEt was used].

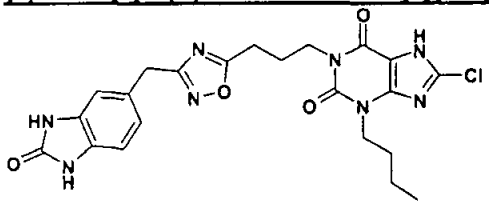
Table 13

Example	Structure	Yield (mg)	LC/MS
226	 3-butyl-8-chloro-1-{3-[3-(3-pyridinylmethyl)-1,2,4-oxadiazol-5-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione	20	m/z 444 $[MH]^+$ RT 2.74min
227	 3-butyl-8-chloro-1-(3-{3-[(5-methyl-3-isoxazolyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione	7.2	m/z 448 $[MH]^+$ RT 3.13min
228	 3-butyl-8-chloro-1-{3-[3-(diphenylmethyl)-1,2,4-oxadiazol-5-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione	47.4	m/z 519 $[MH]^+$ RT 3.71min
229	 3-butyl-8-chloro-1-[3-(3-phenyl-1,2,4-oxadiazol-5-yl)propyl]-3,7-dihydro-1*H*-purine-2,6-dione	36.7	m/z 429 $[MH]^+$ RT 3.36min
230	 3-butyl-8-chloro-1-{3-[3-(4-fluorophenyl)-1,2,4-oxadiazol-5-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione	41.1	m/z 447 $[MH]^+$ RT 3.42min

231	 3-butyl-8-chloro-1-{3-[3-(5-chloro-2-thienyl)-1,2,4-oxadiazol-5-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione	36.7	m/z 469 $[MH]^+$ RT 3.60min
232	 1-[3-(3-{[3,4-bis(methyloxy)phenyl]methyl}-1,2,4-oxadiazol-5-yl)propyl]-3-butyl-8-chloro-3,7-dihydro-1*H*-purine-2,6-dione	47.0	m/z 503 $[MH]^+$ RT 3.14min
233	 3-butyl-8-chloro-1-(3-{3-[(pentafluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione	29.2	m/z 533 $[MH]^+$ RT 3.62min
234	 *N*-[4-({5-[3-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)propyl]-1,2,4-oxadiazol-3-yl}methyl)phenyl]acetamide	29.8	m/z 500 $[MH]^+$ RT 3.01min
235	 3-butyl-8-chloro-1-[3-(3-{[4-(trifluoromethyl)phenyl]methyl}-1,2,4-oxadiazol-5-yl)propyl]-3,7-dihydro-1*H*-purine-2,6-dione	37.7	m/z 511 $[MH]^+$ RT 3.65min

236	 3-butyl-8-chloro-1-{3-[3-(2-naphthalenylmethyl)-1,2,4-oxadiazol-5-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione	47.5	m/z 493 $[MH]^+$ RT 3.69min

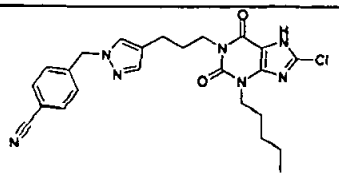
Example 237: 3-Butyl-8-chloro-1-(3-{3-[(2-oxo-2,3-dihydro-1*H*-benzimidazol-5-yl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione

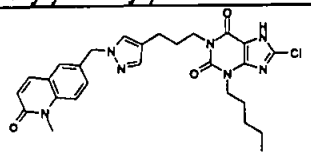
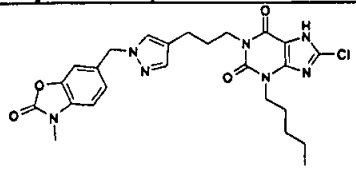
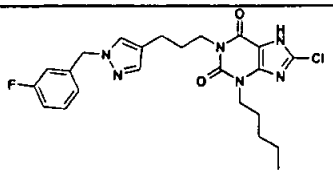
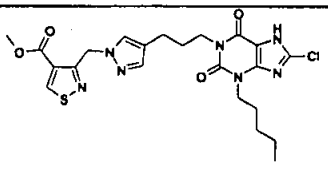


Synthesised by a method analogous to that for **Example 126** with the exception that a further 2 equivalents of 21% sodium ethoxide (0.11ml) was used, the extra heating time was 20min. and the product was isolated by filtration followed by trituration with hot MeOH. Yield 14.5mg.
LC/MS: m/z 499 $[MH]^+$, RT 2.78min.

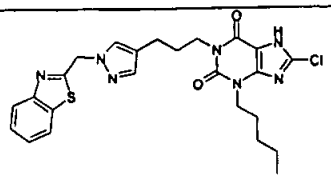
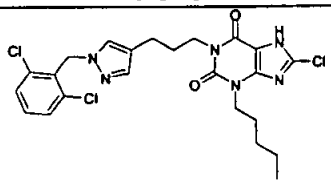
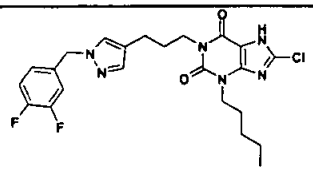
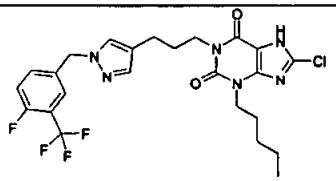
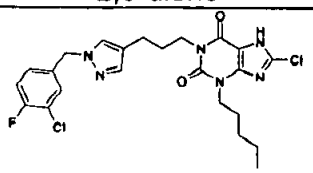
The following compounds (**Table 14**) were prepared by a method analogous to that for **Example 18** [with the exception that **Examples 238-243** were all synthesised on a scale starting from 50mg of 8-chloro-3-pentyl-7-(2-propen-1-yl)-1-[3-(1*H*-pyrazol-4-yl)propyl]-3,7-dihydro-1*H*-purine-2,6-dione; **Examples 241**, **243**, **245**, **246** and **247** were additionally purified by MDAP following aminopropyl SPE; **Example 242** was additionally purified by recrystallisation from MeOH following aminopropyl SPE; for **Example 248**, 128mg (1.2mmol) of sodium carbonate was used; during workup the aqueous phase was adjusted to pH6 prior to extraction; and the product was purified by MDAP then by further HPLC; for **Example 241** solids which precipitated during workup were combined with the EtOAc extracts prior to SPE].

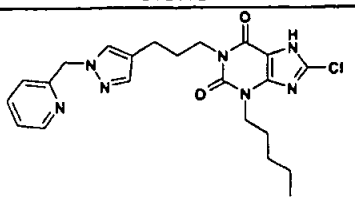
Table 14

Example	Structure	Yield (mg)	LC/MS
238	 4-({4-[3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-	36.0	m/z 480 $[MH]^+$ RT 3.24min

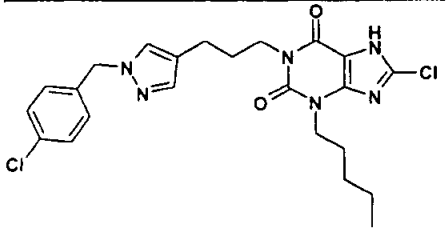
	purin-1-yl)propyl]-1*H*-pyrazol-1-yl}methyl)benzonitrile		
239	 8-chloro-1-(3-{1-[(1-methyl-2-oxo-1,2-dihydro-6-quinolinyl)methyl]-1*H*-pyrazol-4-yl}propyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione	7.6	m/z 536 $[MH]^+$ RT 3.03min
240	 8-chloro-1-(3-{1-[(3-methyl-2-oxo-2,3-dihydro-1,3-benzoxazol-6-yl)methyl]-1*H*-pyrazol-4-yl}propyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione	34.0	m/z 526 $[MH]^+$ RT 3.11min
241	 8-chloro-1-(3-{1-[(3-fluorophenyl)methyl]-1*H*-pyrazol-4-yl}propyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione	26.2	m/z 473 $[MH]^+$ RT 3.38min
242	 methyl 3-({4-[3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)propyl]-1*H*-pyrazol-1-yl}methyl)-4-isothiazolecarboxylate	16.2	m/z 520 $[MH]^+$ RT 3.12min

160

243	 1-{3-[1-(1,3-benzothiazol-2-ylmethyl)-1*H*-pyrazol-4-yl]propyl}-8-chloro-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione	21.0	m/z 512 $[MH]^+$ RT 3.36min
244	 8-chloro-1-(3-{1-[(2,6-dichlorophenyl)methyl]-1*H*-pyrazol-4-yl}propyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione	65.0	m/z 523, 525 [Cl isotopes MH^+] RT 3.77min
245	 8-chloro-1-(3-{1-[(3,4-difluorophenyl)methyl]-1*H*-pyrazol-4-yl}propyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione	35.0	m/z 491 $[MH]^+$ RT 3.61min
246	 8-chloro-1-[3-(1-{[4-fluoro-3-(trifluoromethyl)phenyl]methyl}-1*H*-pyrazol-4-yl)propyl]-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione	17.0	m/z 541 $[MH]^+$ RT 3.76min
247	 8-chloro-1-(3-{1-[(3-chloro-4-	27.0	m/z 507 $[MH]^+$ RT 3.73min

	fluorophenyl)methyl]-1*H*-pyrazol-4-yl}propyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione		
248	 8-chloro-3-pentyl-1-{3-[1-(2-pyridinylmethyl)-1*H*-pyrazol-4-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione	11.4	m/z 456 $[MH]^+$ RT 3.13min

Example 249: 8-Chloro-1-{3-{1-[(4-chlorophenyl)methyl]-1*H*-pyrazol-4-yl}propyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione

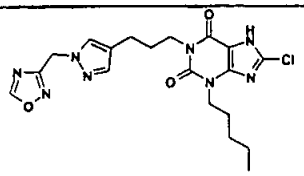
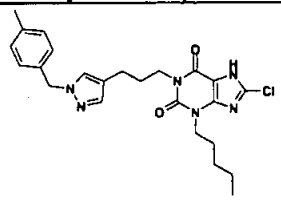
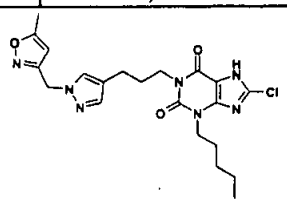
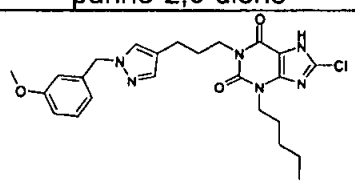
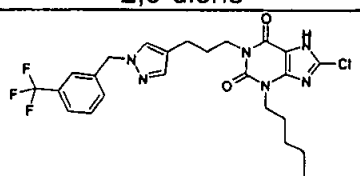


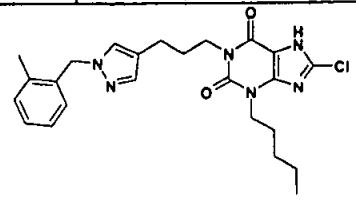
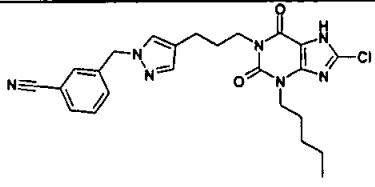
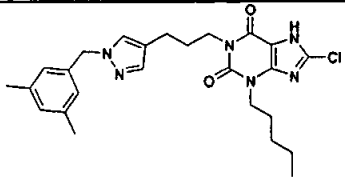
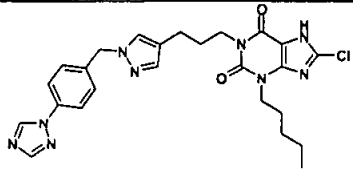
8-Chloro-3-pentyl-7-(2-propen-1-yl)-1-[3-(1*H*-pyrazol-4-yl)propyl]-3,7-dihydro-1*H*-purine-2,6-dione (50mg, 0.123mmol) in dry DMF (1.5ml) was stirred with sodium carbonate (75mg, 0.708mmol) and 4-chlorobenzyl bromide (150mg, 0.73mmol) at 40°C for 18h. The mixture was partitioned between EtOAc and water, the organic phase washed with brine, dried and evaporated. The product was purified by normal phase chromatography on silica (Companion System, EtOAc – cyclohexane gradient) giving an oil (44mg). This was stirred in degassed, dry DMF (1ml) with tetrakis(triphenylphosphine)palladium(0) (19mg) and morpholine (0.072ml) under nitrogen for 6h. The mixture was partitioned between EtOAc and 2M HCl and the organic phase evaporated and purified by the usual aminopropyl SPE procedure. Yield 21.0mg.

LC/MS: m/z 489 $[MH^+]$, RT 3.59min.

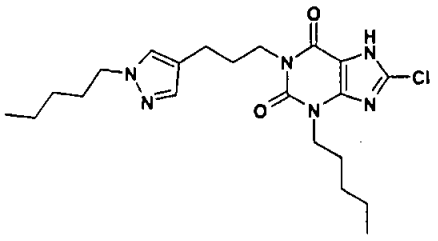
The following compounds (**Table 15**) were prepared by a method analogous to that for **Example 23** [with the exception that for **Example 250** a second portion of $Pd(PPh_3)_4$ was added after 5h, stirring was continued overnight, and final purification was achieved by HPLC; for **Example 252** required additional purification by MDAP; **Example 257** required additional purification by recrystallisation from MeOH; **Example 258** required additional purification by trituration with MeOH].

Table 15

Example	Structure	Yield (mg)	LC/MS
250	 8-chloro-1-{3-[1-(1,2,4-oxadiazol-3-ylmethyl)-1*H*-pyrazol-4-yl]propyl}-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione	7.3	m/z 447 $[MH]^+$ RT 3.06min
251	 8-chloro-1-(3-{1-[(4-methylphenyl)methyl]-1*H*-pyrazol-4-yl}propyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione	23.7	m/z 469 $[MH]^+$ RT 3.49min
252	 8-chloro-1-(3-{1-[(5-methyl-3-isoxazolyl)methyl]-1*H*-pyrazol-4-yl}propyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione	29.0	m/z 460 $[MH]^+$ RT 3.10min
253	 8-chloro-1-[3-(1-{[3-(methyloxy)phenyl]methyl}-1*H*-pyrazol-4-yl)propyl]-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione	56.0	m/z 485 $[MH]^+$ RT 3.41min
254	 8-chloro-3-pentyl-1-[3-(1-{[3-(trifluoromethyl)phenyl]methyl}-1*H*-	47.0	m/z 523 $[MH]^+$ RT 3.61min

	pyrazol-4-yl)propyl]-3,7-dihydro-1*H*-purine-2,6-dione		
255	 8-chloro-1-(3-{1-[(2-methylphenyl)methyl]-1*H*-pyrazol-4-yl}propyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione	44.0	m/z 469 $[MH]^+$ RT 3.54min
256	 3-({4-[3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)propyl]-1*H*-pyrazol-1-yl}methyl)benzonitrile	51.0	m/z 480 $[MH]^+$ RT 3.32min
257	 8-chloro-1-(3-{1-[(3,5-dimethylphenyl)methyl]-1*H*-pyrazol-4-yl}propyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione	36.7	m/z 483 $[MH]^+$ RT 3.66min
258	 8-chloro-3-pentyl-1-[3-(1-{[4-(1*H*-1,2,4-triazol-1-yl)phenyl]methyl}-1*H*-pyrazol-4-yl)propyl]-3,7-dihydro-1*H*-purine-2,6-dione	21.2	m/z 522 $[MH]^+$ RT 3.09min

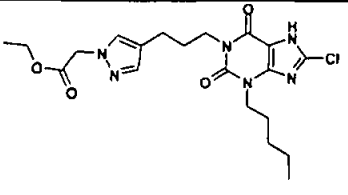
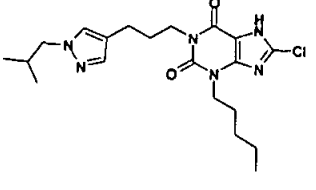
Example 259: 8-Chloro-3-pentyl-1-[3-(1-pentyl-1*H*-pyrazol-4-yl)propyl]-3,7-dihydro-1*H*-purine-2,6-dione

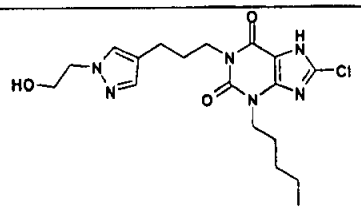
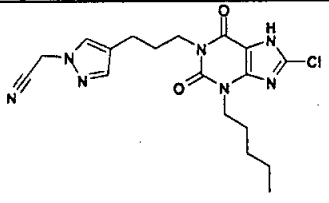


8-Chloro-3-pentyl-7-(2-propen-1-yl)-1-[3-(1*H*-pyrazol-4-yl)propyl]-3,7-dihydro-1*H*-purine-2,6-dione (61mg, 0.15mmol) and sodium carbonate (32mg, 0.3mmol) in dry DMF (1.5ml) was heated with 1-iodopentane (238mg, 1.2mmol) in the microwave reactor at 120°C for 25min. After cooling the mixture was degassed and stirred with tetrakis(triphenylphosphine)palladium(0) (40mg, 0.0346mmol) and morpholine (0.2ml) for 7h. A further 20mg of $Pd(PPh_3)_4$ was then added and stirring continued overnight. The mixture was stirred with EtOAc and 2M HCl for 1h and the organic phase separated and evaporated. The product was purified by aminopropyl SPE (5g) washing with MeOH-THF (1:1), then MeOH, and eluting the product with DCM-MeOH (1:1) containing 5% added AcOH to give the title compound (25mg).
LC/MS: m/z 435 $[MH]^+$, RT 3.65min.

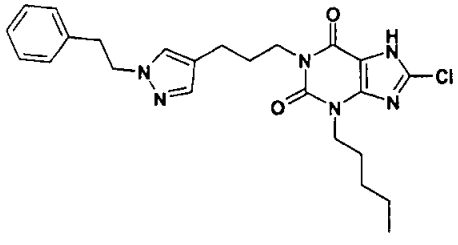
The following compounds (**Table 16**) were prepared by a method analogous to that for **Example 259** [with the exception that the compounds were purified by MDAP and for **Example 261** the total heating time in the microwave reactor was 50min].

Table 16

Example	Structure	Yield (mg)	LC/MS
260	 ethyl {4-[3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)propyl]-1*H*-pyrazol-1-yl}acetate	15.1	m/z 451 $[MH]^+$ RT 3.21min
261	 8-chloro-1-{3-[1-(2-methylpropyl)-1*H*-pyrazol-4-yl]propyl}-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione	1.34	m/z 421 $[MH]^+$ RT 3.48min

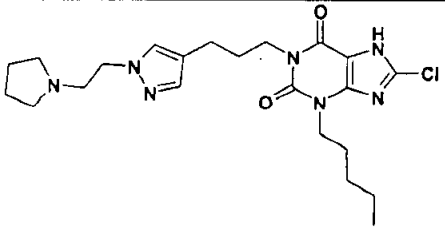
262	 8-chloro-1-{3-[1-(2-hydroxyethyl)-1*H*-pyrazol-4-yl]propyl}-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione	0.32	m/z 409 $[MH]^+$ RT 2.79min
263	 {4-[3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)propyl]-1*H*-pyrazol-1-yl}acetonitrile	9.6	m/z 404 $[MH]^+$ RT 3.12min

Example 264: 8-Chloro-3-pentyl-1-{3-[1-(2-phenylethyl)-1*H*-pyrazol-4-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione



8-Chloro-3-pentyl-7-(2-propen-1-yl)-1-[3-(1*H*-pyrazol-4-yl)propyl]-3,7-dihydro-1*H*-purine-2,6-dione (81mg, 0.2mmol), sodium carbonate (42mg, 0.4mmol) and (2-iodoethyl)benzene (0.174ml, 1.2mmol) were heated together in dry DMF (1ml) under microwave irradiation at 120°C for 25min. Tetrakis(triphenylphosphine)palladium(0) (46mg, 0.04mmol) and morpholine (0.174ml) were added and the mixture stirred for 6h. Further quantities (46mg and 0.174ml) of these reagents were added and stirring continued for a further 60h. Workup and purification as for the examples in **Table 16** gave the title compound (15.5mg).
LC/MS: m/z 469 $[MH]^+$, RT 3.60min.

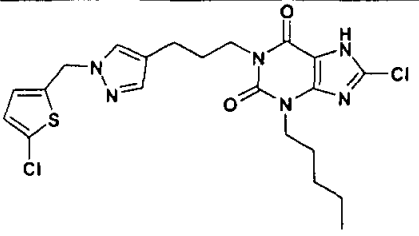
Example 265 : 8-Chloro-3-pentyl-1-(3-{1-[2-(1-pyrrolidinyl)ethyl]-1*H*-pyrazol-4-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione



8-Chloro-3-pentyl-7-(2-propen-1-yl)-1-[3-(1*H*-pyrazol-4-yl)propyl]-3,7-dihydro-1*H*-purine-2,6-dione (61mg, 0.15mmol), sodium carbonate (159mg, 1.5mmol) and 1-(2-chloroethyl)pyrrolidine hydrochloride (127mg, 0.75mmol) were heated together in dry DMF (2ml) at 80°C for 65h. Tetrabutylammonium iodide (55mg, 0.15mmol) was added and heating continued for another 18h. A further quantity of 1-(2-chloroethyl)pyrrolidine hydrochloride (127mg, 0.75mmol) was added and the mixture heated by microwaves at 120°C, then a 3rd aliquot of 1-(2-chloroethyl)pyrrolidine hydrochloride (100mg) was added, with a further 25min at 120°C in the microwave. The mixture was partitioned between water and EtOAc, the organic phase separated, washed with brine and evaporated. This material was partitioned between EtOAc and 2M HCl. The separated aqueous phase was basified to pH9, saturated with NaCl and extracted with EtOAc (x2). The extracts were evaporated and the residue (28mg) stirred in dry degassed DMF (1.5ml) with tetrakis(triphenylphosphine)palladium(0) (50mg) and morpholine (0.2ml) for 6h. The mixture was partitioned between EtOAc and 2M HCl, the aqueous phase filtered, extracted twice with EtOAc and evaporated to dryness. The residue was purified by the aminopropyl SPE procedure, followed by MDAP to yield the title compound (1.9mg).

LC/MS: m/z 462 $[MH]^+$, RT 2.46min.

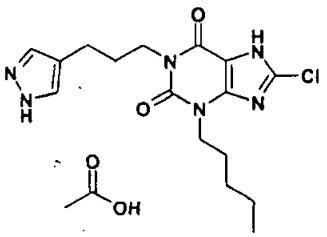
Example 266 : 8-Chloro-1-{3-{1-[(5-chloro-2-thienyl)methyl]-1*H*-pyrazol-4-yl}propyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione



To 8-chloro-3-pentyl-7-(2-propen-1-yl)-1-[3-(1*H*-pyrazol-4-yl)propyl]-3,7-dihydro-1*H*-purine-2,6-dione (61mg, 0.15mmol) in dry THF (1ml) at -78°C, under nitrogen, was added potassium t-butoxide (1M in THF, 0.15ml), followed by 2-chloro-5-(chloromethyl)thiophene (25mg, 0.15mmol). Stirring was continued at -78°C for 15min, then at room temperature for 1h and finally at 60°C for 18h. The solution was degassed and morpholine (0.13ml) and tetrakis(triphenylphosphine)palladium(0) (35mg) added and stirring continued for 6h. Further quantities (0.2ml morpholine, 50mg $Pd(PPh_3)_4$) were added and stirring continued overnight. Worked up by partition between EtOAc and 2M HCl, the organic phase evaporated and purified by the standard aminopropyl SPE procedure followed by MDAP yielding title compound as a white solid (5.1mg).

LC/MS: m/z 495 $[MH]^+$, RT 3.68min.

Example 267 : 8-Chloro-3-pentyl-1-[3-(1*H*-pyrazol-4-yl)propyl]-3,7-dihydro-1*H*-purine-2,6-dione acetate

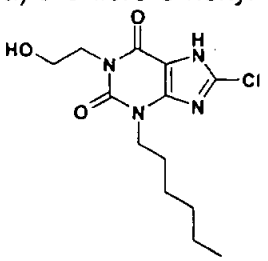


8-Chloro-3-pentyl-7-(2-propen-1-yl)-1-[3-(1*H*-pyrazol-4-yl)propyl]-3,7-dihydro-1*H*-purine-2,6-dione (50mg, 0.124mmol) in dry degassed THF (1.5ml) was stirred with tetrakis(triphenylphosphine)palladium(0) (29mg, 0.025mmol) and morpholine (0.108ml) under nitrogen for 5h. The mixture was partitioned between EtOAc and 0.5M citric acid and the organic phase separated. Two further EtOAc extractions were performed and the combined organics were evaporated and the product purified by aminopropyl SPE (2g), loading and washing with THF-MeOH (1:1) then washing with MeOH and eluting with DCM-MeOH (1:1) containing 5% AcOH. Yield 28.3mg.

LC/MS: m/z 365 $[MH]^+$, RT 2.89min.

Example 268 : 8-Chloro-3-hexyl-1-(2-hydroxyethyl)-3,7-dihydro-1*H*-purine-2,6-dione

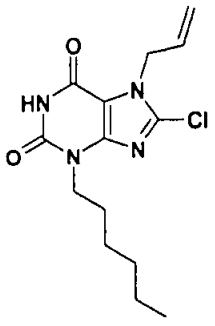
a) 8-Chloro-3-hexyl-1-(2-hydroxyethyl)-3,7-dihydro-1*H*-purine-2,6-dione



8-Chloro-3-hexyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (100mg, 0.322mmol), cesium carbonate (126mg, 0.387mmol) and 2-chloroethanol (29.8mg, 0.37mmol) in dry DMF (3ml) were heated together under nitrogen at 55°C for 42h. The cooled mixture was degassed thoroughly and stirred with tetrakis(triphenylphosphine)palladium(0) (74mg) and morpholine (0.28ml) for 5h. The reaction was worked up by partition between EtOAc and 2M HCl, the organic phase being separated and evaporated. The residue was loaded onto an aminopropyl SPE cartridge (5g) in THF-MeOH (1:1), washed with the same solvent, then with neat MeOH, and the product eluted with DCM-MeOH (1:1) containing AcOH (2.5% rising to 5%). The product thus obtained was further purified by MDAP to afford the title compound (38mg).

LC/MS: m/z 315 $[MH]^+$, RT 2.79min.

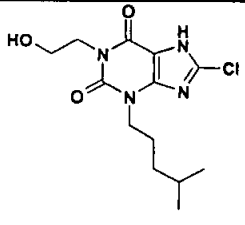
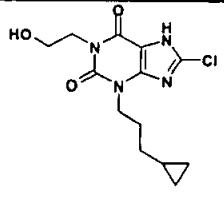
b) 8-Chloro-3-hexyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione



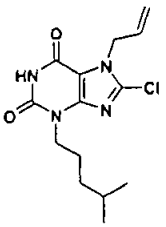
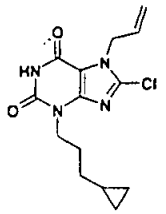
To 8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (226mg, 1mmol) and sodium carbonate (117mg, 1.1mmol) in dry DMF (7ml) was added 1-iodohexane (223mg, 1.05mmol). The mixture was stirred and heated at 50°C for 2 days. After cooling, the mixture was partitioned between EtOAc and water, the organic phase washed with brine, dried over Na_2SO_4 and evaporated. The crude product was recrystallised from EtOAc-cyclohexane (1:2). Yield 146mg.
LC/MS: m/z 311 $[MH]^+$, RT 3.12min.

The following compounds (**Table 17**) were prepared by a method analogous to that for **Example 268**, except for **Example 270** the scale was reduced to 75mg (0.243mmol) of the precursor 8-chloro-3-(3-cyclopropylpropyl)-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione.

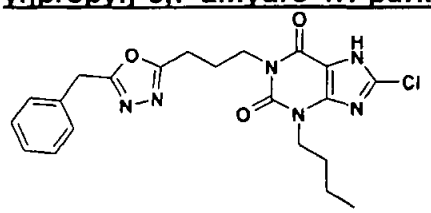
Table 17

Example	Structure	Precursor	Yield (mg)	LC/MS
269	 8-chloro-1-(2-hydroxyethyl)-3-(4-methylpentyl)-3,7-dihydro-1*H*-purine-2,6-dione	8-chloro-3-(4-methylpentyl)-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione	37	m/z 315 $[MH]^+$ RT 2.74min
270	 8-chloro-3-(3-cyclopropylpropyl)-1-(2-hydroxyethyl)-3,7-dihydro-1*H*-purine-2,6-dione	8-chloro-3-(3-cyclopropylpropyl)-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione	26	m/z 313 $[MH]^+$ RT 2.58min

The intermediates were prepared according to the method of **Example 268b**, except that 8-chloro-3-(3-cyclopropylpropyl)-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione was purified by silica SPE (5g) eluting with EtOAc-cyclohexane (2:3).

Intermediate	Name	Scale (mmol)	Alkylating agent	Yield (mg)	LC/MS
	8-chloro-3-(4-methylpentyl)-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione	1	1-bromo-4-methylpentane (173mg)	210	m/z 311[MH]$^+$ RT 3.08min
	8-chloro-3-(3-cyclopropylpropyl)-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione	0.662	3-cyclopropylpropyl 4-methylbenzenesulfonate (170mg)	125	m/z 309 [MH]$^+$ RT 2.93min

Example 271: 3-Butyl-8-chloro-1-{3-[5-(phenylmethyl)-1,3,4-oxadiazol-2-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione

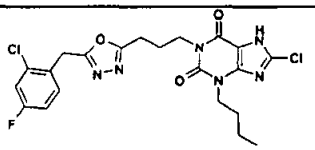
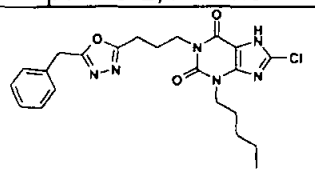
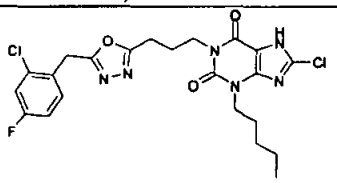
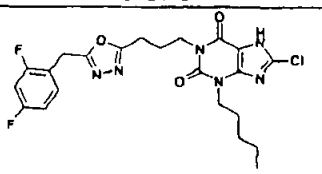


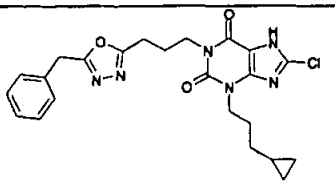
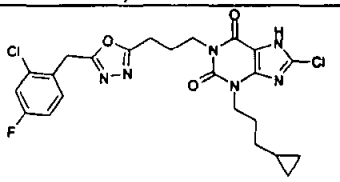
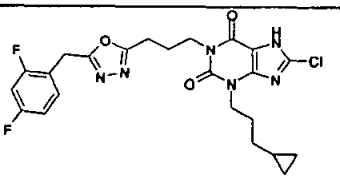
To 3-butyl-8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1H-purine-2,6-dione (99mg, 0.35mmol) in dry DMF (2ml) was added cesium carbonate (137mg, 0.42mmol) followed by a solution in dry DMF (1ml) of 2-(3-chloropropyl)-5-(phenylmethyl)-1,3,4-oxadiazole (99mg, 0.42mmol). The mixture was stirred under nitrogen and heated at 55°C for 2.5h then stirred at room temperature overnight. The mixture was degassed by repeatedly evacuating and admitting nitrogen and then tetrakis(triphenylphosphine)palladium(0) (81mg, 0.07mmol) and morpholine (0.305ml, 3.5mmol) were added and stirring was continued for 5h EtOAc and 2M HCl were added and the mixture stirred for 20min then filtered. The organic phase was separated and evaporated, and the product was purified by aminopropyl SPE (5g) washing with THF-MeOH (1:1) then with MeOH and eluting the acidic product with DCM-MeOH (1:1) containing 5% added AcOH. The product thus obtained was purified further by MDAP to yield the title compound (92mg). LC/MS: m/z 443 [MH]$^+$, RT 3.18min.

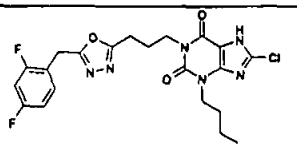
The following compounds (**Table 18**) were prepared by a method analogous to that for **Example 271**, with the exception that **Example 279** was further purified by HPLC.

170

Table 18

Example	Product structure	Xanthine precursor	Alkylating agent	Yield (mg)	LC/MS
272	 3-butyl-8-chloro-1-(3-{5-[(2-chloro-4-fluorophenyl)methyl]-1,3,4-oxadiazol-2-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione	3-butyl-8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1H-purine-2,6-dione (99mg)	2-[(2-chloro-4-fluorophenyl)methyl]-5-(3-chloropropyl)-1,3,4-oxadiazole (121mg)	90	m/z 495 [MH]+ RT 3.34 min
273	 8-chloro-3-pentyl-1-{3-[5-(phenylmethyl)-1,3,4-oxadiazol-2-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione	8-chloro-3-pentyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (104mg)	2-(3-chloropropyl)-5-(phenylmethyl)-1,3,4-oxadiazole (99mg)	98	m/z 457 [MH]+ RT 3.35 min
274	 8-chloro-1-(3-{5-[(2-chloro-4-fluorophenyl)methyl]-1,3,4-oxadiazol-2-yl}propyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione	8-chloro-3-pentyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (104mg)	2-[(2-chloro-4-fluorophenyl)methyl]-5-(3-chloropropyl)-1,3,4-oxadiazole (121mg)	98	m/z 509 [MH]+ RT 3.52 min
275		8-chloro-3-pentyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-	2-(3-chloropropyl)-5-[(2,4-difluorophenyl)	43	m/z 493 [MH]+

	8-chloro-1-(3-{5-[(2,4-difluorophenyl)methyl]-1,3,4-oxadiazol-2-yl}propyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione	purine-2,6-dione (104mg)	methyl]-1,3,4-oxadiazole (111mg)	-	RT 3.40 min
276	 8-chloro-3-(3-cyclopropylpropyl)-1-{3-[5-(phenylmethyl)-1,3,4-oxadiazol-2-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione	8-chloro-3-(3-cyclopropylpropyl)-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (108mg)	2-(3-chloropropyl)-5-(phenylmethyl)-1,3,4-oxadiazole (99mg)	95	m/z 469 [MH]+ RT 3.34 min
277	 8-chloro-1-(3-{5-[(2-chloro-4-fluorophenyl)methyl]-1,3,4-oxadiazol-2-yl}propyl)-3-(3-cyclopropylpropyl)-3,7-dihydro-1*H*-purine-2,6-dione	8-chloro-3-(3-cyclopropylpropyl)-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (108mg)	2-[(2-chloro-4-fluorophenyl)methyl]-5-(3-chloropropyl)-1,3,4-oxadiazole (121mg)	99	m/z 521 [MH]+ RT 3.51 min
278	 8-chloro-3-(3-cyclopropylpropyl)-1-(3-{5-[(2,4-difluorophenyl)methyl]-1,3,4-oxadiazol-2-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione	8-chloro-3-(3-cyclopropylpropyl)-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (108mg)	2-(3-chloropropyl)-5-[(2,4-difluorophenyl)methyl]-1,3,4-oxadiazole (111mg)	49	m/z 505 [MH]+ RT 3.40 min

279	 3-butyl-8-chloro-1-(3-{5-[(2,4-difluorophenyl)methyl]-1,3,4-oxadiazol-2-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione	3-butyl-8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1H-purine-2,6-dione (99mg)	2-(3-chloropropyl)-5-[(2,4-difluorophenyl) methyl]-1,3,4-oxadiazole (111mg)	38.9	m/z 479 $[MH]^+$ RT 3.31 min

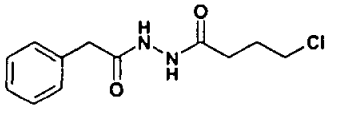
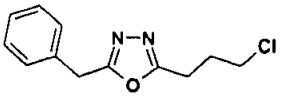
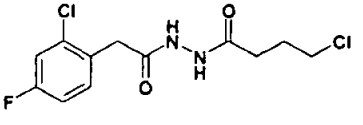
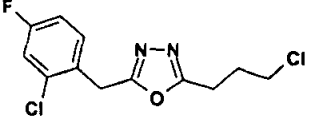
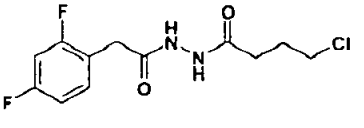
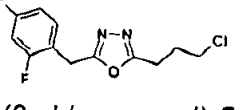
Synthesis of chloropropyl 1,3,4-oxadiazole intermediates from Table 18:

2-[(2-chloro-4-fluorophenyl)methyl]-5-(3-chloropropyl)-1,3,4-oxadiazole

2-(3-chloropropyl)-5-[(2,4-difluorophenyl)methyl]-1,3,4-oxadiazole

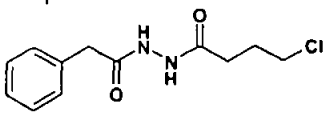
2-(3-chloropropyl)-5-(phenylmethyl)-1,3,4-oxadiazole

Diacyl hydrazines (500mg, synthesis below) were stirred in dry toluene (4ml) and phosphorus oxychloride (4ml) was added. The mixtures were heated at 90°C for 2h then allowed to cool and the solvents evaporated. The residues were dissolved in dry toluene, evaporated and then partitioned between EtOAc and aqueous $NaHCO_3$. The organic phases were washed with brine, dried over Na_2SO_4 and evaporated to give the required oxadiazoles as colourless oils. These were not purified further but reacted directly with the xanthines as above.

Diacyl hydrazine	Oxadiazole product	Yield (mg)	LC/MS
 4-chloro-*N*'-(phenylacetyl)butanohydrazide	 2-(3-chloropropyl)-5-(phenylmethyl)-1,3,4-oxadiazole	446	m/z 237 $[MH]^+$ RT 2.94min
 4-chloro-*N*'-[(2-chloro-4-fluorophenyl)acetyl]butanohydrazide	 2-[(2-chloro-4-fluorophenyl)methyl]-5-(3-chloropropyl)-1,3,4-oxadiazole	405	m/z 289 $[MH]^+$ RT 3.17min
 4-chloro-*N*'-[(2,4-	 2-(3-chloropropyl)-5-[(2,4-	333	m/z 273 $[MH]^+$ RT 3.03min

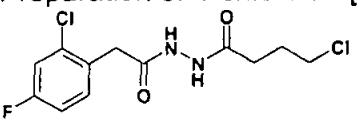
difluorophenyl)acetyl]butanohydrazide	difluorophenyl)methyl]-1,3,4-oxadiazole		

Preparation of 4-chloro-*N'*-(phenylacetyl)butanohydrazide



To 4-chlorobutyryl chloride (1.12ml, 10mmol) in dry DCM (10ml) was added, dropwise, over 40min, a mixture of phenylacetic hydrazide (1.5g, 10mmol) and DIPEA (1.77ml, 10.2mmol) in dry DCM (40ml) at room temperature. A dense white precipitate formed. After a further 20min. 2M HCl (30ml) was added and the title compound (white solid) was filtered off, washed with water and dried (2.24g).
LC/MS: m/z 255 $[MH]^+$, RT 2.20min.

Preparation of 4-chloro-*N'*-[(2-chloro-4-fluorophenyl)acetyl]butanohydrazide

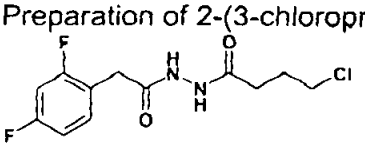


(i) A solution of 2-chloro-4-fluorophenylacetyl chloride (10mmol) in dry DCM (15ml) was added over 20min to a mixture of t-butyl carbazate (1.32g, 10mmol) and DIPEA (1.77ml, 10.2mmol) in dry DCM (20ml). After stirring for a further 2h, the mixture was washed with 1M HCl then with aqueous $NaHCO_3$. A white solid precipitated at this point, which was filtered off, washed with water and DCM then dried to yield 1,1-dimethylethyl 2-[(2-chloro-4-fluorophenyl)acetyl]hydrazinecarboxylate (1.94g).

(ii) This compound (1.92g, 6.34mmol) was suspended in dioxan (2ml) and 4M HCl in dioxan (5ml) was added. A dense white precipitate formed. After 1h the mixture was partitioned between EtOAc and saturated aqueous $NaHCO_3$ and the organic phase washed with brine, dried (Na_2SO_4) and evaporated giving 2-(2-chloro-4-fluorophenyl)acetohydrazide as a white solid (1.07g).

(iii) A mixture of 2-(2-chloro-4-fluorophenyl)acetohydrazide (909mg, 4.5mmol) and DIPEA (0.817ml, 4.7mmol) in dry DCM (65ml) was added over 20min to 4-chlorobutyryl chloride (0.505ml, 4.5mmol) in dry DCM (5ml). After 1.5h, 2M HCl was added and the precipitated 4-chloro-*N'*-[(2-chloro-4-fluorophenyl)acetyl]butanohydrazide was filtered off, washed with water and dried (1.24g).
LC/MS: m/z 307 $[MH]^+$, RT 2.61min.

Preparation of 2-(3-chloropropyl)-5-[(2,4-difluorophenyl)methyl]-1,3,4-oxadiazole



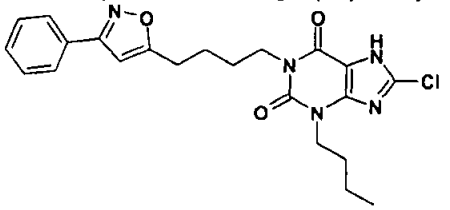
(i) A solution of 2,4-difluorophenylacetyl chloride (10mmol) in dry DCM (15ml) was added over 10min. to a mixture of t-butyl carbazate (1.32g, 10mmol) and DIPEA (1.77ml, 10.2mmol) in dry DCM (20ml). After stirring for 1.5h the mixture was washed with 1M HCl then with aqueous $NaHCO_3$. The organic phase was evaporated to afford 1,1-dimethylethyl 2-[(2,4-difluorophenyl)acetyl]hydrazinecarboxylate as a white solid.

(ii) 1,1-dimethylethyl 2-[(2,4-difluorophenyl)acetyl]hydrazinecarboxylate (10mmol) in dioxan (5ml) was stirred with 4M HCl in dioxan (8ml) for 1.5h. The mixture was partitioned between EtOAc and saturated aqueous $NaHCO_3$ and the organic phase washed with brine, dried (Na_2SO_4) and evaporated. Reaction was incomplete so the residue was stirred again with 4M HCl in dioxan (10ml) for 2.5h. Workup as previously gave 2-(2,4-difluorophenyl)acetohydrazide as a solid (570mg).

(iii) A mixture of 2-(2,4-difluorophenyl)acetohydrazide (570mg, 3.06mmol) and DIPEA (0.553ml, 3.2mmol) in dry DCM (30ml) was added to 4-chlorobutyryl chloride (0.343ml, 3.06mmol) in dry DCM (5ml) over 15min. An immediate white precipitate formed. After stirring for 1h, 2M HCl (20ml) was added and the solid 2-(3-chloropropyl)-5-[(2,4-difluorophenyl)methyl]-1,3,4-oxadiazole was filtered off, washed with water and dried (726mg).
LC/MS: m/z 291 $[MH]^+$, RT 2.45min.

Example 280 : 3-Butyl-8-chloro-1-[4-(3-phenyl-5-isoxazolyl)butyl]-3,7-dihydro-1*H*-purine-2,6-dione

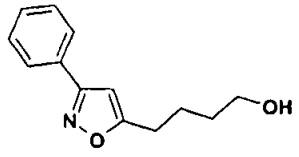
a) 3-Butyl-8-chloro-1-[4-(3-phenyl-5-isoxazolyl)butyl]-3,7-dihydro-1*H*-purine-2,6-dione



3-Butyl-8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (100mg, 0.354mmol) and 4-(3-phenyl-5-isoxazolyl)-1-butanol (77mg, 0.355mmol) were dissolved in dry THF (4ml) under nitrogen. A solution of dibenzyl azodicarboxylate (94%, 224mg, 0.708mmol) in dry THF (2ml) was added. The mixture was cooled to 0°C and a solution of triphenylphosphine (185mg, 0.708mmol) in dry THF (1ml) was added. The mixture was stirred for 20min at 0°C then at room temperature overnight. The mixture was degassed then stirred with morpholine (0.308ml) and tetrakis(triphenylphosphine)palladium(0) (82mg) for 4.5h. A further 60mg of tetrakis(triphenylphosphine)palladium(0) was added and stirring continued overnight. The reaction was worked up by partition between EtOAc and 2M HCl, the organic phase evaporated and purified by aminopropyl SPE (5g) washing with THF-MeOH

(1:1), MeOH and eluting with DCM-MeOH (1:1) containing 5% AcOH. Further purification by MDAP afforded the title compound (56mg).
LC/MS: m/z 442 $[MH]^+$, RT 3.59min.

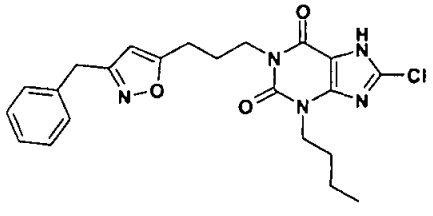
b) 4-(3-Phenyl-5-isoxazolyl)-1-butanol



To *N*-hydroxybenzenecarboximidoyl chloride (622mg, 4mmol) in dry DCM (6ml) was added 5-hexyn-1-ol (431mg, 4.4mmol). The mixture was cooled to 0°C under nitrogen as triethylamine (0.612ml, 4.4mmol) was added dropwise over 10min. Stirred for a further 20min at 0°C then at room temperature overnight. The mixture was washed with water and the organic phase evaporated. The product was purified by silica SPE (20g) eluting with EtOAc-cyclohexane (1:2, then 3:1) to give a white waxy solid (443mg).
LC/MS: m/z 218 $[MH]^+$, RT 2.74min.

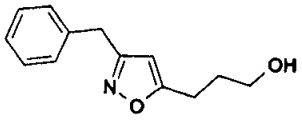
Example 281: 3-Butyl-8-chloro-1-{3-[3-(phenylmethyl)-5-isoxazolyl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione

a) 3-Butyl-8-chloro-1-{3-[3-(phenylmethyl)-5-isoxazolyl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione



Prepared analogously to 3-butyl-8-chloro-1-[4-(3-phenyl-5-isoxazolyl)butyl]-3,7-dihydro-1*H*-purine-2,6-dione (Example 280) using half the molar quantities, starting from 3-butyl-8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (50mg, 0.177mmol) and 3-[3-(phenylmethyl)-5-isoxazolyl]-1-propanol (38.4mg, 0.177mmol). Yield 24.2mg,
LC/MS: m/z 442 $[MH]^+$, RT 3.43min.

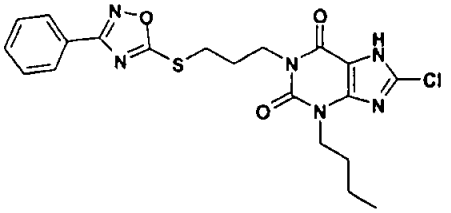
b) 3-[3-(Phenylmethyl)-5-isoxazolyl]-1-propanol



Synthesised as with 4-(3-phenyl-5-isoxazolyl)-1-butanol, using *N*-hydroxy-2-phenylethanimidoyl chloride (253mg, 1.5mmol) and 4-pentyn-1-ol (139mg, 1.65mmol). Yield 61mg of pale yellow oil.
LC/MS: m/z 218 $[MH]^+$, RT 2.62min.

Example 282: 3-Butyl-8-chloro-1-{3-[(3-phenyl-1,2,4-oxadiazol-5-yl)thio]propyl}-3,7-dihydro-1*H*-purine-2,6-dione

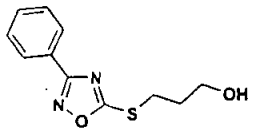
a) 3-Butyl-8-chloro-1-{3-[(3-phenyl-1,2,4-oxadiazol-5-yl)thio]propyl}-3,7-dihydro-1*H*-purine-2,6-dione



Prepared by the method of 3-butyl-8-chloro-1-[4-(3-phenyl-5-isoxazolyl)butyl]-3,7-dihydro-1*H*-purine-2,6-dione starting from 3-butyl-8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (100mg, 0.354mmol) and 3-[(3-phenyl-1,2,4-oxadiazol-5-yl)thio]-1-propanol (83.5mg, 0.354mmol) except that a 2nd aliquot of 250mg of tetrakis(triphenylphosphine)palladium(0) was added during the deprotection step. Yield 19.6mg

LC/MS: m/z 461[MH]$^+$, RT 3.75min.

b) 3-[(3-phenyl-1,2,4-oxadiazol-5-yl)thio]-1-propanol

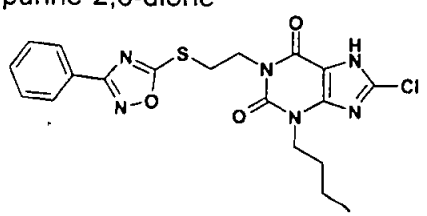


To 3-phenyl-1,2,4-oxadiazole-5(2*H*)-thione (178mg, 1mmol) in dry THF (3ml) was added DIPEA (0.174ml, 1mmol) and 3-bromo-1-propanol (139mg, 1mmol). Stirring was continued for 65h then the mixture was partitioned between EtOAc and water. The organic phase was washed with brine, dried (Na_2SO_4) and evaporated to give title compound as an oil (235mg).

LC/MS: m/z 237 [MH]$^+$, RT 2.94min.

Example 283: 3-Butyl-8-chloro-1-{2-[(3-phenyl-1,2,4-oxadiazol-5-yl)thio]ethyl}-3,7-dihydro-1*H*-purine-2,6-dione

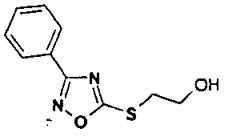
a) 3-Butyl-8-chloro-1-{2-[(3-phenyl-1,2,4-oxadiazol-5-yl)thio]ethyl}-3,7-dihydro-1*H*-purine-2,6-dione



Prepared by a method analogous to that used for Example 270 (3-Butyl-8-chloro-1-[4-(3-phenyl-5-isoxazolyl)butyl]-3,7-dihydro-1*H*-purine-2,6-dione) starting from 3-butyl-8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (141mg, 0.5mmol) and 2-[(3-

phenyl-1,2,4-oxadiazol-5-yl)thio]ethanol (111mg, 0.5mmol). A single portion of tetrakis(triphenylphosphine)palladium(0) (232mg) was used in the deprotection step, however, stirring being continued for 6h. Purification by aminopropyl SPE followed by MDAP afforded the title compound as a white solid (33.1mg).
LC/MS: m/z 447 $[MH]^+$, RT 3.67 min.

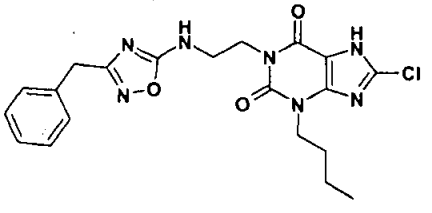
b) 2-[(3-phenyl-1,2,4-oxadiazol-5-yl)thio]ethanol



The title compound was obtained in a similar manner to 3-[(3-phenyl-1,2,4-oxadiazol-5-yl)thio]-1-propanol, from 2-bromoethanol, after a reaction time of 24h and purification by silica SPE (ethyl acetate-cyclohexane 1:1). Yield 176mg.
LC/MS: m/z 223 $[MH]^+$, RT 2.98 min.

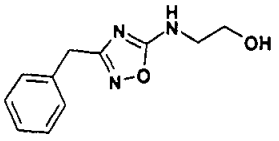
Example 284: 3-Butyl-8-chloro-1-(2-{[3-(phenylmethyl)-1,2,4-oxadiazol-5-yl]amino}ethyl)-3,7-dihydro-1*H*-purine-2,6-dione

a) 3-Butyl-8-chloro-1-(2-{[3-(phenylmethyl)-1,2,4-oxadiazol-5-yl]amino}ethyl)-3,7-dihydro-1*H*-purine-2,6-dione



3-Butyl-8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (64.4mg, 0.228mol), 2-{[3-(phenylmethyl)-1,2,4-oxadiazol-5-yl]amino}ethanol (50mg, 0.228mmol) and dibenzyl azodicarboxylate (136mg, 0.456mmol) were stirred in dry THF (3ml) at 0°C as triphenylphosphine (119mg, 0.456mmol) in dry THF (1ml) was added dropwise. The mixture was stirred at 0°C for 10min. then at room temperature for 2 overnight periods. It was thoroughly degassed and stirred with morpholine (0.2ml) and tetrakis(triphenylphosphine)palladium(0) (53mg, 0.046mmol) for 5h. A further 53mg of the catalyst was then added and stirring continued overnight. The reaction was worked up by partition between EtOAc and 2M HCl, the organic phase evaporated and purified by aminopropyl SPE (5g) washing with THF-MeOH (1:1), MeOH and eluting with DCM-MeOH (1:1) containing 5% AcOH. Further purification by MDAP afforded the title compound (11.8mg).
LC/MS: m/z 444 $[MH]^+$, RT 3.12min.

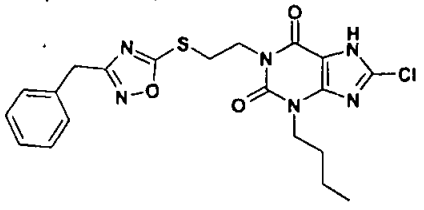
b) 2-{[3-(Phenylmethyl)-1,2,4-oxadiazol-5-yl]amino}ethanol



3-(Phenylmethyl)-5-(trichloromethyl)-1,2,4-oxadiazole (140mg, 0.505mmol) in dry DMF (2ml) was stirred with ethanolamine (0.25ml) for 1.5h. The mixture was partitioned between EtOAc and water, the organic phase washed with water, brine, dried (Na_2SO_4) and evaporated to give a white waxy solid (87mg).
LC/MS: m/z 220 $[MH]^+$, RT 2.22min.

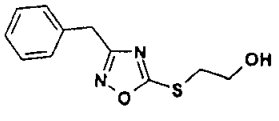
Example 285 : 3-Butyl-8-chloro-1-(2-{[3-(phenylmethyl)-1,2,4-oxadiazol-5-yl]thio}ethyl)-3,7-dihydro-1*H*-purine-2,6-dione

a) 3-Butyl-8-chloro-1-(2-{[3-(phenylmethyl)-1,2,4-oxadiazol-5-yl]thio}ethyl)-3,7-dihydro-1*H*-purine-2,6-dione



3-Butyl-8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (150mg, 0.531mmol) and 2-{[3-(phenylmethyl)-1,2,4-oxadiazol-5-yl]thio}ethanol (125mg, 0.530mmol) in dry THF (4ml) were cooled to 0°C and dibenzyl azodicarboxylate (94%, 336mg, 1.06mmol) in dry THF (2ml) was added followed by triphenylphosphine (278mg, 1.06mmol). The mixture was stirred at 0°C for 15min. then at room temperature for 2 overnight periods. Morpholine (1g) and tetrakis(triphenylphosphine)palladium(0) (250mg, 0.216mmol) were added to the degassed solution, and after 5h a further 100mg of $Pd(PPh_3)_4$ was added and stirring continued for 3 overnight periods. The reaction was worked up by partition between EtOAc and 2M HCl, the organic phase evaporated and purified by aminopropyl SPE (5g) washing with THF-MeOH (1:1), MeOH and eluting with DCM-MeOH (1:1) containing 5% AcOH. Further purification by MDAP afforded the title compound afforded title compound (26mg).
LC/MS: m/z 461$[MH]^+$, RT 3.47min.

b) 2-{[3-(Phenylmethyl)-1,2,4-oxadiazol-5-yl]thio}ethanol

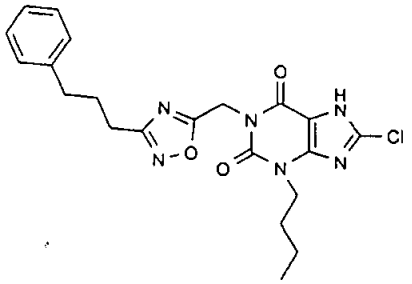


To 3-(phenylmethyl)-1,2,4-oxadiazole-5(2*H*)-thione (384mg, 2mmol) in dry THF (5ml) was added DIPEA (0.348ml, 2mmol) and 2-bromoethanol (250mg, 2mmol). The mixture was stirred at room temperature overnight and then partitioned between EtOAc and 1M HCl. The organic phase was washed with brine, dried, evaporated and purified

by silica SPE (10g) eluting with EtOAc-cyclohexane (1:2) to give title compound (315mg) as a colourless oil.
LC/MS: m/z 237 $[MH]^+$, RT 2.74min.

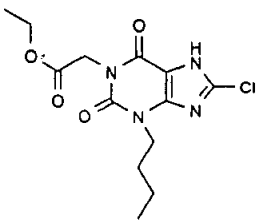
Example 286: 3-Butyl-8-chloro-1-{[3-(3-phenylpropyl)-1,2,4-oxadiazol-5-yl]methyl}-3,7-dihydro-1*H*-purine-2,6-dione

a) 3-Butyl-8-chloro-1-{[3-(3-phenylpropyl)-1,2,4-oxadiazol-5-yl]methyl}-3,7-dihydro-1*H*-purine-2,6-dione



Ethyl (3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)acetate (66mg, 0.2mmol) and (1*Z*)-*N*-hydroxy-4-phenylbutanimidamide (39mg, 0.22mmol) were stirred in dry ethanol (1ml) with ethanolic sodium ethoxide (21%wt. solution, 0.111ml, 0.3mmol) and heated under microwave irradiation at 140 C for 10 min. The cooled mixture was partitioned between ethyl acetate and 2M hydrochloric acid, the organic phase separated and evaporated. The product was purified by MDAP to give the title compound as a solid (31.5mg).
LC/MS: m/z 443 $[MH]^+$, RT 3.56 min.

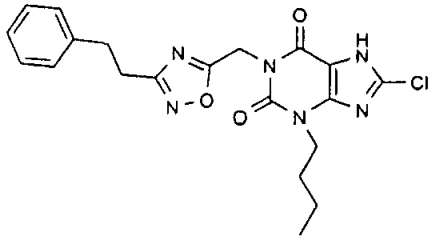
b) Ethyl (3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)acetate



3-Butyl-8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1H-purine-2,6-dione (1.5g, 5.31 mmol) and cesium carbonate (1.903g, 5.84mmol) were stirred together in dry DMF (25ml). Ethyl bromoacetate (0.648ml, 5.84mmol) was added and the mixture was stirred at 55 C overnight. The cooled mixture was degassed using nitrogen and stirred with tetrakis(triphenylphosphine)palladium(0) (1g) and morpholine (3.73ml) for 4.5h. The mixture was partitioned between ethyl acetate (80ml) and 2M HCl (50ml). The organic phase was washed with 3 x 80ml brine, filtered, dried over Na_2SO_4 and evaporated. The product was purified by aminopropyl SPE (20g), washing with THF-MeOH (1:1),

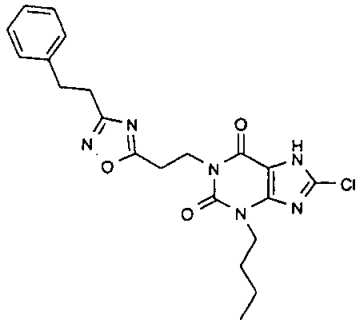
then neat MeOH and eluting the product with DCM-MeOH (1:1) containing acetic acid (2.5% rising to 5%), which gave pure title compound (1.16g).
LC/MS: m/z 329 $[MH]^+$, RT 2.87min.

Example 287: 3-Butyl-8-chloro-1-{[3-(2-phenylethyl)-1,2,4-oxadiazol-5-yl]methyl}-3,7-dihydro-1*H*-purine-2,6-dione



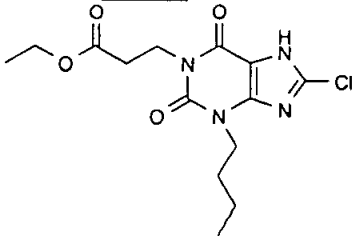
Synthesised by a method analogous to that for **Example 286**, starting from (1*Z*)-*N*-hydroxy-3-phenylpropanimidamide. Yield 22.6mg.
LC/MS: m/z 429 $[MH]^+$, RT 3.43 min.

Example 288: 3-Butyl-8-chloro-1-{2-[3-(2-phenylethyl)-1,2,4-oxadiazol-5-yl]ethyl}-3,7-dihydro-1*H*-purine-2,6-dione



Synthesised by a method analogous to that for **Example 286**, starting from (1*Z*)-*N*-hydroxy-3-phenylpropanimidamide and ethyl 3-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)propanoate. Yield 23.3mg.
LC/MS: m/z 443 $[MH]^+$, RT 3.40 min.

Example 289: Ethyl 3-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)propanoate

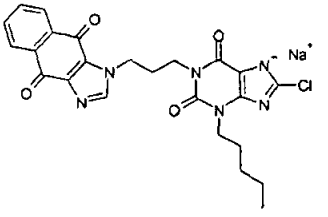
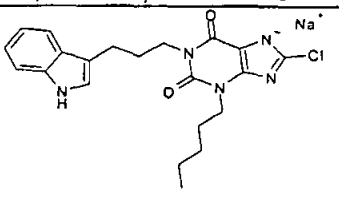
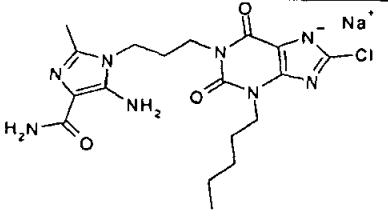


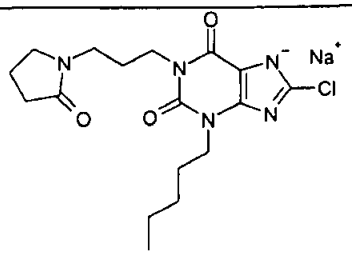
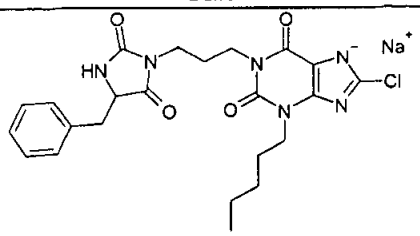
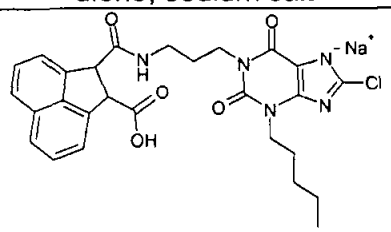
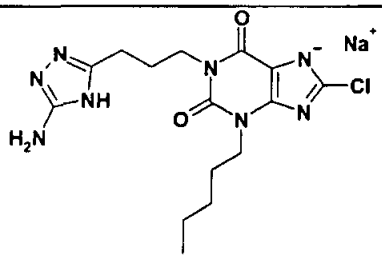
Synthesised as for ethyl (3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)acetate starting from ethyl 3-bromopropanoate (0.749ml, 5.84mmol), except that,

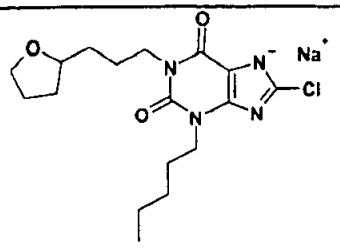
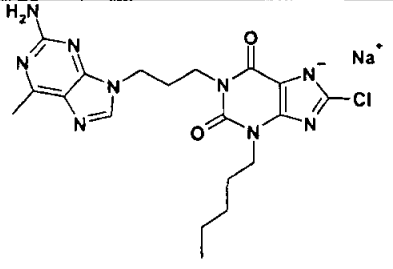
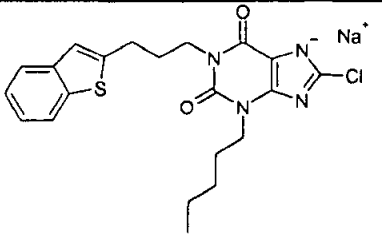
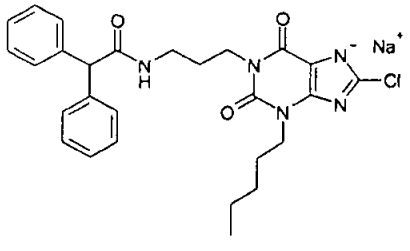
after the initial overnight heating period, further ethyl 3-bromopropanoate (1.5ml) was added, heating was resumed for a further 4h, then a further portion of cesium carbonate (1.903g), followed 2h later by a third portion of ethyl 3-bromopropanoate (1.5ml) were added. Heating at 55 C was then continued for a second overnight period before workup and deprotection as above. Yield 0.404g.
LC/MS: m/z 343 $[MH]^+$, RT 2.90min.

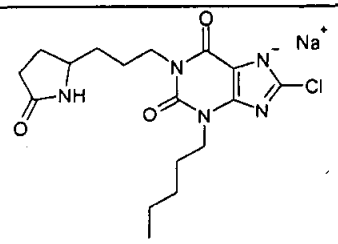
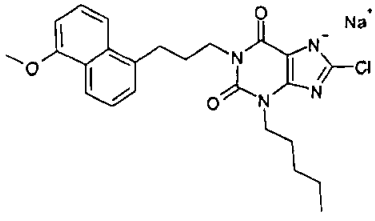
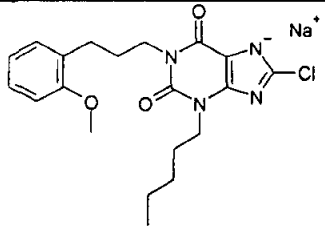
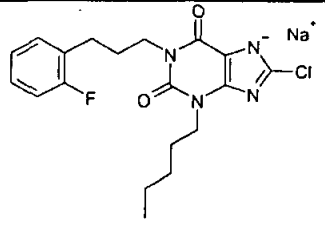
The following compounds (**Table 19**) were prepared by a method analogous to that for ***Example 3***, *with any modification noted in the method A-F.*

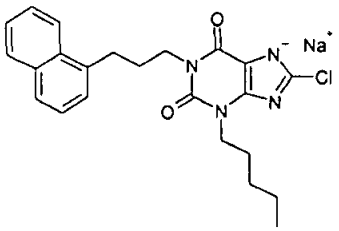
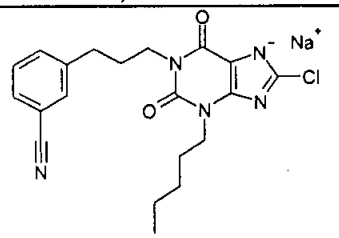
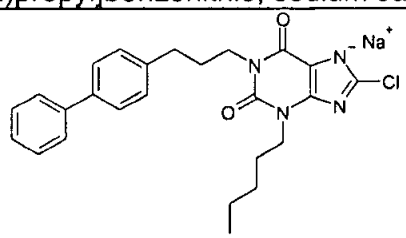
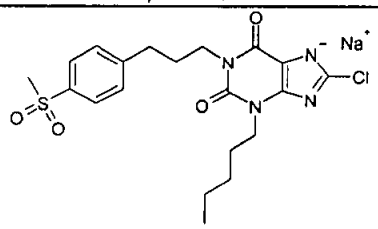
Table 19

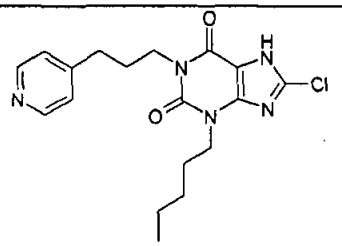
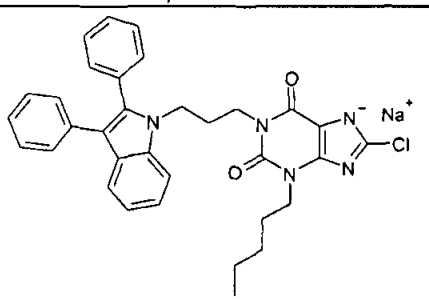
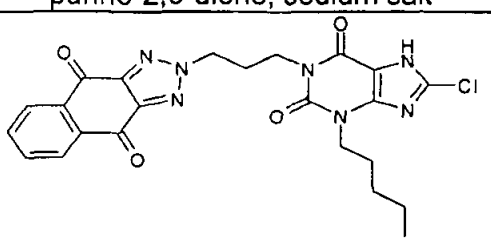
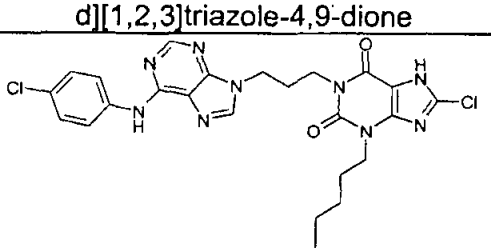
Example	Structure	Yield (mg)	LC/MS	Method
290	 1-[3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)propyl]-1H-naphtho[2,3-d]imidazole-4,9-dione, sodium salt	10	m/z 495 $[MH]^+$ RT 3.30min	A
291	 8-chloro-1-[3-(1H-indol-3-yl)propyl]-3-pentyl-3,7-dihydro-1H-purine-2,6-dione, sodium salt	24	m/z 414 $[MH]^+$ RT 3.72min	A
292	 5-amino-1-[3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)propyl]-2-methyl-1H-imidazole-4-carboxamide, sodium salt	27	m/z 437 $[MH]^+$ RT 2.41min	A

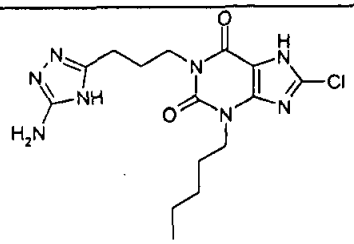
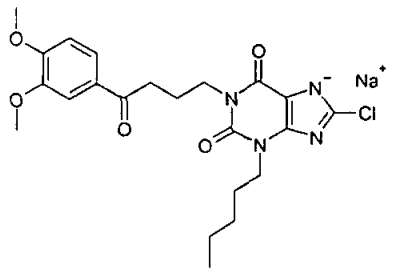
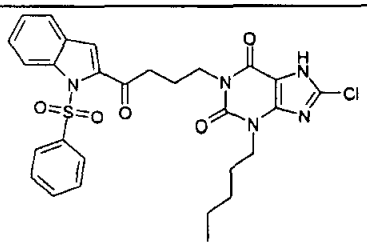
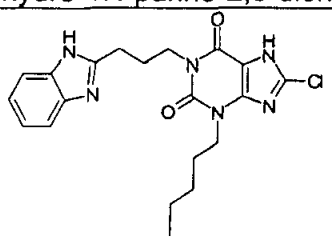
Example	Structure	Yield (mg)	LC/MS	Method
293	 8-chloro-1-[3-(2-oxo-1-pyrrolidinyl)propyl]-3-pentyl-3,7-dihydro-1H-purine-2,6-dione, sodium salt	21	m/z 382 $[MH]^+$ RT 2.86min	A
294	 8-chloro-1-{3-[2,5-dioxo-4-(phenylmethyl)-1-imidazolidinyl]propyl}-3-pentyl-3,7-dihydro-1H-purine-2,6-dione, sodium salt	9	m/z 487 $[MH]^+$ RT 3.15min	A
295	 2-({[3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)propyl]amino}carbonyl)-1,2-dihydro-1-acenaphthylenecarboxylic acid, sodium salt	39	m/z 538 $[MH]^+$ RT 3.46min	A
296	 1-[3-(3-amino-1H-1,2,4-triazol-5-yl)propyl]-8-chloro-3-pentyl-3,7-dihydro-1H-purine-2,6-dione, sodium salt	18	m/z 381 $[MH]^+$ RT 2.33min	A

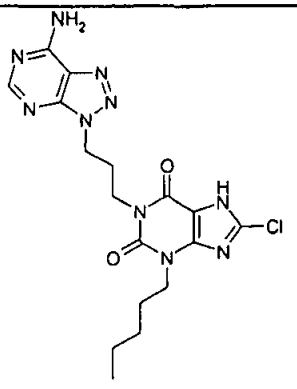
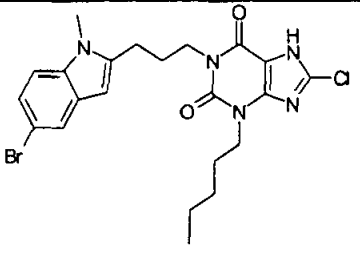
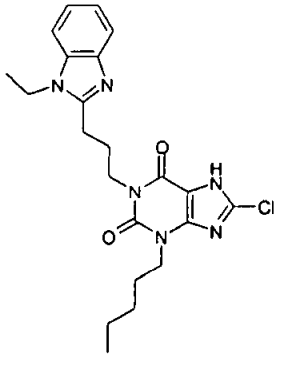
Example	Structure	Yield (mg)	LC/MS	Method
297	 8-chloro-3-pentyl-1-[3-(tetrahydro-2-furanyl)propyl]-3,7-dihydro-1H-purine-2,6-dione, sodium salt	22	m/z 369 $[MH]^+$ RT 3.2min	A
298	 1-[3-(2-amino-6-methyl-9H-purin-9-yl)propyl]-8-chloro-3-pentyl-3,7-dihydro-1H-purine-2,6-dione, sodium salt	8	m/z 446 $[MH]^+$ RT 2.55min	A
299	 1-[3-(1-benzothien-2-yl)propyl]-8-chloro-3-pentyl-3,7-dihydro-1H-purine-2,6-dione, sodium salt	21	m/z 431 $[MH]^+$ RT 3.9min	A
300	 N-[3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)propyl]-2,2-diphenylacetamide, sodium salt	31	m/z 508 $[MH]^+$ RT 3.56min	A

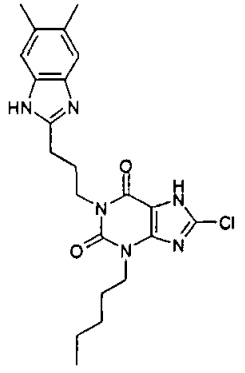
Example	Structure	Yield (mg)	LC/MS	Method
301	 8-chloro-1-[3-(5-oxo-2-pyrrolidinyl)propyl]-3-pentyl-3,7-dihydro-1H-purine-2,6-dione, sodium salt	22	m/z 382 $[MH]^+$ RT 2.76min	A
302	 8-chloro-1-{3-[5-(methyloxy)-1-naphthalenyl]propyl}-3-pentyl-3,7-dihydro-1H-purine-2,6-dione, sodium salt	33	m/z 455 $[MH]^+$ RT 4.01min	A
303	 8-chloro-1-{3-[2-(methyloxy)phenyl]propyl}-3-pentyl-3,7-dihydro-1H-purine-2,6-dione, sodium salt	5	m/z 405 $[MH]^+$ RT 3.71min	A
304	 8-chloro-1-[3-(2-fluorophenyl)propyl]-3-pentyl-3,7-dihydro-1H-purine-2,6-dione, sodium salt	15	m/z 393 $[MH]^+$ RT 3.7min	A

Example	Structure	Yield (mg)	LC/MS	Method
305	 8-chloro-1-[3-(1-naphthalenyl)propyl]-3-pentyl-3,7-dihydro-1H-purine-2,6-dione, sodium salt	15	m/z 425 $[MH]^+$ RT 4.04min	A
306	 3-[3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)propyl]benzonitrile, sodium salt	13	m/z 400 $[MH]^+$ RT 3.51min	A
307	 1-[3-(4-biphenylyl)propyl]-8-chloro-3-pentyl-3,7-dihydro-1H-purine-2,6-dione, sodium salt	19	m/z 451 $[MH]^+$ RT 4.06min	A
308	 8-chloro-1-{3-[4-(methylsulfonyl)phenyl]propyl}-3-pentyl-3,7-dihydro-1H-purine-2,6-dione, sodium salt	30	m/z 453 $[MH]^+$ RT 3.2min	A

Example	Structure	Yield (mg)	LC/MS	Method
309	 8-chloro-3-pentyl-1-[3-(4-pyridinyl)propyl]-3,7-dihydro-1H-purine-2,6-dione	2	m/z 376 $[MH]^+$ RT 2.41min	A
310	 8-chloro-1-[3-(2,3-diphenyl-1H-indol-1-yl)propyl]-3-pentyl-3,7-dihydro-1H-purine-2,6-dione, sodium salt	46	m/z 566 $[MH]^+$ RT 4.23min	A
311	 2-[3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)propyl]-2H-naphtho[2,3-d][1,2,3]triazole-4,9-dione	1	m/z 513 $[MNH4]^+$ RT 3.38min	B
312	 8-chloro-1-(3-{6-[(4-chlorophenyl)amino]-9H-purin-9-yl}propyl)-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	21	m/z 542 $[MH]^+$ RT 3.62min	B

Example	Structure	Yield (mg)	LC/MS	Method
313	 1-[3-(3-amino-1H-1,2,4-triazol-5-yl)propyl]-8-chloro-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	7	m/z 381 $[MH]^+$ RT 2.33min	B
314	 1-{4-[3,4-bis(methyloxy)phenyl]-4-oxobutyl}-8-chloro-3-pentyl-3,7-dihydro-1H-purine-2,6-dione, sodium salt	17	m/z 463 $[MH]^+$ RT 3.24min	B
315	 8-chloro-1-{4-oxo-4-[1-(phenylsulfonyl)-1H-indol-2-yl]butyl}-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	2	m/z 582 $[MH]^+$ RT 3.79min	B
316	 1-[3-(1H-benzimidazol-2-yl)propyl]-8-chloro-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	14	m/z 415 $[MH]^+$ RT 2.45min	B

Example	Structure	Yield (mg)	LC/MS	Method
317	 1-[3-(7-amino-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)propyl]-8-chloro-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	5	m/z 433 $[MH]^+$ RT 2.69min	C
318	 1-[3-(5-bromo-1-methyl-1H-indol-2-yl)propyl]-8-chloro-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	2	m/z 508 $[MH]^+$ RT 4.11min	D
319	 8-chloro-1-[3-(1-ethyl-1H-benzimidazol-2-yl)propyl]-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	17	m/z 443 $[MH]^+$ RT 2.59min	E

Example	Structure	Yield (mg)	LC/MS	Method
320	 8-chloro-1-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)propyl]-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	25	m/z 443 $[MH]^+$ RT 2.61min	F

Method A: Analogous to that for **Example 3**

Method B: Similar to Method A, except material was purified using autopreparative HPLC after purification by aminopropyl SPE.

Method C: Similar to Method A, except material was purified by washing with water after purification by aminopropyl SPE.

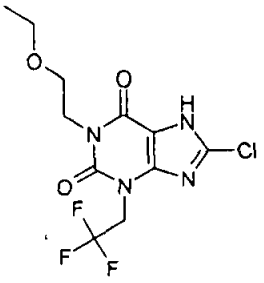
Method D: Similar to Method A, except material was purified by MDAP after purification by aminopropyl SPE.

Method E: Similar to Method A, except material was purified by SCX SPE after initial purification using aminopropyl SPE.

Method F: Similar to Method A, except material was purified using preparative HPLC using a Zorbax Phenyl column.

Example 321: 8-Chloro-1-[3-(ethyloxy)ethyl]-3-(2,2,2-trifluoroethyl)-3,7-dihydro-1*H*-purine-2,6-dione

a) 8-Chloro-1-[3-(ethyloxy)ethyl]-3-(2,2,2-trifluoroethyl)-3,7-dihydro-1*H*-purine-2,6-dione



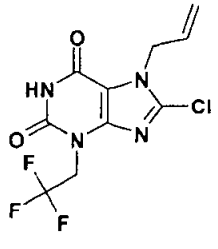
190

To a greenhouse tube equipped with a stirrer was added caesium carbonate (85mg, 0.26mmol), followed by a solution of 8-chloro-7-(2-propen-1-yl)-3-(2,2,2-trifluoroethyl)-3,7-dihydro-1*H*-purine-2,6-dione (69mg, 0.22mmol) in dry DMF (1ml) and then a solution of 1-bromo-3-(ethyloxy)ethane (60mg, 0.39mmol) in dry DMF (1ml). The mixture was heated to 80°C for 5h under nitrogen, then allowed to cool to room temperature for 16h. The reaction mixture was concentrated using a vacuum centrifuge. THF (2.5ml) was added to the mixture, followed by $Pd(PPh_3)_4$ (30mg, 0.026mmol) and morpholine (190uL, 2.2mmol) and the mixture stirred at rt under nitrogen for 72h. The mixture was partitioned between 2N HCl (2ml) and chloroform (4ml), the organic layer separated using a hydrophobic frit, and the aqueous layer extracted with chloroform (2x4ml). Combined organic layers were concentrated under reduced pressure then loaded in 1:1 DCM/MeOH onto an aminopropyl SPE (5g), washing with 1:1 DCM/MeOH and eluting with 20% to 80% acetic acid in 1:1 DCM/MeOH. Solvent was removed under reduced pressure to afford the title compound as a solid (70mg, 93%).

^{1}H NMR (MeOD) δ: 1.11 (t, 3H, J = 7Hz), 3.51 (q, 2H, J = 7Hz), 3.64 (t, 2H, J = 6Hz), 4.18 (t, 2H, J = 6Hz), 4.73 (q, 2H, J = 9Hz).

LC/MS: m/z 341 $[MH]^+$, RT 2.72min.

b) 8-Chloro-7-(2-propen-1-yl)-3-(2,2,2-trifluoroethyl)-3,7-dihydro-1*H*-purine-2,6-dione

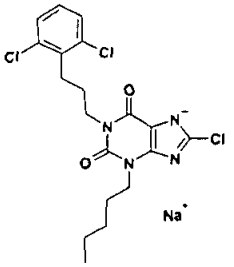


8-Chloro-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (1.5g, 6.62mmol) in dry DMF (50ml) was stirred with sodium carbonate (980mg, 9.25mmol) and 1,1,1-trifluoro-2-iodoethane (1.2g, 5.71mmol) at room temperature for 18h under nitrogen. The mixture was heated at 50°C for 6h then cooled to rt and stirred for a further 10h. The mixture was heated at 120°C for 4h, further 1,1,1-trifluoro-2-iodoethane (426mg, 2.03mmol) added, and the reaction mixture heated at 120°C for a further 3h. The reaction mixture was concentrated under reduced pressure.

A further amount of 8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (3.8g, 16.8mmol) in dry DMF (125ml) was stirred with sodium carbonate (2.5g, 23.1mmol)

and 1,1,1-trifluoro-2-iodoethane (4.1g, 19.5mmol) and the reaction mixture heated at 120°C for 16h under nitrogen. This reaction mixture was combined with the previous crude material and concentrated under reduced pressure. The residue was triturated with DCM, the mixture filtered, and the filtrate concentrated under reduced pressure then dissolved in DCM (20ml). 10ml of this material was purified by silica chromatography using a 100g Silica column, eluting the title compound with a suitable gradient of ethyl acetate/cyclohexane. The remaining 10ml was purified using a Silica RediSep cartridge (130g) on a Companion, eluting the title compound with a suitable gradient of ethyl acetate/cyclohexane. Fractions containing the title compound from both purification modes were combined and concentrated under reduced pressure to give the title compound as a white solid (1.6g, 22% overall yield).
LC/MS: m/z 309 $[MH]^+$, RT 2.59min.

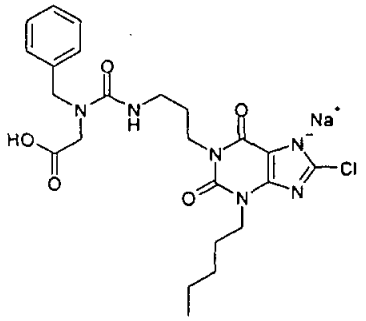
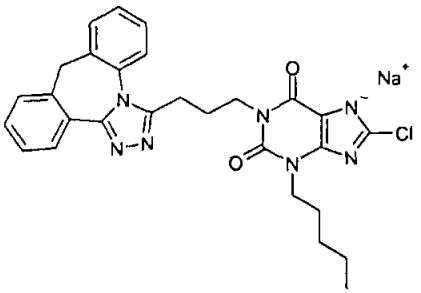
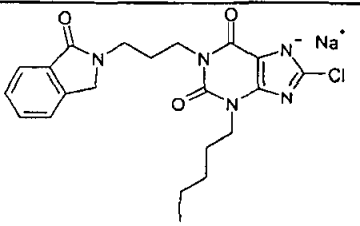
Example 322: 8-Chloro-1-[3-(2,6-dichlorophenyl)propyl]-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione, sodium salt

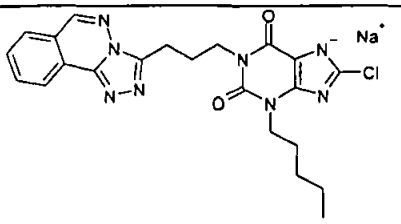
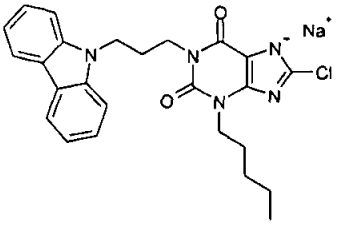
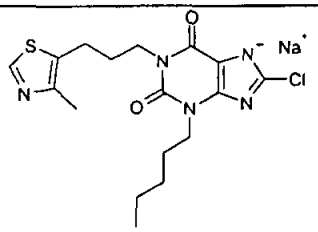
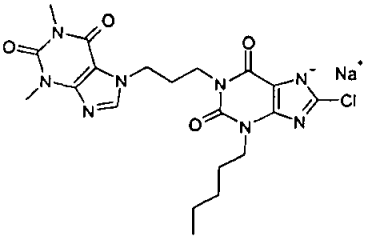


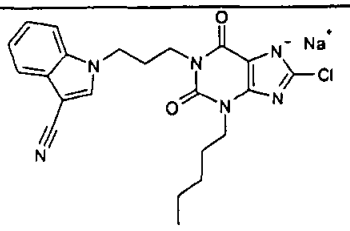
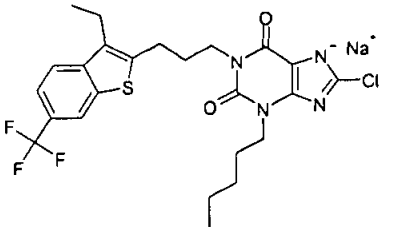
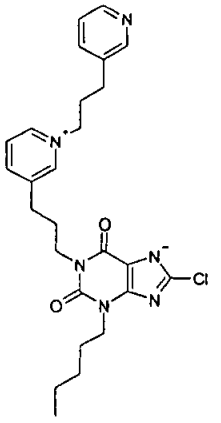
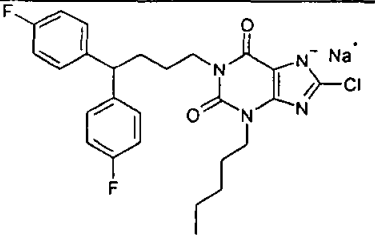
To a solution of 8-chloro-3-pentyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (40mg, 0.14mmol) in dry DMF (0.25ml) was added caesium carbonate (49mg, 0.15mmol) followed by a solution of 2-(3-bromopropyl)-1,3-dichlorobenzene (54mg, 0.20mmol) in dry DMF (0.25ml). The mixtures were stirred at 60°C for 16h, then $Pd(PPh_3)_4$ (16mg, 0.014mmol) added, followed by morpholine (118uL, 1.4mmol) and the mixtures stirred for a further 16h. Solvent was removed using a vacuum centrifuge and the sample dissolved in DMSO (0.25ml) then loaded onto a C18 SPE (5g). 2N NaOH (0.5ml) was added and a suitable gradient of ammonia/water/MeCN used to elute the product. The title compound was isolated as a solid (52mg, 83%).
^1H NMR (DMSO-d_6) δ: 0.84 (t, 3H, J = 7Hz), 1.18 - 1.36 (m, 4H), 1.55 - 1.69 (m, 2H), 1.69 - 1.85 (m, 2H), 2.78 - 2.89 (m, 2H), 3.85 (t, 2H, J = 7Hz), 3.95 (t, 2H, J = 7Hz), 7.23 (dd, 1H, J = 9 and 7Hz), 7.41 (d, 2H, J = 7Hz).
LC/MS: m/z 445 $[MH]^+$, RT 4.05min.

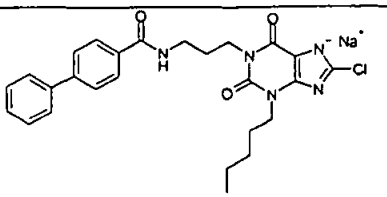
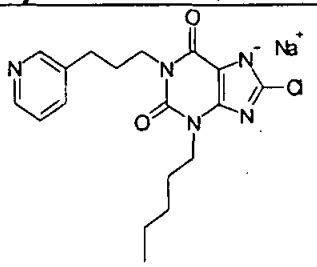
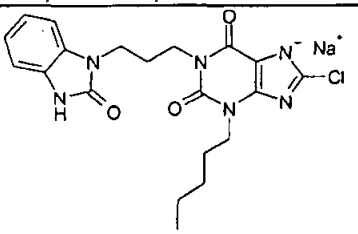
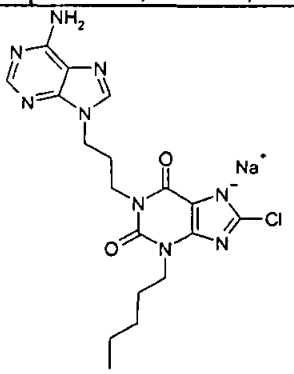
The following compounds (**Table 20**) were prepared using a method analogous to that for the **Example 322**, from the corresponding alkyl halides:

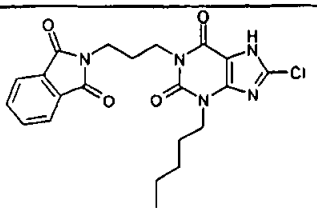
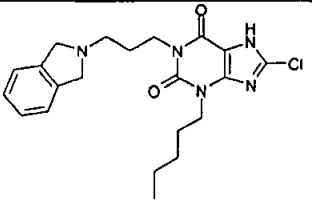
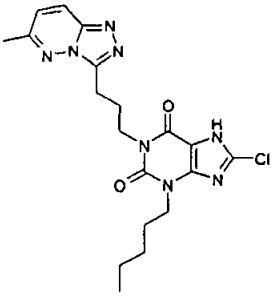
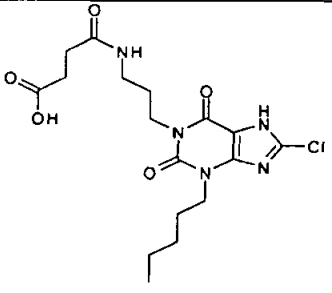
Table 20

Example	Structure	Yield (mg)	LC/MS:	Method
323	 *N*-({[3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)propyl]amino}carbonyl)-*N*-(phenylmethyl)glycine, sodium	57	m/z 505 $[MH]^+$ RT 3.14min	A
324	 8-chloro-1-[3-(9H-dibenzo[c,f][1,2,4]triazolo[4,3-a]azepin-3-yl)propyl]-3-pentyl-3,7-dihydro-1H-purine-2,6-dione, sodium	16	m/z 530 $[MH]^+$ RT 3.36min	A
325	 8-chloro-1-[3-(1-oxo-1,3-dihydro-2H-isoindol-2-yl)propyl]-3-pentyl-3,7-dihydro-1H-purine-2,6-dione, sodium salt	18	m/z 430 $[MH]^+$ RT 3.12min	A

Example	Structure	Yield (mg)	LC/MS:	Method
326	 8-chloro-3-pentyl-1-(3-[1,2,4]triazolo[3,4-a]phthalazin-3-ylpropyl)-3,7-dihydro-1H-purine-2,6-dione, sodium salt	18	m/z 467 $[MH]^+$ RT 2.99min	A
327	 1-[3-(9H-carbazol-9-yl)propyl]-8-chloro-3-pentyl-3,7-dihydro-1H-purine-2,6-dione, sodium salt	30	m/z 464 $[MH]^+$ RT 4.03min	A
328	 8-chloro-1-[3-(4-methyl-1,3-thiazol-5-yl)propyl]-3-pentyl-3,7-dihydro-1H-purine-2,6-dione, sodium salt	42	m/z 396 $[MH]^+$ RT 3.17min	A
329	 7-[3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)propyl]-1,3-dimethyl-3,7-dihydro-1H-purine-2,6-dione, sodium salt	31	m/z 477 $[MH]^+$ RT 2.83min	A

Example	Structure	Yield (mg)	LC/MS:	Method
330	 1-[3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)propyl]-1H-indole-3-carbonitrile, sodium salt	50	m/z 439 $[MH]^+$ RT 3.56min	A
331	 8-chloro-1-{3-[3-ethyl-6-(trifluoromethyl)-1-benzothien-2-yl]propyl}-3-pentyl-3,7-dihydro-1H-purine-2,6-dione, sodium	10	m/z 527 $[MH]^+$ RT 4.3min	A
332	 3-[3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)propyl]-1-[3-(3-pyridinyl)propyl]pyridinium	5	m/z 495 $[MH]^+$ RT 2.21min	A
333	 1-[4,4-bis(4-fluorophenyl)butyl]-8-chloro-3-pentyl-3,7-dihydro-1H-purine-2,6-dione, sodium salt	45	m/z 501 $[MH]^+$ RT 4.01min	A

Example	Structure	Yield (mg)	LC/MS:	Method
334	 N-[3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)propyl]-4-biphenylcarboxamide, sodium salt	33	m/z 494 $[MH]^+$ RT 3.69min	A
335	 8-chloro-3-pentyl-1-[3-(3-pyridinyl)propyl]-3,7-dihydro-1H-purine-2,6-dione, sodium salt	18	m/z 376 $[MH]^+$ RT 2.5min	A
336	 8-chloro-1-[3-(2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)propyl]-3-pentyl-3,7-dihydro-1H-purine-2,6-dione, sodium salt	39	m/z 431 $[MH]^+$ RT 3.13min	A
337	 1-[3-(6-amino-9H-purin-9-yl)propyl]-8-chloro-3-pentyl-3,7-dihydro-1H-purine-2,6-dione, sodium salt	4	m/z432 $[MH]^+$ RT 2.53min	B

Example	Structure	Yield (mg)	LC/MS:	Method
338	 8-chloro-1-[3-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)propyl]-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	1	m/z 444 $[MH]^+$ RT 3.39min	C
339	 8-chloro-1-[3-(1,3-dihydro-2H-isoindol-2-yl)propyl]-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	3	m/z 416 $[MH]^+$ RT 2.87min	C
340	 8-chloro-1-[3-(6-methyl[1,2,4]triazolo[4,3-b]pyridazin-3-yl)propyl]-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	8	m/z 431 $[MH]^+$ RT 2.83min	D
341	 8-chloro-1-[3-(6-methyl[1,2,4]triazolo[4,3-b]pyridazin-3-yl)propyl]-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	3	m/z 414 $[MH]^+$ RT 2.64min	E

Method A: Analogous to that for **Example 3**

Method B: Similar to Method A, except after concentration by vacuum centrifuge, material was partitioned between 2M HCl and DCM, the aqueous layer isolated then purified using C18 SPE in the manner described in Method A.

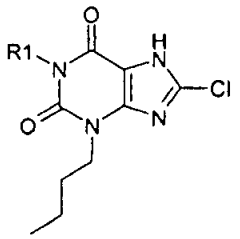
Method C: Similar to Method A, except after concentration by vacuum centrifuge, material was partitioned between 2M HCl and DCM, and the product was isolated from the organic layer after autopreparative HPLC.

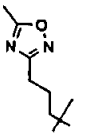
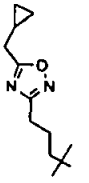
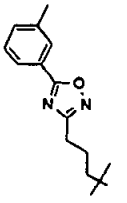
Method D: Similar to Method A, except product was isolated using aminopropyl SPE.

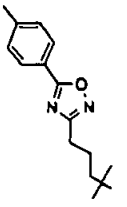
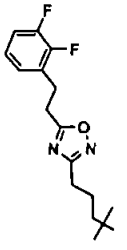
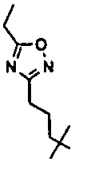
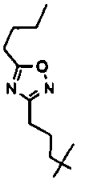
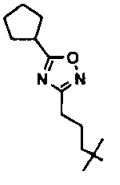
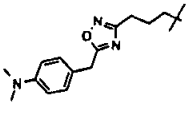
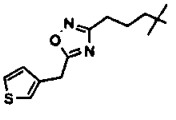
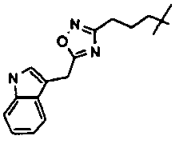
Method E: Similar to Method A, except material was further purified on a phenyl HPLC using a suitable gradient of water/MeOH/MeCN/TFA, then autopreparative HPLC, using a suitable gradient of water/acetonitrile.

The following compounds (**Table 21**) were prepared using a method analogous to that for **Example 142**, from the corresponding acids and (1*Z*)-4-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)-*N*-hydroxybutanimidamide.

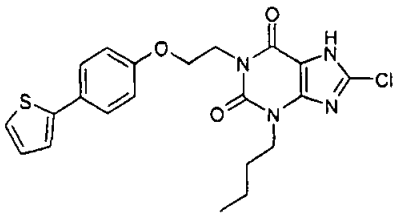
Table 21



Example	Name	Compound: R1 =	LC/MS
342	3-butyl-8-chloro-1-[3-(5-methyl-1,2,4-oxadiazol-3-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione		m/z 367 $[MH]^+$ RT 2.7min
343	3-butyl-8-chloro-1-{3-[5-(cyclopropylmethyl)-1,2,4-oxadiazol-3-yl]propyl}-3,7-dihydro-1H-purine-2,6-dione		m/z 407 $[MH]^+$ RT 3.11min
344	3-butyl-8-chloro-1-{3-[5-(3-methylphenyl)-1,2,4-oxadiazol-3-yl]propyl}-3,7-dihydro-1H-purine-2,6-dione		m/z 443 $[MH]^+$ RT 3.47min

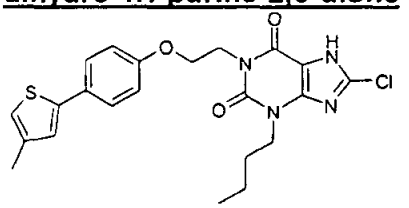
Example	Name	Compound: R1 =	LC/MS
345	3-butyl-8-chloro-1-{3-[5-(4-methylphenyl)-1,2,4-oxadiazol-3-yl]propyl}-3,7-dihydro-1H-purine-2,6-dione		m/z 443 $[MH]^+$ RT 3.34min
346	3-butyl-8-chloro-1-(3-{5-[2-(2,3-difluorophenyl)ethyl]-1,2,4-oxadiazol-3-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione		m/z 493 $[MH]^+$ RT 3.47min
347	3-butyl-8-chloro-1-[3-(5-ethyl-1,2,4-oxadiazol-3-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione		m/z 381 $[MH]^+$ RT 2.9min
348	3-butyl-1-[3-(5-butyl-1,2,4-oxadiazol-3-yl)propyl]-8-chloro-3,7-dihydro-1H-purine-2,6-dione		m/z 409 $[MH]^+$ RT 3.27min
349	3-butyl-8-chloro-1-[3-(5-cyclopentyl-1,2,4-oxadiazol-3-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione		m/z 421 $[MH]^+$ RT 3.29min
350	3-butyl-8-chloro-1-[3-(5-{[4-(dimethylamino)phenyl]methyl}-1,2,4-oxadiazol-3-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione		m/z 486 $[MH]^+$ RT 3.24min
351	3-butyl-8-chloro-1-{3-[5-(3-thienylmethyl)-1,2,4-oxadiazol-3-yl]propyl}-3,7-dihydro-1H-purine-2,6-dione		m/z 449 $[MH]^+$ RT 3.24min
352	3-butyl-8-chloro-1-{3-[5-(1H-indol-3-ylmethyl)-1,2,4-oxadiazol-3-yl]propyl}-3,7-dihydro-1H-purine-2,6-dione		m/z 482 $[MH]^+$ RT 3.29min

Example 353: 3-Butyl-8-chloro-1-(2-{[4-(2-thienyl)phenyl]oxy}ethyl)-3,7-dihydro-1*H*-purine-2,6-dione



A microwave vial containing a magnetic stirrer bar was charged with 2-thienylboronic acid (16mg, 0.125mmol), 1-{2-[(4-bromophenyl)oxy]ethyl}-3-butyl-8-chloro-3,7-dihydro-1H-purine-2,6-dione (50mg, 0.113mmol), aqueous sodium carbonate (1ml, 1M solution) and dimethoxyethane (1ml). This mixture was degassed with nitrogen and then $Pd(PPh_3)_2Cl_2$ (4mg, 5.6x10-6mol) was added. The reaction mixture was capped and heated at 140°C in a microwave for 15min (pressure reached 7bar). The crude reaction mixture was acidified with HCl (2M, 1.5ml), washed with chloroform (2x1ml) and the phases separated. The combined organics were evaporated and the crude product purified by MDAP to afford the title compound (10mg).
LC/MS: m/z 445 $[MH]^+$, RT 3.76min

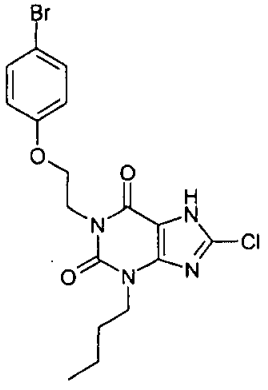
Example 354: 3-Butyl-8-chloro-1-(2-{[4-(4-methyl-2-thienyl)phenyl]oxy}ethyl)-3,7-dihydro-1*H*-purine-2,6-dione



A microwave vial containing a magnetic stirrer bar was charged with (4-methyl-2-thienyl)boronic acid (18mg, 0.125mmol), 1-{2-[(4-bromophenyl)oxy]ethyl}-3-butyl-8-chloro-3,7-dihydro-1H-purine-2,6-dione (50mg, 0.113mmol), aqueous sodium carbonate (1ml, 1M solution) and dimethoxyethane (1ml). This mixture was degassed with nitrogen and then $Pd(PPh_3)_2Cl_2$ (4mg, 0.0056mmol) was added. The reaction mixture was capped and heated at 140°C in a microwave for 15min (pressure reached 7bar). The crude reaction mixture was acidified with HCl (2M, 1.5ml), washed with chloroform (2x1ml) and the phases separated. The combined organics were evaporated and the crude product purified by MDAP to afford the title compound (17mg).
LC/MS: m/z 459 $[MH]^+$, RT 3.9min

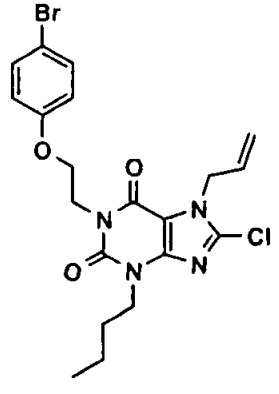
Example 355: 1-{2-[(4-Bromophenyl)oxy]ethyl}-3-butyl-8-chloro-3,7-dihydro-1H-purine-2,6-dione

a) 1-{2-[(4-Bromophenyl)oxy]ethyl}-3-butyl-8-chloro-3,7-dihydro-1H-purine-2,6-dione



1-{2-[(4-Bromophenyl)oxy]ethyl}-3-butyl-8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (2.3g, 4.8mmol) was stirred in a mixture of nitrogen degassed DCM (40ml) and AcOH (4ml). Tetrakis(triphenylphosphine)palladium (1.1g, 0.896mmol) and phenylsilane (5.9ml, 48mmol) were added and the mixture stirred at rt for 2h. This was then evaporated and the residue triturated with a mixture of diethylether:cyclohexane (1:2) to afford the title compound (1.02g, 49%) as a white solid.
LC/MS: m/z 441/443 $[MH]^+$, RT 3.6min

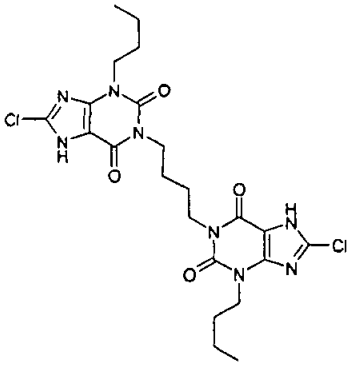
b) 1-{2-[(4-bromophenyl)oxy]ethyl}-3-butyl-8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione



3-Butyl-8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (2.8g, 9.8mmol) in dry DMF (50ml) was added Cs_2CO_3 (6.4g, 19.6mmol) followed by 2-bromoethyl 4-bromophenyl ether (3.6g, 13mmol). The mixture was heated at 80°C for 17h and then allowed to cool. The reaction mixture was evaporated and the crude product partitioned between EtOAc and HCl (2N). The organic phase was separated and washed with brine, dried ($MgSO_4$) and evaporated to give the crude product. This was purified by silica SPE (50g), eluting with cyclohexane:ethylacetate (10:1 to 1:1) to afford the title compound as a cream coloured solid (2.9g, 62%).
LC/MS: m/z 381/483 $[MH]^+$, RT 3.87min.

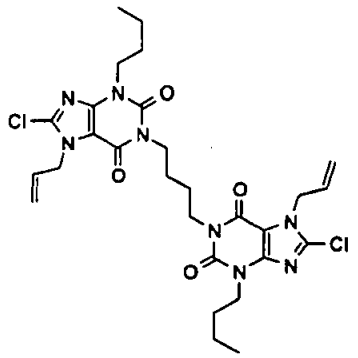
Example 356: 1,1'-(1,4-Butanediyl)bis(3-butyl-8-chloro-3,7-dihydro-1*H*-purine-2,6-dione)

a) 1,1'-(1,4-Butanediyl)bis(3-butyl-8-chloro-3,7-dihydro-1*H*-purine-2,6-dione)



1,1'-(1,4-Butanediyl)bis[3-butyl-8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione] (24mg, 0.039mmol) was stirred in a mixture of nitrogen degassed DCM (2ml) and AcOH (0.2ml). Tetrakis(triphenylphosphine)palladium (38mg, 0.033mmol) and phenylsilane (42uL, 0.39mmol) were added and the mixture stirred at rt for 2h. This was then evaporated and the crude product purified by reverse phase chromatography (5-95% gradient, H_2O: CH_3CN) to afford the title compound (2mg).
LC/MS: m/z 539 $[MH]^+$, RT 3.33min

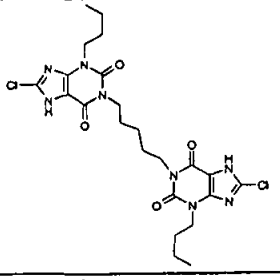
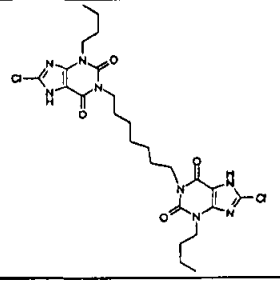
b) 1,1'-(1,4-Butanediyl)bis[3-butyl-8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione]



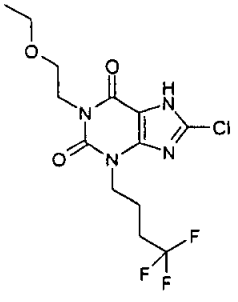
3-Butyl-8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (60mg, 0.212mmol) in dry DMF (1ml) was added Cs_2CO_3 (207mg, 0.636mol) followed by 1,4-diiodobutane (16uL, 0.106mmol). The mixture was heated at 80°C for 17h and then allowed to cool. The reaction mixture was partitioned between DCM and HCl (2M). The organic phase was separated and washed with brine, dried ($MgSO_4$) and evaporated to give the crude product. This was purified by MDAP to afford the title compound as a cream coloured solid (24mg).
LC/MS: m/z 619 $[MH]^+$, RT 3.95min.

The following compounds (**Table 22**) were prepared using a method analogous to that for **Example 356**.

Table 22

Example	Name	Structure	Yield	LC/MS:
357	3-butyl-1-[5-(3-butyl-8-chloro-2,6-dioxo-2,3,6,9-tetrahydro-1*H*-purin-1-yl)pentyl]-8-chloro-3,7-dihydro-1*H*-purine-2,6-dione		2.4mg	m/z 553 $[MH]^+$ RT 3.43min
358	3-butyl-1-[7-(3-butyl-8-chloro-2,6-dioxo-2,3,6,9-tetrahydro-1*H*-purin-1-yl)heptyl]-8-chloro-3,7-dihydro-1*H*-purine-2,6-dione		3.6mg	m/z 581 $[MH]^+$ RT 3.72min

Example 359: 8-Chloro-1-[2-(ethyloxy)ethyl]-3-(4,4,4-trifluorobutyl)-3,7-dihydro-1*H*-purine-2,6-dione



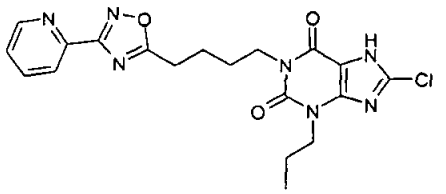
A solution of 8-chloro-7-(2-propen-1-yl)-3-(4,4,4-trifluorobutyl)-3,7-dihydro-1H-purine-2,6-dione (84mg, 0.25mmol) in DMF (1ml) was treated with caesium carbonate (163mg, 0.5mmol) and 1-bromo-2-(ethyloxy)ethane (42mg, 0.275mmol). The mixture was heated at 80°C for 4h and then cooled.

The reaction mixture was degassed with nitrogen and then treated with morpholine (220uL) and tetrakis(triphenylphosphine)palladium (29mg, 0.025mmol) and stirred for 4h. The reaction mixture was partitioned between chloroform and HCl (2M). The organic phase was separated and evaporated. The crude product was loaded on to an aminopropyl SPE. The non acidic impurities were eluted with a mixture of DCM and MeOH and the desired product eluted with 10%AcOH in DCM. Evaporation afforded the title compound (77mg).

LC/MS: m/z 369 $[MH]^+$, RT 1.96min.

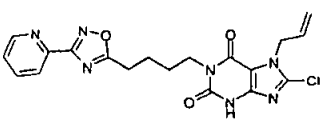
Example 360: 8-Chloro-3-propyl-1-{4-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione

a) 8-Chloro-3-propyl-1-{4-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione



A solution of 8-chloro-7-(2-propen-1-yl)-1-{4-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione (40mg, 0.09mmol) in DMF (3ml) was treated with potassium carbonate (15mg, 0.11mmol) and 1-iodopropane (19mg, 0.11mmol). The mixture was heated at 40°C for 3h then at 70°C for a further 3h. The mixture was cooled and degassed by the successive application of vacuum and nitrogen gas. The mixture was then treated with a solution of tetrakis(triphenylphosphine)palladium(0) (10mg, 0.009mmol) and morpholine (0.1ml, 1.2mmol) and then stirred overnight. The mixture was evaporated and partitioned between chloroform (2ml) and water (2ml). The aqueous phase was extracted with further chloroform (2ml) and the combined organics evaporated and the residue dissolved in methanol (2ml). The solution was applied to a 1g aminopropyl SPE and eluted with methanol and then with 5% acetic acid in methanol. Product-containing fractions were pooled and evaporated and the product further purified by MDAP to reveal 8-chloro-3-propyl-1-{4-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione (1.4mg) as a white solid.
LC/MS: m/z 430 $[MH]^+$, RT 2.84min.

b) 8-Chloro-7-(2-propen-1-yl)-1-{4-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione

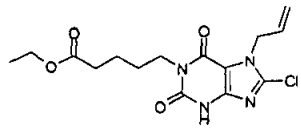


A suspension of *N*-hydroxy-2-pyridinecarboximidamide (1.15g, 8.4mmol) in anhydrous THF (20ml) was treated with sodium methoxide (0.38g, 7.0mmol) and the mixture stirred for 5min. The mixture was treated with ethyl 5-[8-chloro-2,6-dioxo-7-(2-propen-1-yl)-2,3,6,7-tetrahydro-1*H*-purin-1-yl]pentanoate (2g, 5.6mmol) and the stirred for about 5min until all the material had dissolved. The mixture was then sealed and heated in a microwave at 120°C for 15min then cooled and partitioned between ethyl acetate (100ml) and saturated aqueous sodium bicarbonate (50ml). The aqueous phase was extracted with further ethyl acetate (50ml) and the combined organics dried ($MgSO_4$), filtered and evaporated. The product was purified by flash chromatography using a gradient elution from 1:9 ethyl acetate/cyclohexane to ethyl acetate to reveal 8-

chloro-7-(2-propen-1-yl)-1-{4-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione (1.49g) as a white solid.
LC/MS: m/z 428 $[MH]^+$, RT 2.70min.

Similarly prepared was 8-chloro-1-(3-{3-[(2,4-difluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione using ethyl 4-[8-chloro-2,6-dioxo-7-(2-propen-1-yl)-2,3,6,7-tetrahydro-1*H*-purin-1-yl]butanoate.
LC/MS: m/z 463 $[MH]^+$, RT 3.09min.

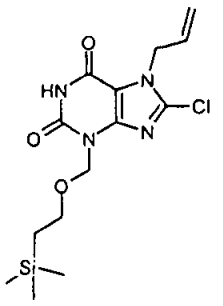
c) Ethyl 5-[8-chloro-2,6-dioxo-7-(2-propen-1-yl)-2,3,6,7-tetrahydro-1*H*-purin-1-yl]pentanoate



A solution of 8-chloro-7-(2-propen-1-yl)-3-({[2-(trimethylsilyl)ethyl]oxy}methyl)-3,7-dihydro-1*H*-purine-2,6-dione (10g, 28mmol) in DMF (10ml) was treated with potassium carbonate (4.8g, 35mmol) and ethyl 5-bromopentanoate (6.5g, 31mmol) and then heated to 70°C for 3h, cooled and evaporated. The residue was partitioned between ethyl acetate (100ml) and water (50ml). The organic phase was dried ($MgSO_4$), filtered and evaporated and the crude intermediate dissolved in dichloromethane (90ml), treated with trifluoroacetic acid (17ml) and the mixture stirred at ambient temperature overnight. Toluene (50ml) was added and the mixture evaporated to dryness. The product was purified by flash chromatography using a gradient elution from cyclohexane to ethyl acetate to reveal 8.65g of ethyl 5-[8-chloro-2,6-dioxo-7-(2-propen-1-yl)-2,3,6,7-tetrahydro-1*H*-purin-1-yl]pentanoate as a white solid.
LC/MS: m/z 355 $[MH]^+$, RT 2.75min.

Similarly prepared was ethyl 4-[8-chloro-2,6-dioxo-7-(2-propen-1-yl)-2,3,6,7-tetrahydro-1*H*-purin-1-yl]butanoate.
LC/MS: m/z 341 $[MH]^+$, RT 2.61min.

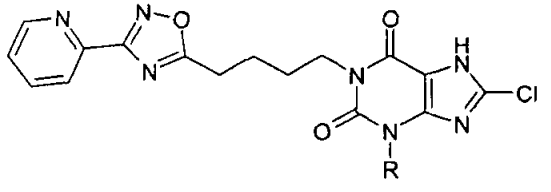
d) 8-Chloro-7-(2-propen-1-yl)-3-({[2-(trimethylsilyl)ethyl]oxy}methyl)-3,7-dihydro-1H-purine-2,6-dione



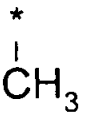
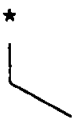
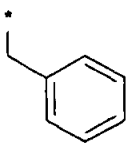
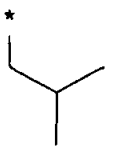
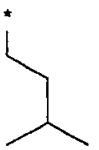
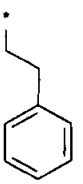
To a solution of 8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1H-purine-2,6-dione (5g, 22.1mmol) in DMF (80ml) was added 2-2-(trimethylsilyl)ethoxymethyl chloride (4.3ml, 24.2mmol) and sodium carbonate (2.6g, 24.2mmol). After stirring at room temperature overnight further 2-2-(trimethylsilyl)ethoxymethyl chloride (4.3ml, 24.2mmol) and sodium carbonate (1.3g, 12.1mmol) were added and stirring continued for 2h. The reaction mixture was then partitioned between 5% LiCl aq and ethyl acetate. The organic extract was separated, washed with brine, dried ($MgSO_4$) and concentrated. Purification by Biotage™ chromatogratphy using a silica cartridge eluting 1:4-1:2 ethyl acetate/cyclohexane afforded the title compound (3.14g, 40%).
m/z 374 [MNH_4^+]

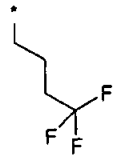
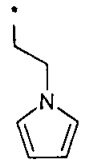
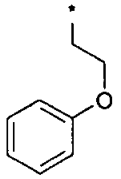
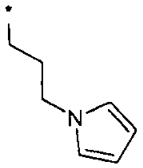
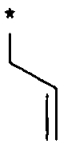
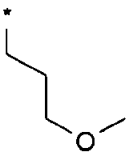
The following compounds (**Table 23**) were prepared by a method analogous to that for **Example 360**, from 8-chloro-7-(2-propen-1-yl)-1-{4-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione and the appropriate alkylating agent.

Table 23



Example	R =	Name	Yield (mg)	m/z	RT (min)
361		8-chloro-1-{4-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	2.5	388	2.37

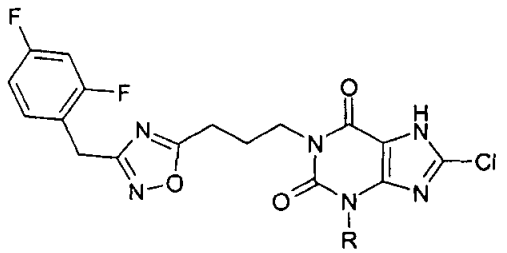
Example	R =	Name	Yield (mg)	m/z	RT (min)
362		8-chloro-3-methyl-1-{4-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	1.7	402	2.53
363		8-chloro-3-ethyl-1-{4-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	1.4	416	2.66
364		8-chloro-3-(phenylmethyl)-1-{4-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	1.3	478	3.09
365		8-chloro-3-(2-methylpropyl)-1-{4-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	2.0	444	2.99
366		8-chloro-3-(3-methylbutyl)-1-{4-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	1.6	458	3.21
367		8-chloro-3-(2-phenylethyl)-1-{4-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	2.1	492	3.18

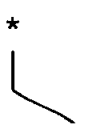
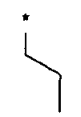
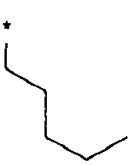
Example	R =	Name	Yield (mg)	m/z	RT (min)
368		8-chloro-1-{4-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]butyl}-3-(4,4,4-trifluorobutyl)-3,7-dihydro-1*H*-purine-2,6-dione	2.1	498	3.07
369		8-chloro-1-{4-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]butyl}-3-[2-(1*H*-pyrrol-1-yl)ethyl]-3,7-dihydro-1*H*-purine-2,6-dione	2.7	481	2.89
370		8-chloro-3-[2-(phenyloxy)ethyl]-1-{4-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	1.7	508	3.11
371		8-chloro-1-{4-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]butyl}-3-[3-(1*H*-pyrrol-1-yl)propyl]-3,7-dihydro-1*H*-purine-2,6-dione	2.1	495	3.01
372		8-chloro-3-(2-propen-1-yl)-1-{4-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	1.3	428	2.73
373		8-chloro-3-[3-(methyloxy)propyl]-1-{4-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	1.0	460	2.65

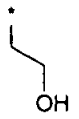
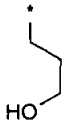
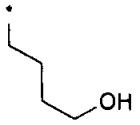
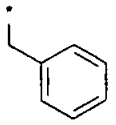
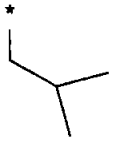
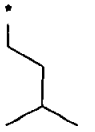
The following compounds (Table 24) were prepared by a method analogous to that for **Example 360**, from 8-chloro-1-(3-{3-[(2,4-difluorophenyl)methyl]-1,2,4-oxadiazol-5-

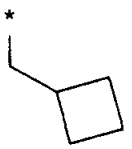
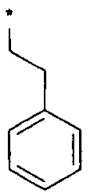
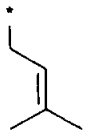
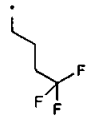
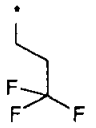
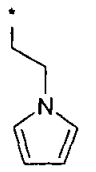
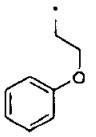
yl}propyl)-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione and the appropriate alkylating agent.

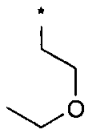
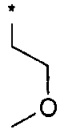
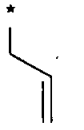
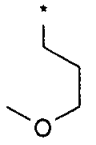
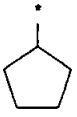
Table 24



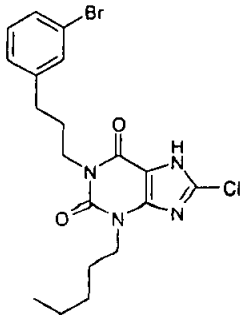
Example	R =	Name	Yield (mg)	m/z	RT (min)
374		8-chloro-1-(3-{3-[(2,4-difluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione	2.5	423	2.71
375		8-chloro-1-(3-{3-[(2,4-difluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3-methyl-3,7-dihydro-1*H*-purine-2,6-dione	1.7	437	2.92
376		8-chloro-1-(3-{3-[(2,4-difluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3-ethyl-3,7-dihydro-1*H*-purine-2,6-dione	1.4	451	3.06
377		8-chloro-1-(3-{3-[(2,4-difluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3-propyl-3,7-dihydro-1*H*-purine-2,6-dione	2.2	465	3.22
378		8-chloro-1-(3-{3-[(2,4-difluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione	2.6	493	3.54

Example	R =	Name	Yield (mg)	m/z	RT (min)
379		8-chloro-1-(3-{3-[(2,4-difluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3-(2-hydroxyethyl)-3,7-dihydro-1*H*-purine-2,6-dione	2.7	467	2.72
380		8-chloro-1-(3-{3-[(2,4-difluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3-(3-hydroxypropyl)-3,7-dihydro-1*H*-purine-2,6-dione	2.0	481	2.77
381		8-chloro-1-(3-{3-[(2,4-difluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3-(4-hydroxybutyl)-3,7-dihydro-1*H*-purine-2,6-dione	1.4	495	2.80
382		8-chloro-1-(3-{3-[(2,4-difluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3-(phenylmethyl)-3,7-dihydro-1*H*-purine-2,6-dione	1.6	513	3.43
383		8-chloro-3-(cyclopropylmethyl)-1-(3-{3-[(2,4-difluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione	1.8	477	3.30
384		8-chloro-1-(3-{3-[(2,4-difluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3-(2-methylpropyl)-3,7-dihydro-1*H*-purine-2,6-dione	3.5	479	3.36
385		8-chloro-1-(3-{3-[(2,4-difluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3-(3-methylbutyl)-3,7-dihydro-1*H*-purine-2,6-dione	3.1	493	3.53

Example	R =	Name	Yield (mg)	m/z	RT (min)
386		8-chloro-3-(cyclobutylmethyl)-1-(3-{3-[(2,4-difluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione	2.2	491	3.45
387		8-chloro-1-(3-{3-[(2,4-difluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3-(2-phenylethyl)-3,7-dihydro-1*H*-purine-2,6-dione	2.4	527	3.50
388		8-chloro-1-(3-{3-[(2,4-difluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3-(3-methyl-2-buten-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione	3.1	491	3.46
389		8-chloro-1-(3-{3-[(2,4-difluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3-(4,4,4-trifluorobutyl)-3,7-dihydro-1*H*-purine-2,6-dione	3.0	533	3.39
390		8-chloro-1-(3-{3-[(2,4-difluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3-(3,3,3-trifluoropropyl)-3,7-dihydro-1*H*-purine-2,6-dione	2.7	519	3.34
391		8-chloro-1-(3-{3-[(2,4-difluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3-[2-(1*H*-pyrrol-1-yl)ethyl]-3,7-dihydro-1*H*-purine-2,6-dione	2.0	516	3.27
392		8-chloro-1-(3-{3-[(2,4-difluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3-[2-(phenyloxy)ethyl]-3,7-dihydro-1*H*-purine-2,6-dione	1.6	543	3.44

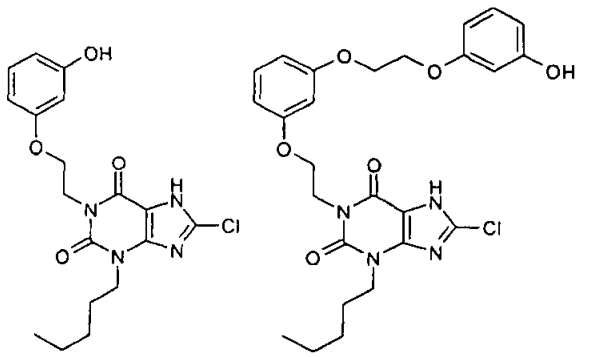
Example	R =	Name	Yield (mg)	m/z	RT (min)
393		8-chloro-1-(3-{3-[(2,4-difluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3-[2-(ethyloxy)ethyl]-3,7-dihydro-1*H*-purine-2,6-dione	2.8	495	3.11
394		8-chloro-1-(3-{3-[(2,4-difluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3-[2-(methyloxy)ethyl]-3,7-dihydro-1*H*-purine-2,6-dione	2.6	481	2.98
395		8-chloro-1-(3-{3-[(2,4-difluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione	3.1	463	3.17
396		8-chloro-1-(3-{3-[(2,4-difluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3-[3-(methyloxy)propyl]-3,7-dihydro-1*H*-purine-2,6-dione	2.1	495	3.04
397		8-chloro-3-cyclopentyl-1-(3-{3-[(2,4-difluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione	2.5	491	3.52

Example 398: 1-[3-(3-Bromophenyl)propyl]-8-chloro-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione



A solution of 3-(3-bromophenyl)-propan-1-ol (1.627g, 7.56mmol) in THF (65ml) was treated with 8-chloro-3-pentyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (2.04g, 6.87mmol) under nitrogen. PPh_3 (2.164g, 8.25mmol) was added to the stirred mixture after 2min and after a further 6min DBAD (1.9g, 8.25mmol) was added in one portion. The mixture was stirred for 2.5h and then left to react for 16h. The mixture was degassed by applying a vacuum and then nitrogen was introduced. $Pd(PPh_3)_4$ (794mg, 0.69mmol) was added and the mixture degassed once more. Morpholine (6ml, 68.8mmol) was added and the mixture was stirred under nitrogen for 6h. The mixture was partitioned between 2M HCl (aq) and EtOAc. The organic layer was separated, washed with brine, dried ($MgSO_4$) and concentrated. The residue was taken up into MeOH and purified by passing down an aminopropyl SPE, the product eluted with 2-5% AcOH/MeOH. The title compound was obtained as an off-white solid (2.48g, 79%). LC/MS: m/z 455, 453 $[MH]^+$, RT 3.85min.

Example 399: 8-Chloro-1-{2-[(3-hydroxyphenyl)oxy]ethyl}-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione and Example 400: 8-chloro-1-(2-{[3-({2-[(3-hydroxyphenyl)oxy]ethyl}oxy)phenyl]oxy}ethyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione



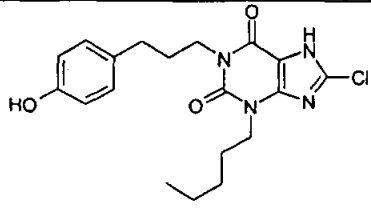
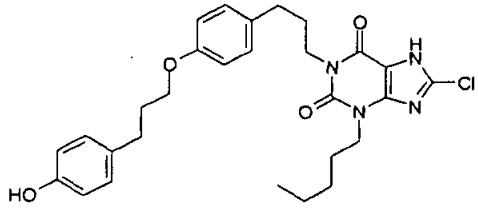
A solution of 2-(2-hydroxyethyl)-resorcinol (1.156g, 7.5mmol) in THF (60ml) was treated with 8-chloro-3-pentyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (2.016g, 6.79mmol) under nitrogen. PPh_3 (2.138g, 8.15mmol) was added to the stirred mixture after 4min and after a further 8min DBAD (1.88g, 8.16mmol) was added in one portion. The mixture was stirred for 1h 50min and then left to react for 16h. The mixture was degassed by applying a vacuum and then nitrogen was introduced. $Pd(PPh_3)_4$ (785mg, 0.68mmol) was added and the mixture degassed once more. Morpholine (5.9ml, 67.7mmol) was added and the mixture was stirred under nitrogen for 4.5h. The mixture was partitioned between 2M HCl (aq) and EtOAc. The organic layer was separated, washed with brine, dried ($MgSO_4$) and concentrated. The residue was taken up into MeOH and purified by passing it down an aminopropyl SPE, the product gradient elution with 2-5% AcOH/MeOH. The fractions containing product were evaporated to give a pale yellow foam (2.39g) and a pale yellow gum (213mg). The foam was dissolved in dichloromethane (50ml) and passed through a hydrophobic frit. The solution was evaporated and dried in vacuo to give 8-chloro-1-{2-[(3-

hydroxyphenyl)oxy]ethyl}-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione as a white solid (1.919g, containing 15% 8-chloro-1-(2-{[3-({2-[(3-hydroxyphenyl)oxy]ethyl}oxy)phenyl]oxy}ethyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione).

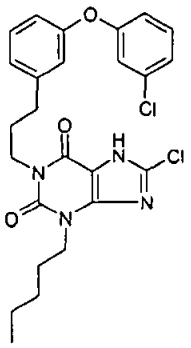
The gum was purified by MDAP to give 8-chloro-1-{2-[(3-hydroxyphenyl)oxy]ethyl}-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione as a white solid (126mg).
LC/MS: m/z 393 $[MH]^+$, RT 3.23min
as well as
8-chloro-1-(2-{[3-({2-[(3-hydroxyphenyl)oxy]ethyl}oxy)phenyl]oxy}ethyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione as a pale yellow solid (38mg).
LC/MS: m/z 529 $[MH]^+$, RT 3.62min.

The following compounds (**Table 25**) were prepared using a method analogous to that for 8-chloro-1-{2-[(3-hydroxyphenyl)oxy]ethyl}-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione above, from the corresponding alcohol.

Table 25

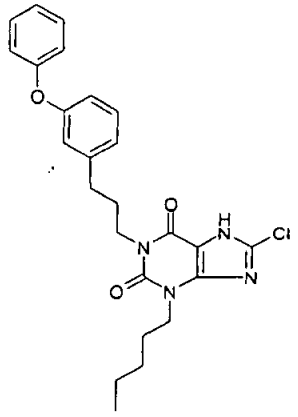
Example	Structure	Yield (mg)	LC/M:
401	 8-chloro-1-[3-(4-hydroxyphenyl)propyl]-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione	58	m/z 391 $[MH]^+$ RT 3.38min
402	 8-chloro-1-[3-(4-{[3-(4-hydroxyphenyl)propyl]oxy}phenyl)propyl]-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione	12	m/z 525 $[MH]^+$ RT 4.07min

Example 403: 8-Chloro-1-(3-{3-[(3-chlorophenyl)oxy]phenyl}propyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione



1-[3-(3-Bromophenyl)propyl]-8-chloro-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione (100mg, 0.22mmol) was dissolved in dioxan (0.75ml). Copper (1) iodide (9mg, 0.05mmol), N,N-dimethylglycine hydrochloride (9mg, 0.06mmol), cesium carbonate (215mg, 0.66mmol) and 3-chlorophenol (52mg, 0.4mmol) were added to the solution. The mixture was heated under microwave irradiation at 200°C for 10min, followed by another 10min at 200°C after which the cooled mixture was filtered and the residue washed with EtOAc and MeOH. The filtrate and washings were combined and evaporated under reduced pressure to leave a red/brown solid. The solid was partitioned between DCM and water. The phases were separated by hydrophobic frit and the organic evaporated under reduced pressure to leave a solid. The solid was purified by MDAP to give the title compound as a yellow solid/ gum (27mg, 24%).
LC/MS: m/z 501 $[MH]^+$, RT 4.25min.

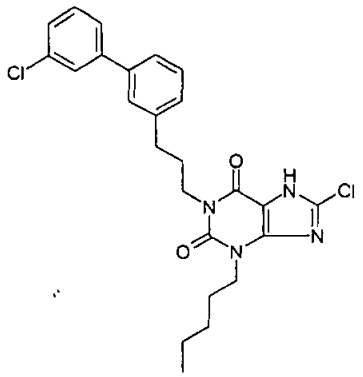
Example 404: 8-Chloro-3-pentyl-1-{3-[3-(phenyloxy)phenyl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione



1-[3-(3-Bromophenyl)propyl]-8-chloro-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione (100mg, 0.22mmol), copper (1) iodide (4mg, 0.02mmol), N,N-dimethylglycine hydrochloride (9mg, 0.06mmol) cesium carbonate (144mg, 0.44mmol) and phenol (31mg, 0.33mmol) were placed in dioxan (0.44ml). Then the mixture was heated in the microwave at 150°C for 3.3min, then further quantities of cesium carbonate (72mg, 0.22mmol), copper (1) iodide (6mg, 0.03mmol) and dioxan (0.44ml) were added to the mixture and heated in the microwave at 170°C for 10min, followed by another 10min at 200°C. The cooled mixture was filtered and the residue washed with EtOAc. The filtrate

and washings were combined and evaporated under reduced pressure to leave a dark brown gum. The gum was purified by MDAP to give the title compound as a pale cream solid (44mg, 42%).
LC/MS: m/z 467 $[MH]^+$, RT 4.14min.

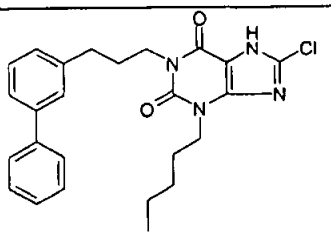
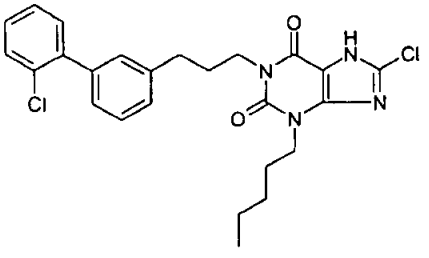
Example 405: 8-Chloro-1-[3-(3'-chloro-3-biphenylyl)propyl]-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione



A mixture of 1-[3-(3-bromophenyl)propyl]-8-chloro-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione (100mg, 0.22mmol) and 3-chlorophenyl boronic acid (35mg, 0.22mmol) was stirred in isopropanol (0.35ml). A solution of sodium carbonate (70mg, 0.66mmol) in water (0.35ml) was added to the mixture followed by 10% palladium on carbon (6mg, Degussa type E101 NE/W). The mixture was heated in the microwave at 160°C for 10min, then filtered (glass fibre filter) and the residues washed with IPA. The filtrate and washings were combined and evaporated under reduced pressure to leave a gum. The gum was partitioned between DCM and water. The organic phase was separated and the aqueous phase extracted with EtOAc. The combined organic phases were dried ($MgSO_4$) and concentrated to leave a foam. The foam was purified by MDAP to give the title compound as a colourless gum (40mg, 37%).
LC/MS: m/z 485 $[MH]^+$, RT 4.27min.

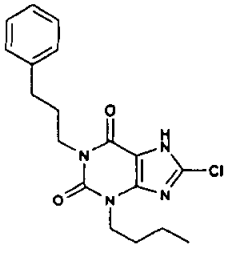
The following compounds (**Table 26**) were prepared using a method analogous to that for 8-chloro-1-[3-(3'-chloro-3-biphenylyl)propyl]-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione (Example 405) above, from the corresponding boronic acid, except that the 2-chorophenyl analogue was heated in the microwave at 160°C for 10min twice while in the work up 1M hydrochloric acid was used instead of water. Also the EtOAc extraction was omitted.

Table 26

Example	Structure	Yield (mg)	LC/MS:
406	 1-[3-(3-biphenylyl)propyl]-8-chloro-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione	51	m/z 451 $[MH]^+$ RT 4.02min
407	 8-chloro-1-[3-(2'-chloro-3-biphenylyl)propyl]-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione	56	m/z 485 $[MH]^+$ RT 4.15min

Example 408: 3-Butyl-8-chloro-1-(3-phenylpropyl)-3,7-dihydro-1*H*-purine-2,6-dione

a) 3-Butyl-8-chloro-1-(3-phenylpropyl)-3,7-dihydro-1*H*-purine-2,6-dione

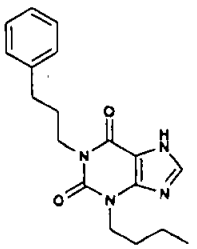


3-Butyl-1-(3-phenylpropyl)-3,7-dihydro-1*H*-purine-2,6-dione (100mg, 0.31mmol) and NCS (41mg, 0.31mmol) were suspended in MeCN (5ml) and heated at 120°C under microwave irradiation for 10min. The reaction mixture was concentrated under reduced pressure and the title compound isolated using HPLC.

^{1}H NMR ($CDCl_3$) δ: 0.96 (3H, t), 1.37-1.43 (2H, m), 1.70-1.78 (2H, m), 2.00-2.09 (2H, m), 2.73 (2H, t), 4.08 (2H, t), 4.14 (2H, t), 7.13-7.26 (5H, m), 12.6 (1H, br.s).

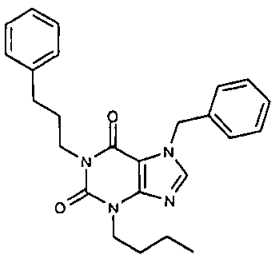
LC/MS: m/z 361 $[MH]^+$.

b) 3-Butyl-1-(3-phenylpropyl)-3,7-dihydro-1*H*-purine-2,6-dione



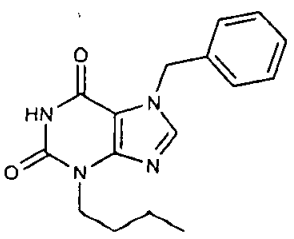
3-Butyl-7-(phenylmethyl)-1-(3-phenylpropyl)-3,7-dihydro-1*H*-purine-2,6-dione (0.6g, 1.44mmol) was dissolved in acetic acid (35ml), 20% palladium hydroxide on carbon (0.366g) was added, and the mixture was shaken under hydrogen (at 50psi) overnight. The catalyst was removed by filtration through Celite® and washed with acetic acid. The filtrate was concentrated under reduced pressure and the title compound isolated using HPLC (0.385g, 82%).
LC/MS: m/z 327 $[MH]^+$.

c) 3-Butyl-7-(phenylmethyl)-1-(3-phenylpropyl)-3,7-dihydro-1*H*-purine-2,6-dione



7-Benzyl-3-butyl-3,7-dihydro-1*H*-purine-2,6-dione (0.5g, 1.68mmol) and potassium carbonate (0.347g, 2.5mmol) were suspended in DMF (20ml), (3-bromopropyl)benzene (390mg, 1.96mmol) was added. The reaction mixture was stirred at ambient temperature overnight. The reaction mixture was evaporated to dryness and the residue was partitioned between water and ethyl acetate. The organic layer was washed with water, followed by brine, dried over anhydrous sodium sulphate and concentrated under reduced pressure to yield the title compound.
^{1}H NMR ($CDCl_3$) δ: 0.95 (3H, t), 1.34-1.43 (2H, m), 1.68-1.76 (2H, m), 1.98-2.07 (2H, m), 2.71 (2H, t), 4.05-4.10 (4H, m), 5.49 (2H, s), 7.19-7.24 (5H, m), 7.33-7.38 (5H, m), 7.52 (1H, s).
LC/MS: m/z 417 $[MH]^+$.

d) 7-Benzyl-3-butyl-3,7-dihydro-1*H*-purine-2,6-dione

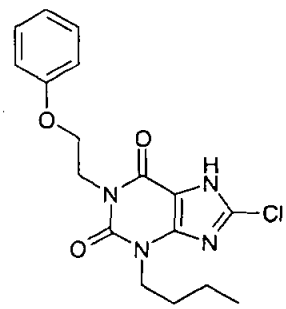


7-Benzyl-3,7-dihydro-1H-purine-2,6-dione (17.14g, 70.8mmol) **[Synthetic Communications, 20(16), *2459-2467*, 1990]** and potassium carbonate (11.43g, 82.8mmol) were suspended in DMF (400ml) at 40°C. After stirring for thirty minutes, butyl iodide (8.76ml, 77.0mmol) was added, and the mixture was stirred at 40°C overnight. 50% Aqueous acetic acid (60ml) was added, and the solution was concentrated under reduced pressure. The residue was suspended in water (500ml), and the products were extracted into chloroform. The organics were collected, concentrated, and product was isolated using flash chromatography eluting with 1% methanol in dichloromethane (9.49g, 45%).

^{1}H NMR ($CDCl_3$) δ: 0.95 (3H, t), 1.34-1.41 (2H, m), 1.70-1.78 (2H, m), 4.05 (2H, t), 5.46 (2H, s), 7.31-7.40 (5H, m), 7.56 (1H, s), 8.21 (1H, br.s).
LC/MS: m/z 299 $[MH]^+$.

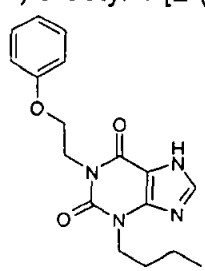
Example 409: 3-Butyl-8-chloro-1-[2-(phenyloxy)ethyl]-3,7-dihydro-1*H*-purine-2,6-dione

a) 3-Butyl-8-chloro-1-[2-(phenyloxy)ethyl]-3,7-dihydro-1*H*-purine-2,6-dione



The title compound was prepared using the procedure for 3-butyl-8-chloro-1-(3-phenylpropyl)-3,7-dihydro-1*H*-purine-2,6-dione, from 3-butyl-1-[2-(phenyloxy)ethyl]-3,7-dihydro-1*H*-purine-2,6-dione and NCS.
^{1}H NMR ($CDCl_3$) δ: 0.95 (3H, t), 1.36-1.45 (2H, m), 1.71-1.79 (2H, m), 4.11 (2H, t), 4.29 (2H, t), 4.54 (2H, t), 6.87-6.94 (3H, m), 7.21-7.27 (2H, m), 13.10 (1H, br.s).
LC/MS: m/z 363 $[MH]^+$.

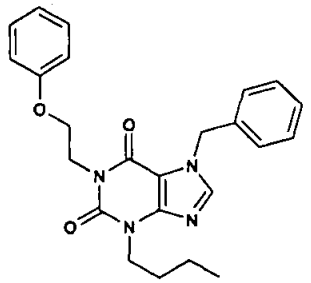
b) 3-Butyl-1-[2-(phenyloxy)ethyl]-3,7-dihydro-1*H*-purine-2,6-dione



The title compound was prepared using the procedure outlined for 3-butyl-1-(3-phenylpropyl)-3,7-dihydro-1*H*-purine-2,6-dione, from 3-butyl-7-(phenylmethyl)-1-[2-(phenyloxy)ethyl]-3,7-dihydro-1*H*-purine-2,6-dione.

LC/MS: m/z 329 $[MH]^+$.

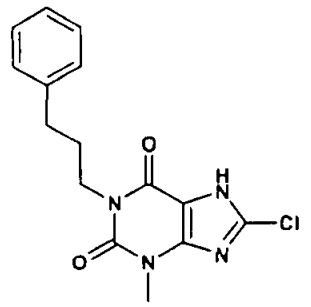
c) 3-Butyl-7-(phenylmethyl)-1-[2-(phenyloxy)ethyl]-3,7-dihydro-1*H*-purine-2,6-dione



The title compound was prepared using the procedure outlined for 3-butyl-7-(phenylmethyl)-1-(3-phenylpropyl)-3,7-dihydro-1*H*-purine-2,6-dione, from 7-benzyl-3-butyl-3,7-dihydro-1*H*-purine-2,6-dione and 2-bromoethyl phenyl ether.
^{1}H NMR ($CDCl_3$) δ: 0.95 (3H, t), 1.35-1.44 (2H, m), 1.69-1.78 (2H, m), 4.07-4.11 (2H, m), 4.26 (2H, t), 4.434 (2H, t), 5.49 (2H, s), 6.87-7.38 (10H, m), 7.55 (1H, s).
LC/MS: m/z 419 $[MH]^+$.

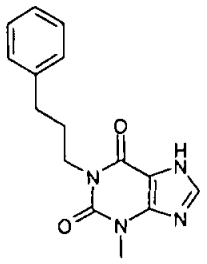
Example 410: 8-Chloro-3-methyl-1-(3-phenylpropyl)-3,7-dihydro-1*H*-purine-2,6-dione

a) 8-Chloro-3-methyl-1-(3-phenylpropyl)-3,7-dihydro-1*H*-purine-2,6-dione



The title compound was prepared using the procedure outlined for 3-butyl-8-chloro-1-(3-phenylpropyl)-3,7-dihydro-1*H*-purine-2,6-dione, from 3-methyl-1-(3-phenylpropyl)-3,7-dihydro-1*H*-purine-2,6-dione and NCS.
^{1}H NMR ($CDCl_3$) δ: 2.01-2.12 (2H, m), 2.74 (2H, t), 3.57 (3H, s), 4.14 (2H, t), 6.99-7.24 (5H, m), 12.5 (1H, br.s).
LC/MS: m/z 319 $[MH]^+$.

b) 3-Methyl-1-(3-phenylpropyl)-3,7-dihydro-1*H*-purine-2,6-dione

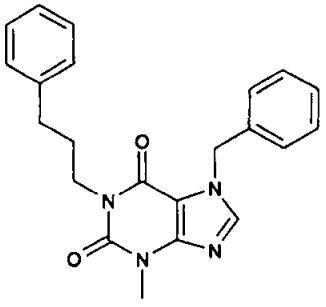


220

The title compound was prepared using the procedure outlined for 3-butyl-1-(3-phenylpropyl)-3,7-dihydro-1*H*-purine-2,6-dione, from 3-methyl-7-(phenylmethyl)-1-(3-phenylpropyl)-3,7-dihydro-1*H*-purine-2,6-dione.

LC/MS: m/z 285 $[MH]^+$.

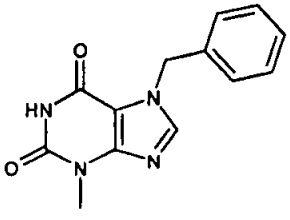
c) 3-Methyl-7-(phenylmethyl)-1-(3-phenylpropyl)-3,7-dihydro-1*H*-purine-2,6-dione



The title compound was prepared using the procedure outlined for 3-butyl-7-(phenylmethyl)-1-(3-phenylpropyl)-3,7-dihydro-1*H*-purine-2,6-dione, from 3-methyl-7-(phenylmethyl)-3,7-dihydro-1*H*-purine-2,6-dione and (3-bromopropyl)benzene.

LC/MS: m/z 375 $[MH]^+$.

d) 3-Methyl-7-(phenylmethyl)-3,7-dihydro-1*H*-purine-2,6-dione



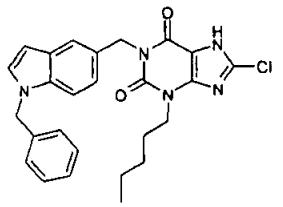
The title compound was prepared using the procedure described for 7-benzyl-3-butyl-3,7-dihydro-1*H*-purine-2,6-dione using methyl iodide (0.28ml, 4.46mmol). Purification was achieved by trituration. The product was isolated as a solid, insoluble in chloroform and water (0.334g, 57%).

^1H NMR (DMSO-d_6) δ: 3.34 (3H, s), 5.44 (2H, s), 7.26-7.37 (5H, m), 8.21 (1H, s), 11.13 (1H, s).

LC/MS: m/z 257 $[MH]^+$.

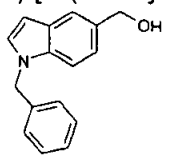
Example 411: 8-Chloro-3-pentyl-1-{[1-(phenylmethyl)-1*H*-indol-5-yl]methyl}-3,7-dihydro-1*H*-purine-2,6-dione

a) 8-Chloro-3-pentyl-1-{[1-(phenylmethyl)-1*H*-indol-5-yl]methyl}-3,7-dihydro-1*H*-purine-2,6-dione



8-Chloro-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione (156mg, 0.5mmol) was dissolved in anhydrous THF (5ml) under nitrogen and [1-(phenylmethyl)-1*H*-indol-5-yl]methanol (138mg, 0.58mmol) was added. After several minutes triphenylphosphine (168mg, 0.63mmol) was added followed 5-10min later by DBAD (155mg, 0.67mmol) and the solution stirred for 18h. The mixture was degassed by applying a vacuum and then nitrogen was introduced. $Pd(PPh_3)_4$ (63mg, 0.054mmol) was added and the mixture degassed once more. Morpholine (0.461ml, 5.3mmol) was added and the mixture was stirred under nitrogen for 24h. A further quantity of $Pd(PPh_3)_4$ (58mg, 0.05mmol) was added and the mixture was stirred under nitrogen for 96h. The mixture was diluted with EtOAc and washed with 2M HCl (5ml) then brine (15ml), dried ($MgSO_4$) and concentrated. The crude material was purified by an aminopropyl SPE (eluent MeOH to wash through the impurities, then with 3-4% AcOH/MeOH). The product fractions were combined and concentrated to give the title compound as a white solid (43mg, 17%).
LC/MS: m/z 476 $[MH]^+$, RT 3.78min.

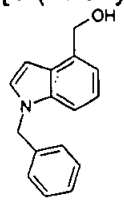
b) [1-(Phenylmethyl)-1*H*-indol-5-yl]methanol



Methyl 1-(phenylmethyl)-1*H*-indole-5-carboxylate (1.17g, 4.4mmol) was dissolved in anhydrous THF under nitrogen and cooled to -5°C. 1M Lithium aluminiumhydride in diethylether (4.0ml) was added slowly. The cooling bath was removed and the reaction mixture was left overnight at room temperature. The reaction was quenched by the sequential addition of water (0.15ml), 15% NaOH (0.15ml) followed by water (0.45ml) then ethyl acetate and sodium sulphate were added and the mixture stirred for 0.5h. The insoluble material was filtered and washed well with ethyl acetate. The filtrate was concentrated *in vacuo* to give the title compound as a cream solid which darkened on standing (1.04g, 100%).
LC/MS: m/z 238 $[MH]^+$, RT 3.03min.

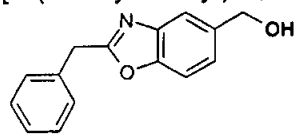
The following alcohols were prepared by reduction of the corresponding methyl ester in a similar manner:

[1-(Phenylmethyl)-1*H*-indol-4-yl]methanol



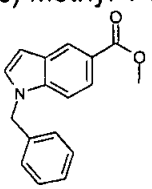
LC/MS: m/z 238 $[MH]^+$, RT 3.03min.

[2-(Phenylmethyl)-1,3-benzoxazol-4-yl]methanol



LC/MS: m/z 240 $[MH]^+$, RT 2.02min.

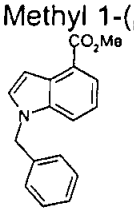
c) Methyl 1-(phenylmethyl)-1*H*-indole-5-carboxylate



Methyl 1*H*-indole-5-carboxylate (1.0g, 5.7mmol) was dissolved in anhydrous DMF under nitrogen and cooled to 2°C. Sodium hydride (0.25g, 6.3mmol, 60% in paraffin) was added. After 0.5h benzyl bromide (0.75ml, 6.0mmol) was added and the reaction mixture stirred for 4hr at room temperature, then left overnight. The reaction mixture was poured into water (50ml) and ethyl acetate (10ml). The aqueous phase was extracted further with ethyl acetate (50ml). The combined organic phases were washed with dil. ammonia then brine, dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified on a 50g Si SPE (gradient elution cyclohexane/ethyl acetate 8% to 16%). The relevant fractions were concentrated *in vacuo* to give the title compound as a white solid (1.17g, 77%)

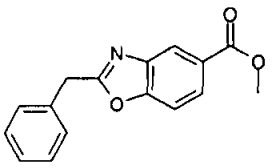
LC/MS: m/z 266 $[MH]^+$, RT 3.60min.

Methyl 1-(phenylmethyl)-1*H*-indole-4-carboxylate was prepared in a similar manner



LC/MS: m/z 266 $[MH]^+$, RT 3.58min.

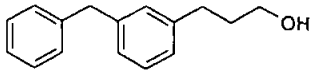
Methyl 2-(phenylmethyl)-1,3-benzoxazole-5-carboxylate



Trimethylbenzylorthoformate (1.34g, 6.8mmol) was dissolved in methanol (2ml) and methyl-3-amino-hydoxybenzoate (0.56g, 3.35mmol) was added followed by conc. hydrochloric acid (9.1ml). The mixture was stirred at reflux for 4.75h, allowed to cool and evaporated *in vacuo*. The residue was partitioned between diethyl ether (10ml) and 2M NaOH solution (5ml). The organic phase was washed with water (5ml) and the combined aqueous phases were back extracted with ether (10ml). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to leave an orange oil (1.37g). The crude product was purified on silica (40g SPE, gradient elution cyclohexane/ethyl acetate 0-100%) to give the title compound as a white solid (0.72g, 80%).

LC/MS: m/z 268 $[MH]^+$, RT 3.27min.

3-[3-(Phenylmethyl)phenyl]-1-propanol



3-[3-(phenylcarbonyl)phenyl]propanoic acid (491mg, 1.96mmol) was dissolved in anhydrous THF under nitrogen and cooled to 0°C. 1M $LiAlH_4$ in ether (2.13ml) was added slowly and the reaction mixture was stirred at room temperature for 20h. The reaction was cooled in ice and tetrahydrofuran (5ml) and 1M $LiAlH_4$ in ether solution (2.2ml) added. The reaction mixture was heated at reflux for 7hr then left at room temperature for 3 days. The reaction was quenched with sequentially, water (0.16ml), 15% NaOH (0.16ml) and water (0.47ml) then diluted with ethyl acetate and dried with sodium sulphate. The insoluble material was filtered and thoroughly washed with ethyl acetate. The filtrate was concentrated *in vacuo* to give 3-{3-[hydroxy(phenyl)methyl]phenyl}-1-propanol as a white opaque oil (0.42g, 90%)

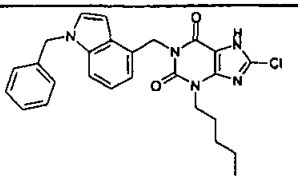
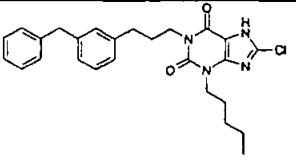
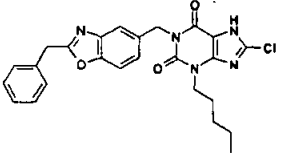
LC/MS: m/z 243 $[MH]^+$, RT 2.71min.

The above material (200mg, 0.82mmol) was dissolved in anhydrous dichloromethane (5ml) and triethylsilane (0.53ml, 3.2mmol) followed by trifluoroacetic acid (0.36ml, 4.1mmol) were added. The reaction mixture was stirred for 1h then washed with saturated sodium hydrogen carbonate solution. The organic phase was filtered through a hydrophobic frit and concentrated *in vacuo*. The crude product was purified over silica (4g SPE, gradient elution cyclohexane/ethyl acetate 0-30%) to give the title compound as a colourless oil (68mg, 37%).

LC/MS: m/z 227 $[MH]^+$, RT 3.25min.

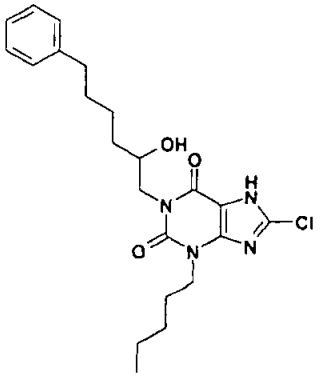
The following compounds (**Table 27**) were prepared using a method analogous to that for 8-chloro-3-pentyl-1-{[1-(phenylmethyl)-1*H*-indol-5-yl]methyl}-3,7-dihydro-1*H*-purine-2,6-dione from the corresponding alcohols as described above.

Table 27

Example	Structure	Yield (mg)	LC/MS:
412	 8-chloro-3-pentyl-1-{[1-(phenylmethyl)-1*H*-indol-4-yl]methyl}-3,7-dihydro-1*H*-purine-2,6-dione	49	m/z 476 $[MH]^+$ RT 3.82min
413	 8-chloro-3-pentyl-1-{3-[3-(phenylmethyl)phenyl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione	70	m/z 465 $[MH]^+$ RT 4.01min
414	 8-chloro-3-pentyl-1-{[2-(phenylmethyl)-1,3-benzoxazol-5-yl]methyl}-3,7-dihydro-1*H*-purine-2,6-dione	174	m/z 478 $[MH]^+$ RT 3.70min

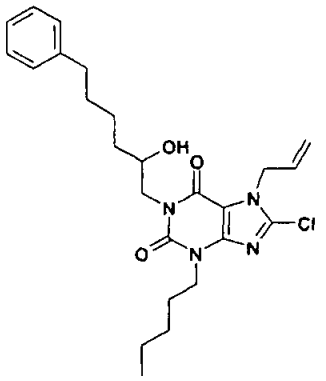
Example 415: 8-Chloro-1-(2-hydroxy-6-phenylhexyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione

a) 8-Chloro-1-(2-hydroxy-6-phenylhexyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione



A solution of 8-chloro-1-(2-hydroxy-6-phenylhexyl)-3-pentyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (0.084g, 0.18mmol) and $Pd(PPh_3)_4$ (0.042g, 0.035mmol) in THF (5ml) was degassed (sequential evacuation followed by addition of nitrogen x 3) then morpholine (0.25ml, 2.8mmol) added and the mixture stirred overnight. The solution was loaded onto an aminopropyl SPE (5g) and eluted with MeOH to remove by-products then with 5%AcOH/MeOH to isolate the title compound, after concentration, as an oil (0.022g, 29%).
LC/MS: m/z 433 $[MH]^+$

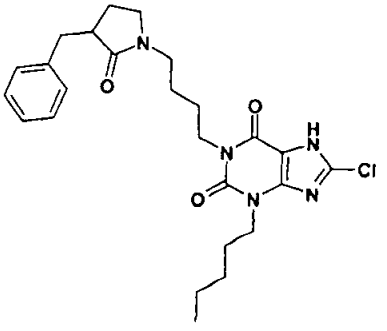
b) 8-Chloro-1-(2-hydroxy-6-phenylhexyl)-3-pentyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione



To a solution of 8-chloro-3-pentyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (0.107g, 0.36mmol) and 1-chloro-6-phenyl-2-hexanol (0.107g, 0.5mmol) in DMF (5ml) was added cesium carbonate (0.24g, 0.74mmol) and the mixture heated at 60°C for 3h, whereupon a further 80mg of cesium carbonate was added and heating continued at 100°C for 18h. The solution was allowed to cool, concentrated and the residues purified by chromatography over silica (20g SPE, eluting with first with DCM then DCM/10%ether) to yield the title compound as a yellow oil (0.085mg, 53%).
LC/MS: m/z 473 $[MH]^+$

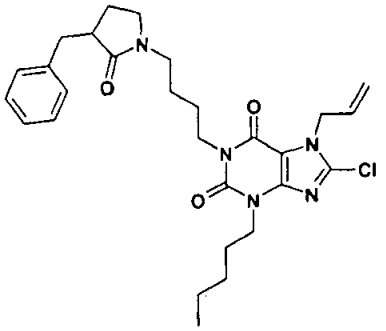
Example 416: 8-Chloro-1-{4-[2-oxo-3-(phenylmethyl)-1-pyrrolidinyl]butyl}-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione

a) 8-Chloro-1-{4-[2-oxo-3-(phenylmethyl)-1-pyrrolidinyl]butyl}-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione



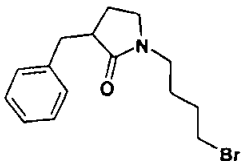
A solution of 8-chloro-1-{4-[2-oxo-3-(phenylmethyl)-1-pyrrolidinyl]butyl}-3-pentyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (0.35g, 0.67mmol), $Pd(PPh_3)_4$ (0.082g, 0.07mmol) and morpholine (0.6ml, 6.7mmol) in THF (10ml) was degassed (sequential evacuation followed by addition of nitrogen x 3) then stirred for 4h. The solution was then loaded onto an aminopropyl SPE (5g) and eluted first with MeOH then 5%AcOH/MeOH to provide the title compound containing a small impurity. Further purification over silica (10g SPE, gradient elution ether/ethyl acetate 1:0 to 0:1) provided the title compound as a clear oil (0.10g, 31%).
LC/MS: m/z 486 $[MH]^+$

b) 8-Chloro-1-{4-[2-oxo-3-(phenylmethyl)-1-pyrrolidinyl]butyl}-3-pentyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione



Prepared as with 8-chloro-1-(2-hydroxy-6-phenylhexyl)-3-pentyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione using 1-(4-bromobutyl)-3-(phenylmethyl)-2-pyrrolidinone as the alkylating agent, potassium carbonate as base and heating at 50°C for 18h. Yield 86%.
LC/MS: m/z 526 $[MH]^+$

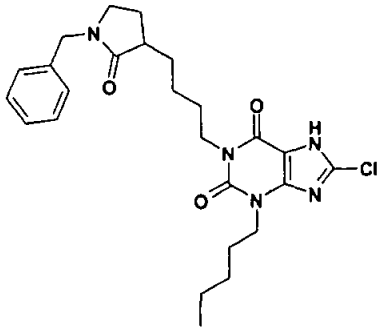
c) 1-(4-bromobutyl)-3-(phenylmethyl)-2-pyrrolidinone



To a solution of 3-(phenylmethyl)-2-pyrrolidinone (0.23g, 1.3mmol) and 1,4-dibromobutane (0.57g, 4.2mmol) in DMF (5ml) was added sodium t-butoxide (0.151g, 1.6mmol) and the solution stirred for 18h. The solution was concentrated and the residues chromatographed over silica (20g SPE, eluting first with cyclohexane then with DCM) to provide the title compound as a colourless oil containing a trace of DMF (0.25g, 61%).
LC/MS: m/z 311 $[MH]^+$

Example 417: 8-Chloro-1-{4-[2-oxo-1-(phenylmethyl)-3-pyrrolidinyl]butyl}-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione

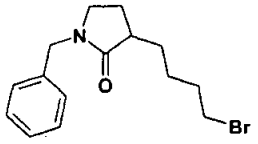
a) 8-Chloro-1-{4-[2-oxo-1-(phenylmethyl)-3-pyrrolidinyl]butyl}-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione



To a solution of 8-chloro-3-pentyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (0.086g, 0.29mmol) and 3-(4-bromobutyl)-1-(phenylmethyl)-2-pyrrolidinone (0.17g, 0.55mmol, 1:1 mixture with 2-(phenylmethyl)-2-azaspiro[4.4]nonan-1-one) in THF (5ml) was added potassium carbonate (0.08g, 0.58mmol) and the mixture heated and stirred at 50°C for 18h. The solution was allowed to cool then degassed (sequential evacuation followed by addition of nitrogen x 3) and $Pd(PPh_3)_4$ (0.09g, 0.077mmol) followed by morpholine (0.2ml, 2.2mmol) added and the solution stirred at ambient temperature for 18h. The solution was separated between ethyl acetate and dil HCl and the organics washed with brine, dried and concentrated. Purification of the residues using an aminopropyl SPE (5g) eluting first with MeOH then 5%AcOH/MeOH yielded the title compound as a yellow oil which crystallised on standing under ether (0.031g, 22%).

LC/MS: m/z 486 $[MH]^+$

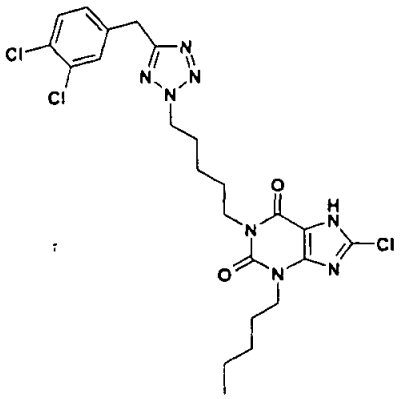
b) 3-(4-Bromobutyl)-1-(phenylmethyl)-2-pyrrolidinone



To a solution of 1-(phenylmethyl)-2-pyrrolidinone (0.47g, 2.7mmol) in THF (10ml) at -78°C was added lithium hexamethyldisilylazine (2.8ml, 2.7mmol, 1M solution) over 5min. After 15min 1,4-dibromobutane (0.32ml, 2.7mmol) was added and the solution allowed to attain ambient temperature over 2h then stirred for a further 18h. The solution was separated between ethyl acetate and water and the organics isolated, dried and concentrated. Chromatography over silica (20g SPE) eluting with cyclohexane then DCM and finally ether provided a clear oil which was a 1:1 mixture of the title compound and 2-(phenylmethyl)-2-azaspiro[4.4]nonan-1-one (0.17g). This was used in the next step without further purification.

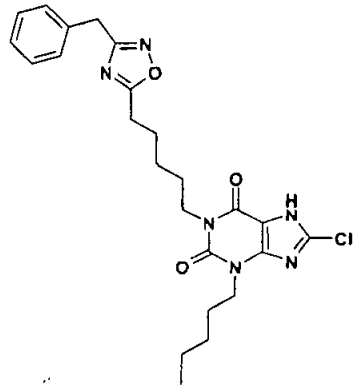
LC/MS: m/z 310, 312 $[MH]^+$

Example 418: 8-Chloro-1-(5-{5-[(3,4-dichlorophenyl)methyl]-2*H*-tetrazol-2-yl}pentyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione



To a solution of 8-chloro-3-pentyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (0.18g, 0.61mmol) in THF (5ml) was added 5-{5-[(3,4-dichlorophenyl)methyl]-2*H*-tetrazol-2-yl}-1-pentanol (0.191g, 0.61mmol; prepared in similar fashion to **Example 35**), triphenylphosphine (0.36g, 1.3mmol) and finally dibenzylazodicarboxylate (0.40g, 1.3mmol). The solution was stirred for 18h after which $Pd(PPh_3)_4$ (0.16g, 0.137mmol) followed by morpholine (0.75ml, 8.3mmol) was added and the solution stirred at ambient temperature for 6h. The solution was loaded onto an aminopropyl SPE (5g) and eluted with MeOH then 5%AcOH/MeOH to yield the title compound containing minor impurities. Further chromatography (silica SPE, 20g) eluting with ether yielded the title compound as a white solid (0.061g, 18%).
LC/MS: m/z 553 $[MH]^+$

Example 419: 8-Chloro-3-pentyl-1-{5-[3-(phenylmethyl)-1,2,4-oxadiazol-5-yl]pentyl}-3,7-dihydro-1*H*-purine-2,6-dione

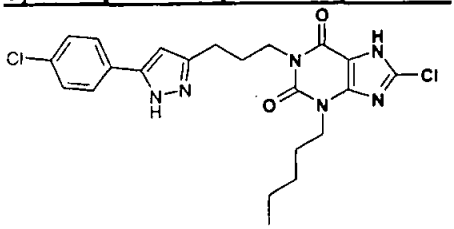


To a solution of 8-chloro-3-pentyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (0.093g, 0.3mmol) in THF (5ml) was added 5-[3-(phenylmethyl)-1,2,4-oxadiazol-5-yl]-1-pentanol (0.077g, 0.3mmol; prepared in similar fashion to **Example 87b**), triphenylphosphine (0.17g, 0.6mmol) and finally dibenzylazodicarboxylate (0.20g, 0.6mmol). The solution was stirred for 18h, degassed, after which $Pd(PPh_3)_4$ (0.08g, 0.07mmol) followed by morpholine (0.35ml, 3.9mmol) was added and the solution stirred at ambient temperature for 6h. The solution was loaded onto an aminopropyl

SPE (5g) and eluted with MeOH then 5%AcOH/MeOH to yield the title compound as a cream solid (0.051g, 34%).
LC/MS: m/z 485 $[MH]^+$

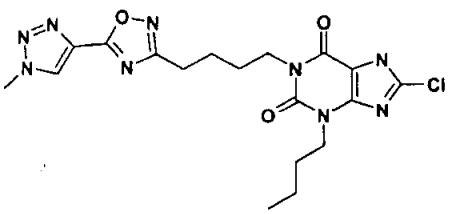
230

Example 420: 8-Chloro-1-{3-[5-(4-chlorophenyl)-1*H*-pyrazol-3-yl]propyl}-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione



Prepared as with 8-chloro-1-(5-{5-[(3,4-dichlorophenyl)methyl]-2*H*-tetrazol-2-yl}pentyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione using 3-[5-(4-chlorophenyl)-1*H*-pyrazol-3-yl]-1-propanol. The final product material was washed with ether to yield the title compound as a cream solid (30%).
LC/MS: m/z 475 $[MH]^+$

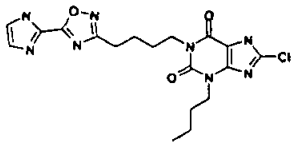
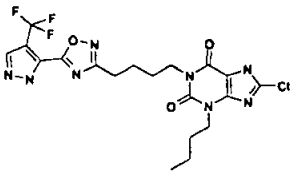
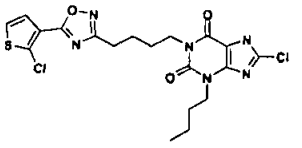
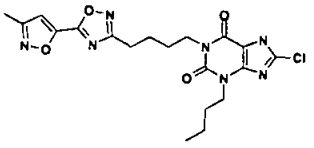
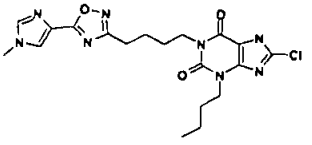
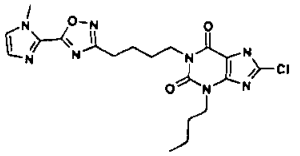
Example 421: 3-Butyl-8-chloro-1-{4-[5-(1-methyl-1*H*-1,2,3-triazol-4-yl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione

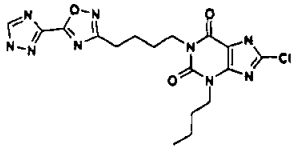
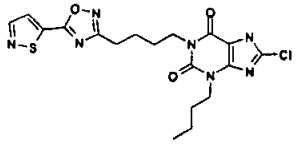
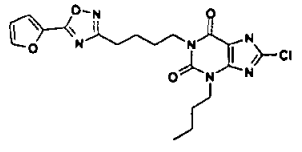
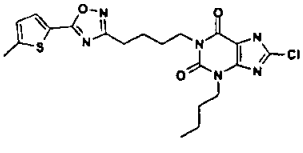
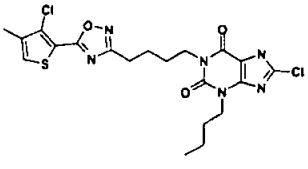
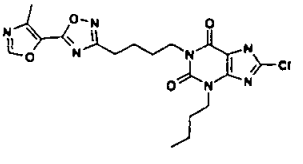
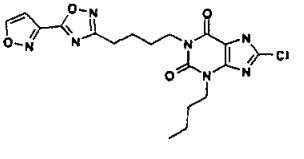


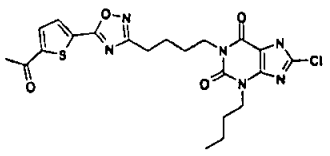
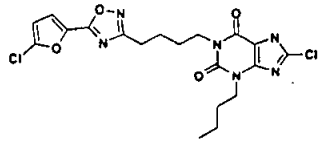
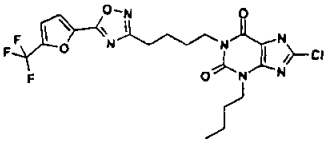
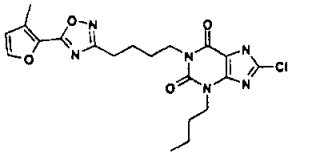
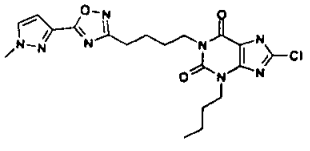
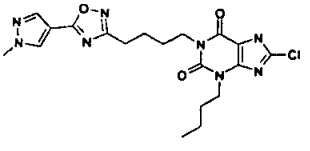
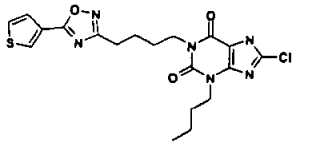
A solution of the 1-methyl-1*H*-1,2,3-triazole-4-carboxylic acid (18mg, 0.14mmol) in DMF (0.5ml) was treated with CDI (23mg, 0.14mmol) at rt for 1h. A solution of (1Z)-5-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)-N-hydroxypentanimidamide (50mg, 0.14mmol) in DMSO (0.4ml) was added to the mixture then heated to 100°C for 18h. The reaction mixture was purified by MDAP to give the title compound as a white solid (18mg).
LC/MS: m/z 448 $[MH]^+$, RT 2.86min.

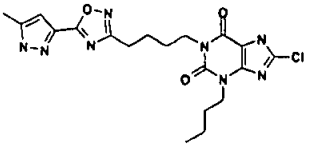
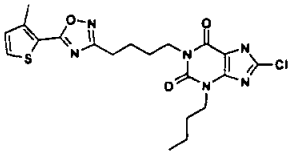
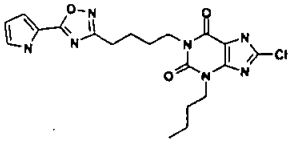
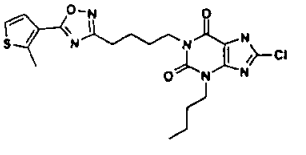
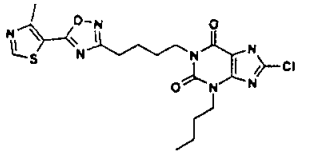
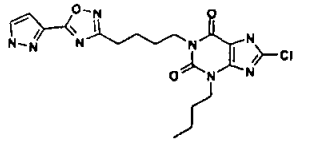
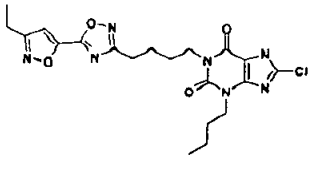
The following compounds (**Table 28**) were prepared using a method analogous to that for **Example 421**, using the appropriate carboxylic acid.

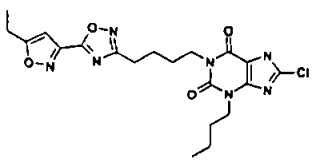
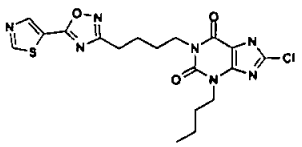
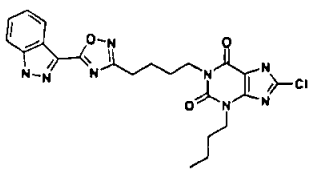
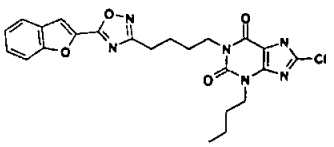
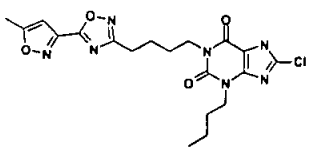
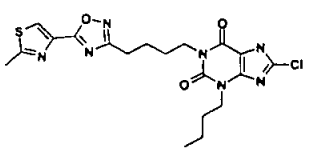
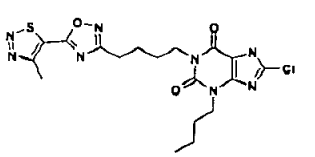
Table 28

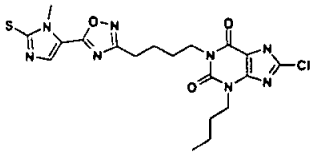
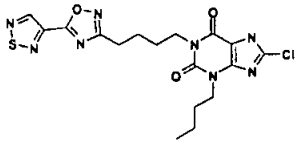
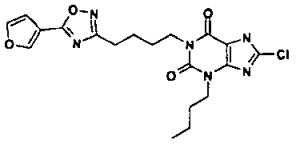
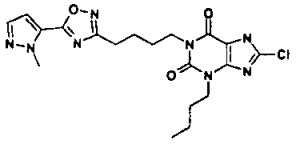
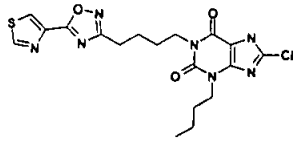
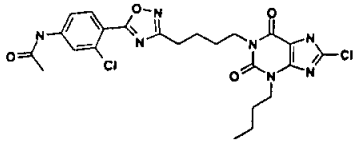
Example	Structure	Name	Yield (mg)	LC/MS
422		3-butyl-8-chloro-1-{4-[5-(1*H*-imidazol-2-yl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	16	m/z 433 $[MH]^+$ RT 2.79min
423		3-butyl-8-chloro-1-(4-{5-[4-(trifluoromethyl)-1*H*-pyrazol-5-yl]-1,2,4-oxadiazol-3-yl}butyl)-3,7-dihydro-1*H*-purine-2,6-dione	19	m/z 501 $[MH]^+$ RT 3.28min
424		3-butyl-8-chloro-1-{4-[5-(2-chloro-3-thienyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	26	m/z 483 $[MH]^+$ RT 3.59min
425		3-butyl-8-chloro-1-{4-[5-(3-methyl-5-isoxazolyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	25	m/z 448 $[MH]^+$ RT 3.21min
426		3-butyl-8-chloro-1-{4-[5-(1-methyl-1*H*-imidazol-4-yl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	16	m/z 447 $[MH]^+$ RT 2.74min
427		3-butyl-8-chloro-1-{4-[5-(1-methyl-1*H*-imidazol-2-yl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	9	m/z 447 $[MH]^+$ RT 2.91min

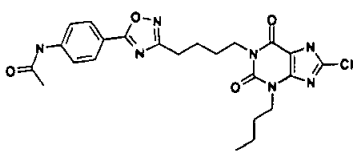
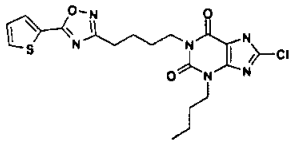
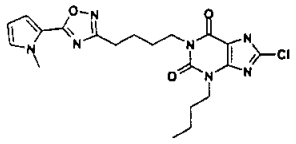
428		3-butyl-8-chloro-1-{4-[5-(1*H*-1,2,4-triazol-3-yl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	10	m/z 434 $[MH]^+$ RT 2.73min
429		3-butyl-8-chloro-1-{4-[5-(5-isothiazolyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	17	m/z 450 $[MH]^+$ RT 3.34min
430		3-butyl-8-chloro-1-{4-[5-(2-furanyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	26	m/z 433 $[MH]^+$ RT 3.27min
431		3-butyl-8-chloro-1-{4-[5-(5-methyl-2-thienyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	29	m/z 463 $[MH]^+$ RT 3.61min
432		3-butyl-8-chloro-1-{4-[5-(3-chloro-4-methyl-2-thienyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	30	m/z 497 $[MH]^+$ RT 3.76min
433		3-butyl-8-chloro-1-{4-[5-(4-methyl-1,3-oxazol-5-yl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	25	m/z 448 $[MH]^+$ RT 3.13min
434		3-butyl-8-chloro-1-{4-[5-(3-isoxazolyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	23	m/z 434 $[MH]^+$ RT 3.20min

435		1-{4-[5-(5-acetyl-2-thienyl)-1,2,4-oxadiazol-3-yl]butyl}-3-butyl-8-chloro-3,7-dihydro-1*H*-purine-2,6-dione	28	m/z 491 $[MH]^+$ RT 3.43min
436		3-butyl-8-chloro-1-{4-[5-(5-chloro-2-furanyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	27	m/z 467 $[MH]^+$ RT 3.51min
437		3-butyl-8-chloro-1-(4-{5-[5-(trifluoromethyl)-2-furanyl]-1,2,4-oxadiazol-3-yl}butyl)-3,7-dihydro-1*H*-purine-2,6-dione	27	m/z 501 $[MH]^+$ RT 3.61min
438		3-butyl-8-chloro-1-{4-[5-(3-methyl-2-furanyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	27	m/z 447 $[MH]^+$ RT 3.43min
439		3-butyl-8-chloro-1-{4-[5-(1-methyl-1*H*-pyrazol-3-yl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	25	m/z 447 $[MH]^+$ RT 3.02min
440		3-butyl-8-chloro-1-{4-[5-(1-methyl-1*H*-pyrazol-4-yl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	8	m/z 447 $[MH]^+$ RT 2.99min
441		3-butyl-8-chloro-1-{4-[5-(3-thienyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	19	m/z 449 $[MH]^+$ RT 3.43min

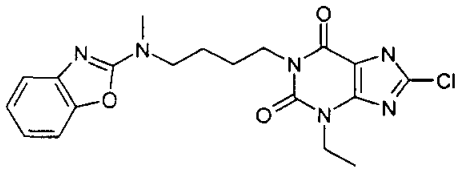
442		3-butyl-8-chloro-1-{4-[5-(5-methyl-1*H*-pyrazol-3-yl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	26	m/z 447 $[MH]^+$ RT 3.03min
443		3-butyl-8-chloro-1-{4-[5-(3-methyl-2-thienyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	27	m/z 463 $[MH]^+$ RT 3.62min
444		3-butyl-8-chloro-1-{4-[5-(1*H*-pyrrol-2-yl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	13	m/z 432 $[MH]^+$ RT 3.26min
445		3-butyl-8-chloro-1-{4-[5-(2-methyl-3-thienyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	18	m/z 463 $[MH]^+$ RT 3.64min
446		3-butyl-8-chloro-1-{4-[5-(4-methyl-1,3-thiazol-5-yl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	24	m/z 464 $[MH]^+$ RT 3.26min
447		3-butyl-8-chloro-1-{4-[5-(1*H*-pyrazol-3-yl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	20	m/z 433 $[MH]^+$ RT 3.00min
448		3-butyl-8-chloro-1-{4-[5-(3-ethyl-5-isoxazolyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	20	m/z 462 $[MH]^+$ RT 3.43min

449		3-butyl-8-chloro-1-{4-[5-(5-ethyl-3-isoxazolyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	23	m/z 462 $[MH]^+$ RT 3.46min
450		3-butyl-8-chloro-1-{4-[5-(1,3-thiazol-5-yl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	20	m/z 450 $[MH]^+$ RT 3.13min
451		3-butyl-8-chloro-1-{4-[5-(1*H*-indazol-3-yl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	24	m/z 483 $[MH]^+$ RT 3.50min
452		1-{4-[5-(1-benzofuran-2-yl)-1,2,4-oxadiazol-3-yl]butyl}-3-butyl-8-chloro-3,7-dihydro-1*H*-purine-2,6-dione	6	m/z 483 $[MH]^+$ RT 3.72min
453		3-butyl-8-chloro-1-{4-[5-(5-methyl-3-isoxazolyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	13	m/z 448 $[MH]^+$ RT 3.30min
454		3-butyl-8-chloro-1-{4-[5-(2-methyl-1,3-thiazol-4-yl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	20	m/z 464 $[MH]^+$ RT 3.14min
455		3-butyl-8-chloro-1-{4-[5-(4-methyl-1,2,3-thiadiazol-5-yl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-	14	m/z 465 $[MH]^+$ RT 3.40min

		2,6-dione		
456		3-butyl-8-chloro-1-{4-[5-(3-methyl-2-thioxo-2,3-dihydro-1*H*-imidazol-4-yl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	16	m/z 479 $[MH]^+$ RT 3.08min
457		3-butyl-8-chloro-1-{4-[5-(1,2,5-thiadiazol-3-yl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	24	m/z 451 $[MH]^+$ RT 3.27min
458		3-butyl-8-chloro-1-{4-[5-(3-furanyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	21	m/z 433 $[MH]^+$ RT 3.29min
459		3-butyl-8-chloro-1-{4-[5-(1-methyl-1*H*-pyrazol-5-yl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	23	m/z 447 $[MH]^+$ RT 3.22min
460		3-butyl-8-chloro-1-{4-[5-(1,3-thiazol-4-yl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	20	m/z 450 $[MH]^+$ RT 3.06min
461		*N*-(4-{3-[4-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)butyl]-1,2,4-oxadiazol-5-yl}-3-chlorophenyl)acetamide	23	m/z 534 $[MH]^+$ RT 3.44min

462		*N*-(4-{3-[4-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)butyl]-1,2,4-oxadiazol-5-yl}phenyl)acetamide	16	m/z 500 $[MH]^+$ RT 3.23min
463		3-butyl-8-chloro-1-{4-[5-(2-thienyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	27	m/z 449 $[MH]^+$ RT 3.45min
464		3-butyl-8-chloro-1-{4-[5-(1-methyl-1*H*-pyrrol-2-yl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	15	m/z 446 $[MH]^+$ RT 3.45min

Example 465 : 1-{4-[1,3-Benzoxazol-2-yl(methyl)amino]butyl}-8-chloro-3-ethyl-3,7-dihydro-1*H*-purine-2,6-dione



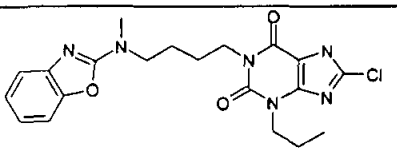
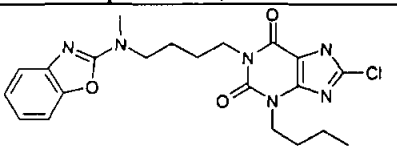
A solution of 2-chloro-1,3-benzoxazole (0.46g, 3mmol) in THF (20ml) was treated with 1-methylpyrrolidine (0.26g, 3mmol) and the reaction mixture heated at reflux for 6h, then cooled and evaporated to dryness. Purification by flash chromatography [Isco Companion, 12g Redisep cartridge, gradient elution from cyclohexane to cyclohexane/diethyl ether (3:2)] revealed 0.52g (73% yield) of *N*-(4-chlorobutyl)-*N*-methyl-1,3-benzoxazol-2-amine as a colourless oil. LC/MS: m/z 239 $[MH]^+$, RT 3.12min.

A solution of 8-chloro-3-ethyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (0.112g, 0.44mmol) in DMF (10ml) was treated with potassium carbonate (0.08g, 0.6mmol) and *N*-(4-chlorobutyl)-*N*-methyl-1,3-benzoxazol-2-amine (0.12g, 0.5mmol). The reaction mixture was heated at 75°C for 18h and then cooled to ambient temperature. The mixture was degassed by the repeated application of vacuum followed by backfilling with nitrogen gas and then treated with tetrakis(triphenylphosphine)palladium(0) (0.03g, 0.026mmol) and morpholine (0.5ml, 5.7mmol). Stirred for 4h under a nitrogen atmosphere at ambient temperature after which time the mixture was evaporated to dryness and the residue partitioned between

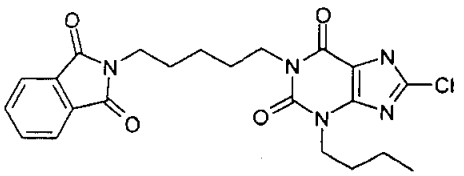
chloroform (40ml) and saturated aqueous ammonium chloride (40ml). The organic phase was evaporated to dryness and the residue dissolved in methanol (5ml) and added to a 5g aminopropyl SPE cartridge which was subsequently washed with methanol and the product eluted with a 5% solution of acetic acid in methanol. Combined product-containing fractions were evaporated to dryness and the product purified by MDAP to give the title compound as a white solid (0.043g, 23%).
LC/MS: m/z 417 $[MH]^+$, RT 2.91min.

The following compounds (**Table 29**) were prepared by a method analogous to that for **Example 465**.

Table 29

Example	Structure	Precursor	Yield (mg)	LC/MS
466	 1-{4-[1,3-benzoxazol-2-yl(methyl)amino]butyl}-8-chloro-3-propyl-3,7-dihydro-1*H*-purine-2,6-dione	8-chloro-7-(2-propen-1-yl)-3-propyl-3,7-dihydro-1*H*-purine-2,6-dione	47	m/z 431 $[MH]^+$ RT 3.09min
467	 1-{4-[1,3-benzoxazol-2-yl(methyl)amino]butyl}-3-butyl-8-chloro-3,7-dihydro-1*H*-purine-2,6-dione	3-butyl-8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1H-purine-2,6-dione	61	m/z 445 $[MH]^+$ RT 3.28min

Example 468 : 3-Butyl-8-chloro-1-[5-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)pentyl]-3,7-dihydro-1*H*-purine-2,6-dione



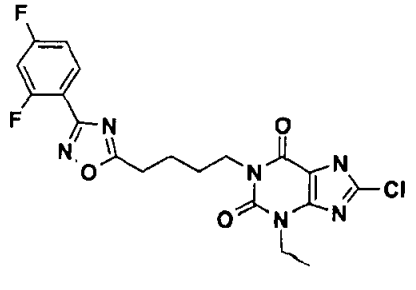
A solution of 3-butyl-8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1H-purine-2,6-dione (0.5g, 1.8mmol) in DMF (20ml) was treated with potassium carbonate (0.3g, 2.1mmol) and 1,5-dibromopentane (1.2ml, 8.9mmol) and then heated at 50°C for 2h. The mixture was cooled and evaporated to dryness. The residue was partitioned between ethyl acetate

(30ml) and saturated aqueous sodium bicarbonate (30ml). The aqueous phase was extracted with a further ethyl acetate (30ml) and the combined organics dried over magnesium sulfate, filtered and evaporated to dryness. The product was purified by flash chromatography [Isco Companion, 40g Redisep carteidge, gradient elution from cyclohehane to cyclohexane/ethyl acetate (1:1)] to reveal 0.663g (87%) of 1-(5-bromopentyl)-3-butyl-8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione as a colourless oil. LC/MS: m/z 431/433 $[MH]^+$, RT 3.76min.

To a solution of 1-(5-bromopentyl)-3-butyl-8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (0.642g, 1.5mmol) in DMF (10ml) was added potassium phthalimide (0.303g, 1.6mmol) and the mixture heated at 50°C for 2h then cooled. The mixture was degassed by the repeated application of vacuum followed by backfilling with nitrogen gas and then treated with tetrakis(triphenylphosphine)palladium(0) (0.173g, 0.15mmol) and morpholine (1.3ml, 15mmol). The mixture was allowed to stand at ambient temperature under a blanket of nitrogen for 18h after which time the mixture was evaporated and the residue partitioned between chloroform (30ml) and saturated aqueous ammonium chloride (30ml). The aqueous phase was extracted with a further chloroform (30ml) and the combined organics dried over magnesium sulfate, filtered and evaporated. The residue was dissolved in methanol (5ml) and added to a 10g aminopropyl SPE cartridge which was subsequently washed with methanol and the product eluted with a 5% solution of acetic acid in methanol. Product-containing fractions were evaporated and then purification by MDAP to give N-[5-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)pentyl]-2-(4-morpholinylcarbonyl)benzamide as a white solid (0.137g,LC/MS: m/z 545 $[MH]^+$, RT 2.77min) and the title compound as a white solid (0.239g, 35%).
LC/MS: m/z 458 $[MH]^+$, RT 3.33min.

Example 469 : 8-Chloro-1-{4-[3-(2,4-difluorophenyl)-1,2,4-oxadiazol-5-yl]butyl}-3-ethyl-3,7-dihydro-1*H*-purine-2,6-dione

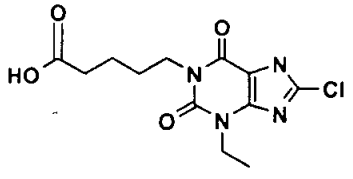
a) 8-Chloro-1-{4-[3-(2,4-difluorophenyl)-1,2,4-oxadiazol-5-yl]butyl}-3-ethyl-3,7-dihydro-1*H*-purine-2,6-dione



A solution of 5-(8-chloro-3-ethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)pentanoic acid (0.05g, 0.16mmol) in DMSO (1ml) was treated with CDI (0.029g, 0.18mmol) and the mixture stirred at room temperature for 1h. Subsequently, the mixture was treated with 2,4-difluorobenzamidoxime (0.03g, 0.18mmol) and then heated to 120°C for 30 min. The product was purified from the crude mixture using MDAP. Product-containing fractions were evaporated using a stream of nitrogen and the resulting colourless gum triturated in ether and dried to reveal the title compound as a white solid (50mg, 70%).
LC/MS: m/z 451 $[MH]^+$, RT 2.23min.

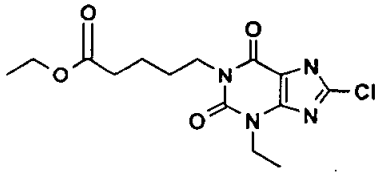
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b) 5-(8-chloro-3-ethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)pentanoic acid



A solution of ethyl 5-(8-chloro-3-ethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)pentanoate (2.3g, 6.7mmol) in methanol (75ml) was treated with water (3ml) and lithium hydroxide (0.481g, 20.1mmol) and the mixture stirred at 40°C for 17h. The mixture was evaporated to dryness and the residue treated with 50ml of ethyl acetate and 50ml of water. The 2 phases were separated and the aqueous phase adjusted to pH5 using 2M aqueous hydrochloric acid. The precipitated product was filtered off and dried to yield 5-(8-chloro-3-ethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)pentanoic acid as a white solid (1.99g, 95%).
LC/MS: m/z 315 $[MH]^+$, RT 2.34min.

c) Ethyl 5-(8-chloro-3-ethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)pentanoate



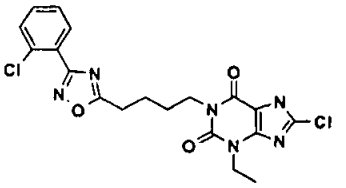
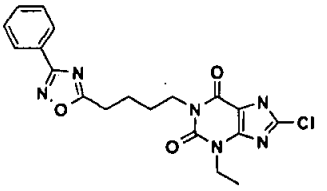
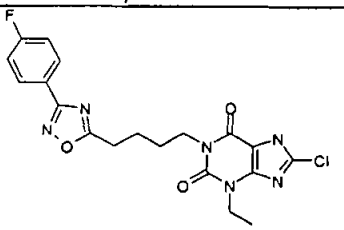
A solution of 8-chloro-7-(2-propen-1-yl)-3-ethyl-3,7-dihydro-1*H*-purine-2,6-dione (3g, 11.8mmol) in DMF (40ml) was treated with potassium carbonate (1.9g, 14.1mmol) and ethyl 5-bromopentanoate (2.24ml, 14.1mmol) and the mixture heated in a nitrogen atmosphere at 70°C for 5h and then cooled. The mixture was degassed by the repeated application of vacuum followed by backfilling with nitrogen gas and then treated with tetrakis(triphenylphosphine)palladium(0) (1.36g, 1.1mmol) and morpholine (10.3ml, 118mmol). The mixture was stirred in a nitrogen atmosphere for 4h and then evaporated to dryness. The residue was partitioned between 100ml of ethyl acetate and 100ml of water. The aqueous phase was re-extracted with 100ml of ethyl acetate

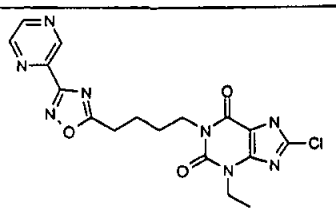
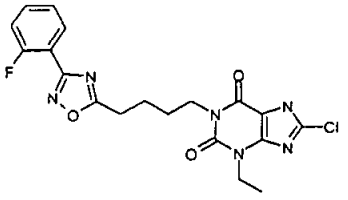
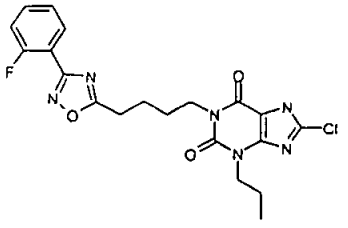
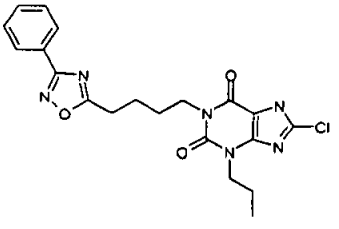
and the combined organics dried over magnesium sulfate, filtered and evaporated. The residue was triturated in diethyl ether, filtered and dried to reveal ethyl 5-(8-chloro-3-ethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)pentanoate compound as a white solid (2.3g, 57%).

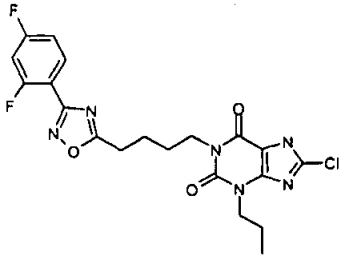
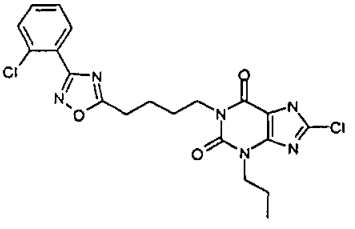
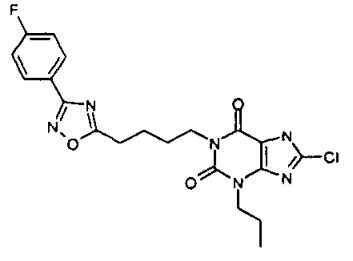
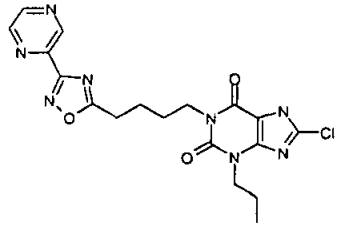
LC/MS: m/z 343 $[MH]^+$, RT 2.73min.

The following compounds (**Table 30**) were prepared by a method analogous to that for **Example 469**.

Table 30

Example	Structure	Precursor	Yield (mg)	LC/MS
470	 8-chloro-1-{4-[3-(2-chlorophenyl)-1,2,4-oxadiazol-5-yl]butyl}-3-ethyl-3,7-dihydro-1*H*-purine-2,6-dione	5-(8-chloro-3-ethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)pentanoic acid	33	m/z 449 $[MH]^+$ RT 3.27min
471	 8-chloro-1-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)butyl]-3-ethyl-3,7-dihydro-1*H*-purine-2,6-dione	5-(8-chloro-3-ethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)pentanoic acid	32	m/z 415 $[MH]^+$ RT 3.22min
472	 8-chloro-3-ethyl-1-{4-[3-(4-fluorophenyl)-1,2,4-oxadiazol-5-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	5-(8-chloro-3-ethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)pentanoic acid	31	m/z 433 $[MH]^+$ RT 3.26min

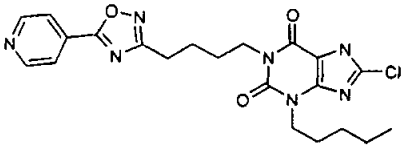
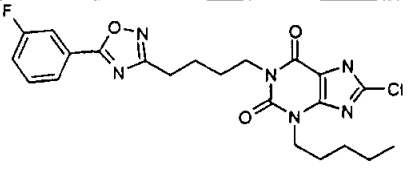
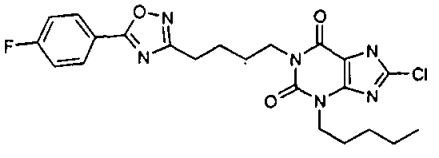
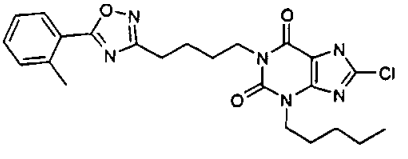
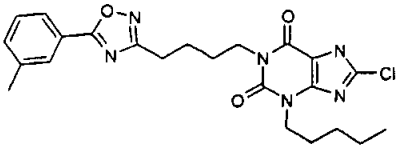
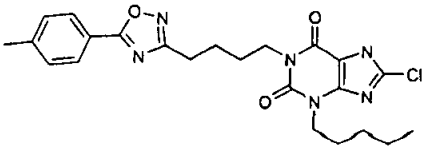
473	 8-chloro-3-ethyl-1-{4-[3-(2-pyrazinyl)-1,2,4-oxadiazol-5-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	5-(8-chloro-3-ethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)pentanoic acid	2	m/z 417 $[MH]^+$ RT 2.54min
474	 8-chloro-3-ethyl-1-{4-[3-(2-fluorophenyl)-1,2,4-oxadiazol-5-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	5-(8-chloro-3-ethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)pentanoic acid	38	m/z 433 $[MH]^+$ RT 3.12min
475	 8-chloro-1-{4-[3-(2-fluorophenyl)-1,2,4-oxadiazol-5-yl]butyl}-3-propyl-3,7-dihydro-1*H*-purine-2,6-dione	5-(8-chloro-3-propyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)pentanoic acid	29	m/z 447 $[MH]^+$ RT 3.28min
476	 8-chloro-1-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)butyl]-3-propyl-3,7-dihydro-1*H*-purine-2,6-dione	5-(8-chloro-3-propyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)pentanoic acid	11	m/z 429 $[MH]^+$ RT 3.35min

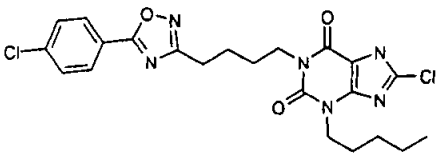
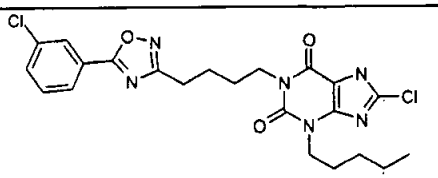
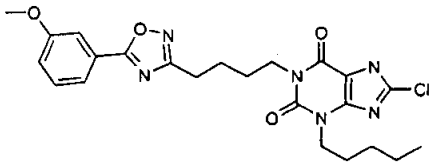
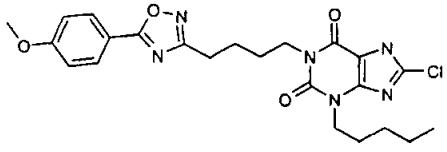
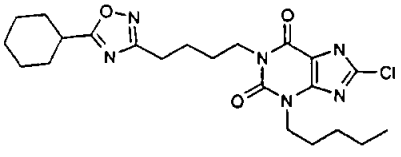
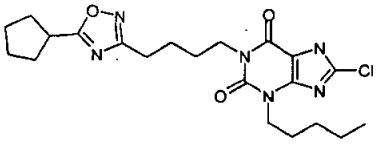
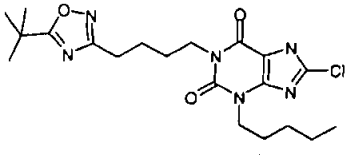
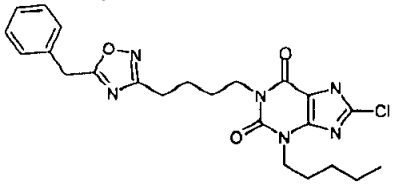
477	 8-chloro-1-{4-[3-(2,4-difluorophenyl)-1,2,4-oxadiazol-5-yl]butyl}-3-propyl-3,7-dihydro-1*H*-purine-2,6-dione	5-(8-chloro-3-propyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)pentanoic acid	32	m/z 465 $[MH]^+$ RT 3.40min
478	 8-chloro-1-{4-[3-(2-chlorophenyl)-1,2,4-oxadiazol-5-yl]butyl}-3-propyl-3,7-dihydro-1*H*-purine-2,6-dione	5-(8-chloro-3-propyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)pentanoic acid	25	m/z 463 $[MH]^+$ RT 3.40min
479	 8-chloro-1-{4-[3-(4-fluorophenyl)-1,2,4-oxadiazol-5-yl]butyl}-3-propyl-3,7-dihydro-1H-purine-2,6-dione	5-(8-chloro-3-propyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)pentanoic acid	26	m/z 447 $[MH]^+$ RT 3.44min
480	 8-chloro-3-propyl-1-{4-[3-(2-pyrazinyl)-1,2,4-oxadiazol-5-yl]butyl}-3,7-dihydro-1H-	5-(8-chloro-3-propyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)pentanoic acid	25	m/z 431 $[MH]^+$ RT 3.09min

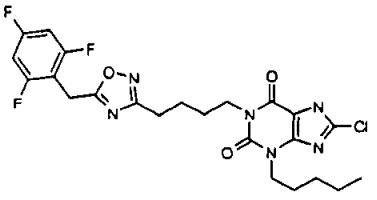
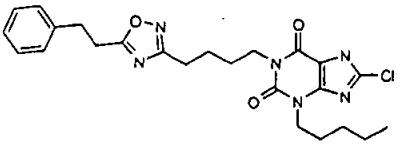
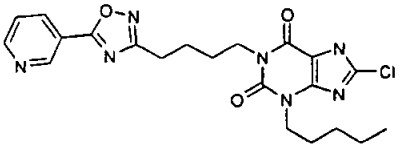
	purine-2,6-dione			

The following compounds (**Table 31**) were prepared using a method analogous to that for **Example 158**, using the appropriate acid.

Table 31

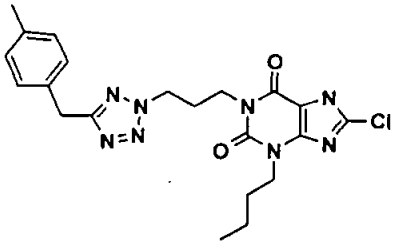
Example	Structure	Name	Yield (mg)	LC/MS
481		8-chloro-3-pentyl-1-{4-[5-(4-pyridinyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	8.0	m/z 458 $[MH]^+$ RT 3.25min
482		8-chloro-1-{4-[5-(3-fluorophenyl)-1,2,4-oxadiazol-3-yl]butyl}-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione	9.1	m/z 475 $[MH]^+$ RT 3.73min
483		8-chloro-1-{4-[5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl]butyl}-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione	16.1	m/z 475 $[MH]^+$ RT 3.69min
484		8-chloro-1-{4-[5-(2-methylphenyl)-1,2,4-oxadiazol-3-yl]butyl}-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione	22.9	m/z 471 $[MH]^+$ RT 3.82min
485		8-chloro-1-{4-[5-(3-methylphenyl)-1,2,4-oxadiazol-3-yl]butyl}-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione	18.0	m/z 471 $[MH]^+$ RT 3.81min
486		8-chloro-1-{4-[5-(4-methylphenyl)-1,2,4-oxadiazol-3-yl]butyl}-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione	25.0	m/z 471 $[MH]^+$ RT 3.80min

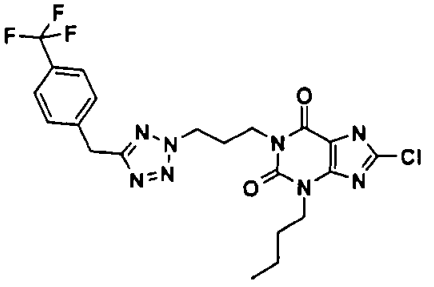
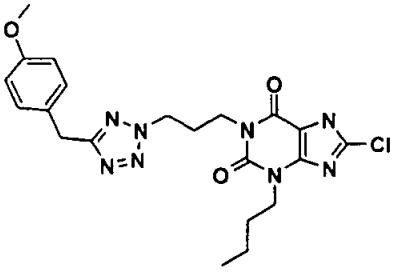
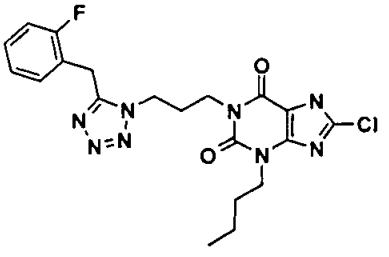
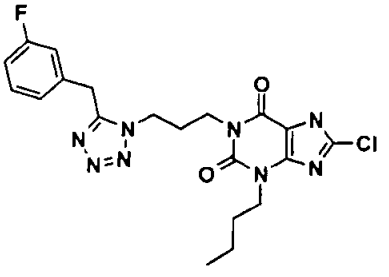
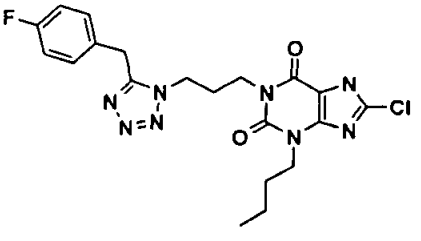
487		8-chloro-1-{4-[5-(4-chlorophenyl)-1,2,4-oxadiazol-3-yl]butyl}-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione	16.6	m/z 491 $[MH]^+$ RT 3.89min
488		8-chloro-1-{4-[5-(3-chlorophenyl)-1,2,4-oxadiazol-3-yl]butyl}-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione	12.8	m/z 491 $[MH]^+$ RT 3.91min
489		8-chloro-1-(4-{5-[3-(methyloxy)phenyl]-1,2,4-oxadiazol-3-yl}butyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione	23.0	m/z 487 $[MH]^+$ RT 3.71min
490		8-chloro-1-(4-{5-[4-(methyloxy)phenyl]-1,2,4-oxadiazol-3-yl}butyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione	15.8	m/z 487 $[MH]^+$ RT 3.67min
491		8-chloro-1-[4-(5-cyclohexyl-1,2,4-oxadiazol-3-yl)butyl]-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione	16.1	m/z 463 $[MH]^+$ RT 3.73min
492		8-chloro-1-[4-(5-cyclopentyl-1,2,4-oxadiazol-3-yl)butyl]-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione	11.7	m/z 449 $[MH]^+$ RT 3.59min
493		8-chloro-1-{4-[5-(1,1-dimethylethyl)-1,2,4-oxadiazol-3-yl]butyl}-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione	19.8	m/z 437 $[MH]^+$ RT 3.52min
494		8-chloro-3-pentyl-1-{4-[5-(phenylmethyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-	21.0	m/z 471 $[MH]^+$ RT 3.55min

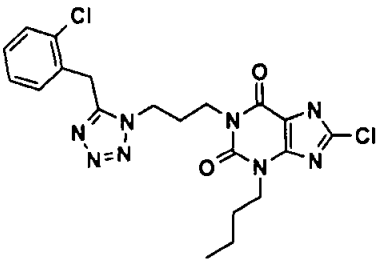
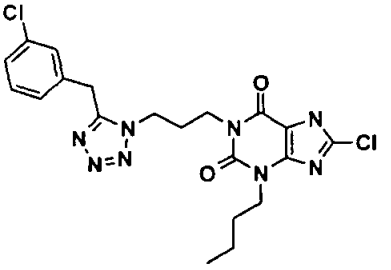
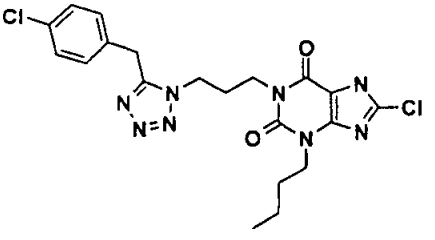
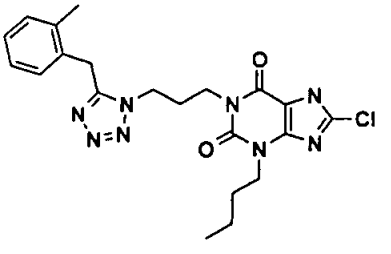
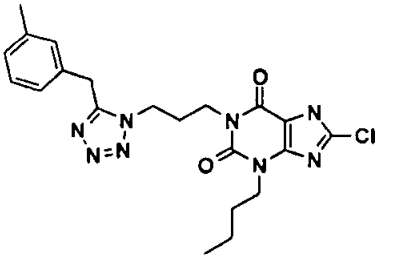
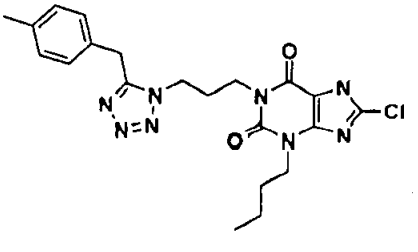
		1*H*-purine-2,6-dione		
495		8-chloro-3-pentyl-1-(4-{5-[(2,4,6-trifluorophenyl)methyl]-1,2,4-oxadiazol-3-yl}butyl)-3,7-dihydro-1*H*-purine-2,6-dione	29.3	m/z 525 $[MH]^+$ RT 3.62min
496		8-chloro-3-pentyl-1-{4-[5-(2-phenylethyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	18.4	m/z 485 $[MH]^+$ RT 3.64min
497		8-chloro-3-pentyl-1-{4-[5-(3-pyridinyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	8.2	m/z 458 $[MH]^+$ RT 3.23min

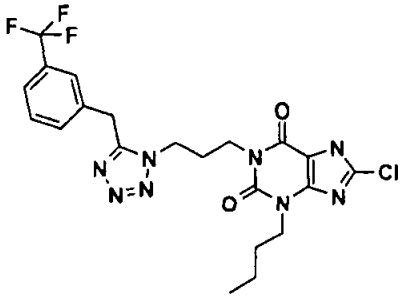
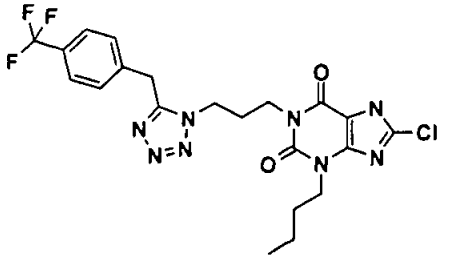
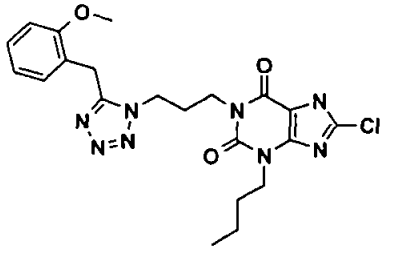
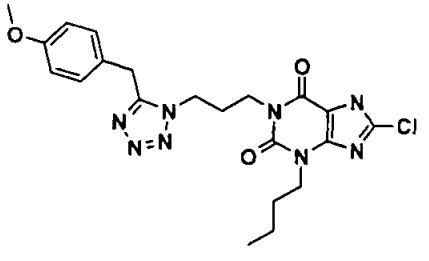
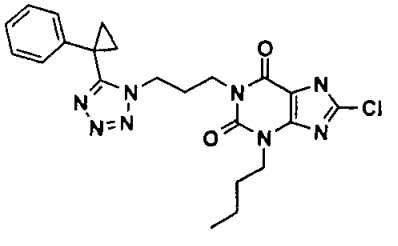
The following compounds (**Table 32**) were prepared using a method analogous to that for **Example 36**, using the appropriate tetrazole and 3-[3-alkyl-8-chloro-2,6-dioxo-7-(2-propen-1-yl)-2,3,6,7-tetrahydro-1*H*-purin-1-yl]propyl methanesulfonate. MDAP was employed to further purify those compounds insufficiently pure following normal phase chromatography.

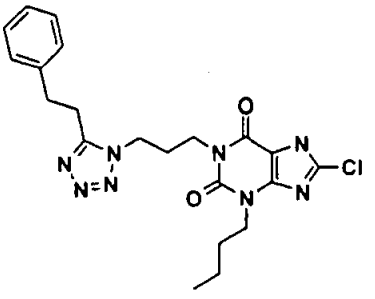
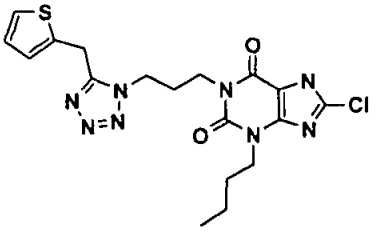
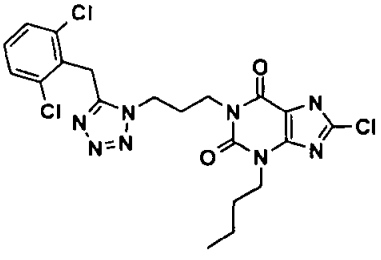
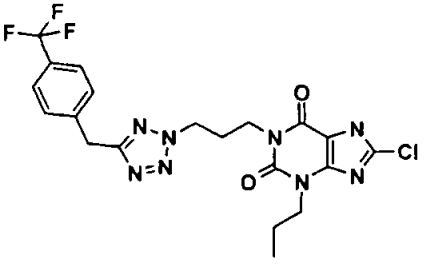
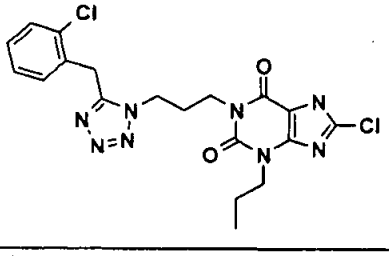
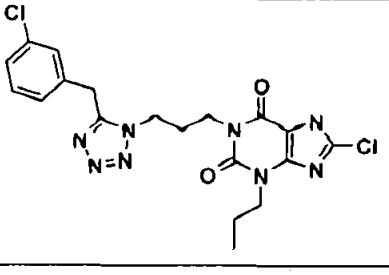
Table 32

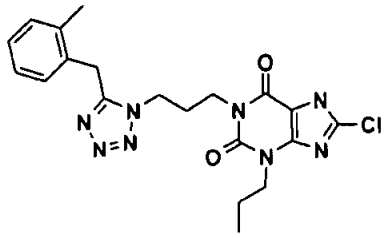
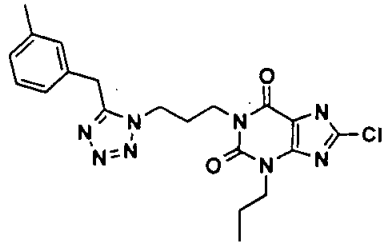
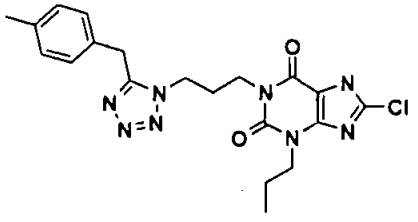
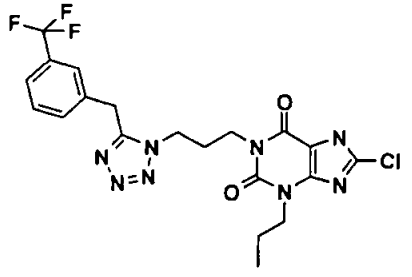
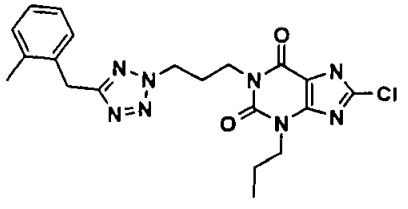
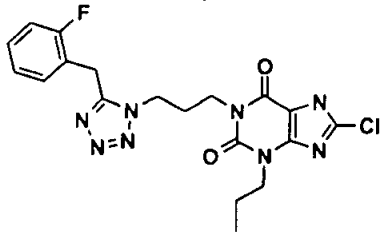
Example	Structure	Name	Yield (mg)	LC/MS
498		3-butyl-8-chloro-1-(3-{5-[(4-methylphenyl)methyl]-2H-tetrazol-2-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	35.1	m/z 457 $[MH]^+$ RT 3.40min

499		3-butyl-8-chloro-1-[3-(5-{[4-(trifluoromethyl)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione	43.6	m/z 511 $[MH]^+$ RT 3.52min
500		3-butyl-8-chloro-1-[3-(5-{[4-(methyloxy)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione	38.2	m/z 473 $[MH]^+$ RT 3.24min
501		3-butyl-8-chloro-1-(3-{5-[(2-fluorophenyl)methyl]-1H-tetrazol-1-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	13.7	m/z 461 $[MH]^+$ RT 3.07min
502		3-butyl-8-chloro-1-(3-{5-[(3-fluorophenyl)methyl]-1H-tetrazol-1-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	15.0	m/z 461 $[MH]^+$ RT 3.10min
503		3-butyl-8-chloro-1-(3-{5-[(4-fluorophenyl)methyl]-1H-tetrazol-1-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	17.7	m/z 461 $[MH]^+$ RT 3.10min

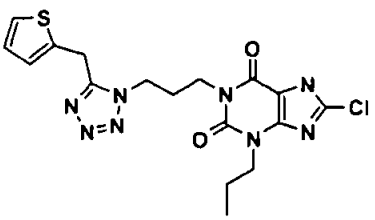
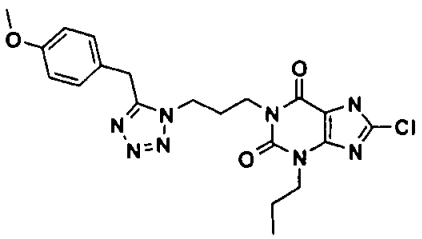
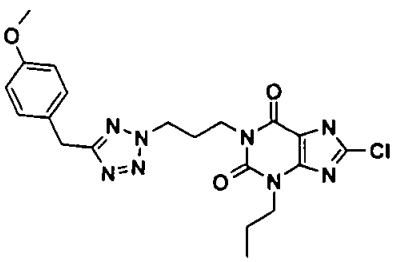
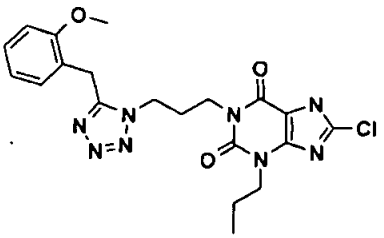
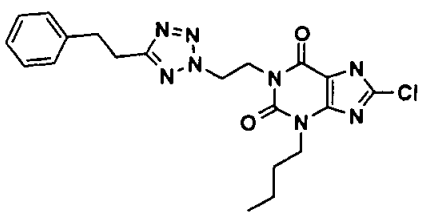
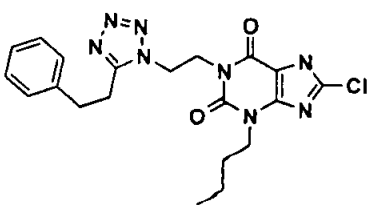
504		3-butyl-8-chloro-1-(3-{5-[(2-chlorophenyl)methyl]-1H-tetrazol-1-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	8.4	m/z 477 $[MH]^+$ RT 3.17min
505		3-butyl-8-chloro-1-(3-{5-[(3-chlorophenyl)methyl]-1H-tetrazol-1-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	16.4	m/z 477 $[MH]^+$ RT 3.23min
506		3-butyl-8-chloro-1-(3-{5-[(4-chlorophenyl)methyl]-1H-tetrazol-1-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	17.0	m/z 477 $[MH]^+$ RT 3.24min
507		3-butyl-8-chloro-1-(3-{5-[(2-methylphenyl)methyl]-1H-tetrazol-1-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	15.1	m/z 457 $[MH]^+$ RT 3.15min
508		3-butyl-8-chloro-1-(3-{5-[(3-methylphenyl)methyl]-1H-tetrazol-1-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	18.6	m/z 457 $[MH]^+$ RT 3.18min
509		3-butyl-8-chloro-1-(3-{5-[(4-methylphenyl)methyl]-1H-tetrazol-1-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	16.3	m/z 457 $[MH]^+$ RT 3.19min

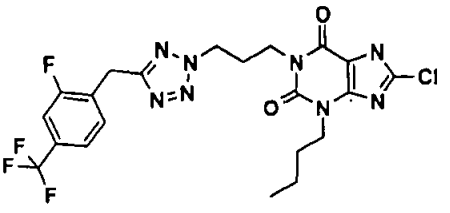
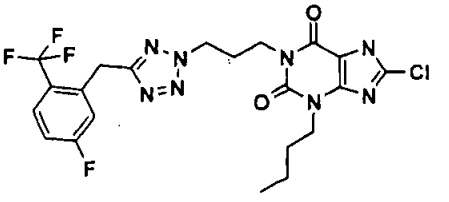
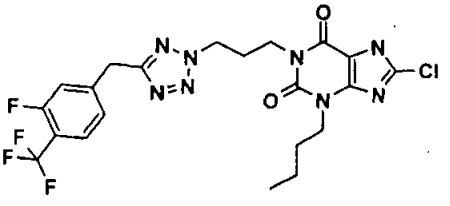
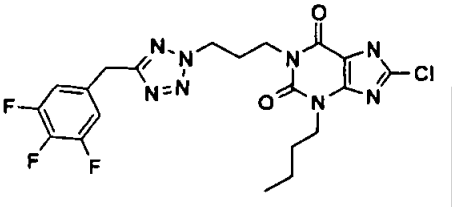
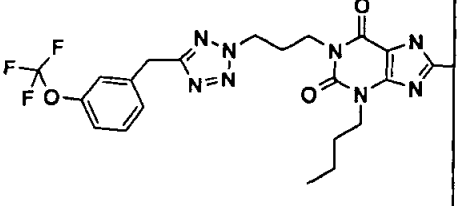
510		3-butyl-8-chloro-1-[3-(5-{[3-(trifluoromethyl)phenyl]methyl}-1H-tetrazol-1-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione	17.7	m/z 511 $[MH]^+$ RT 3.31min
511		3-butyl-8-chloro-1-[3-(5-{[4-(trifluoromethyl)phenyl]methyl}-1H-tetrazol-1-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione	21.6	m/z 511 $[MH]^+$ RT 3.33min
512		3-butyl-8-chloro-1-[3-(5-{[2-(methyloxy)phenyl]methyl}-1H-tetrazol-1-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione	16.3	m/z 473 $[MH]^+$ RT 3.10min
513		3-butyl-8-chloro-1-[3-(5-{[4-(methyloxy)phenyl]methyl}-1H-tetrazol-1-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione	20.8	m/z 473 $[MH]^+$ RT 3.05min
514		3-butyl-8-chloro-1-{3-[5-(1-phenylcyclopropyl)-1H-tetrazol-1-yl]propyl}-3,7-dihydro-1H-purine-2,6-dione	14.1	m/z 468 $[MH]^+$ RT 3.16min

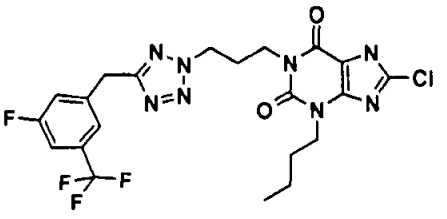
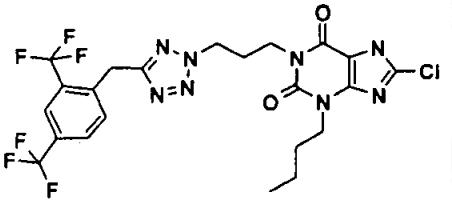
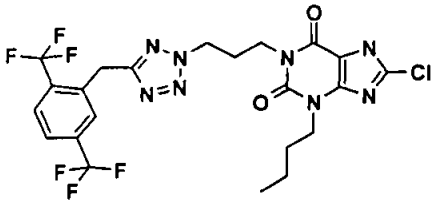
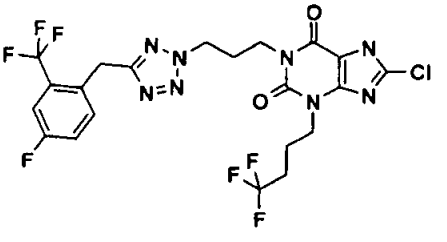
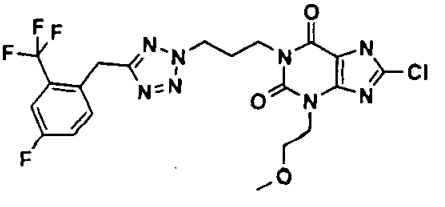
515		3-butyl-8-chloro-1-{3-[5-(2-phenylethyl)-1H-tetrazol-1-yl]propyl}-3,7-dihydro-1H-purine-2,6-dione	21.0	m/z 457 $[MH]^+$ RT 3.15min
516		3-butyl-8-chloro-1-{3-[5-(2-thienylmethyl)-1H-tetrazol-1-yl]propyl}-3,7-dihydro-1H-purine-2,6-dione	11.8	m/z 448 $[MH]^+$ RT 3.02min
517		3-butyl-8-chloro-1-(3-{5-[(2,6-dichlorophenyl)methyl]-1H-tetrazol-1-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	12.4	m/z 512 $[MH]^+$ RT 3.27min
518		8-chloro-3-propyl-1-[3-(5-{[4-(trifluoromethyl)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione	15.5	m/z 497 $[MH]^+$ RT 3.38min
519		8-chloro-1-(3-{5-[(2-chlorophenyl)methyl]-1H-tetrazol-1-yl}propyl)-3-propyl-3,7-dihydro-1H-purine-2,6-dione	1.6	m/z 463 $[MH]^+$ RT 3.00min
520		8-chloro-1-(3-{5-[(3-chlorophenyl)methyl]-1H-tetrazol-1-yl}propyl)-3-propyl-3,7-dihydro-1H-purine-2,6-dione	7.1	m/z 463 $[MH]^+$ RT 3.06min

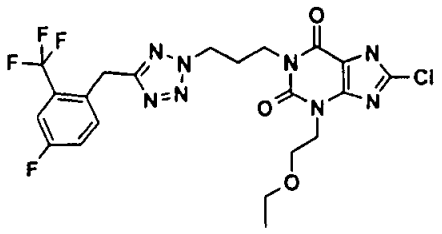
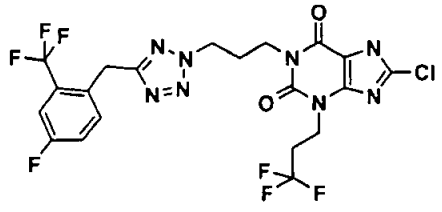
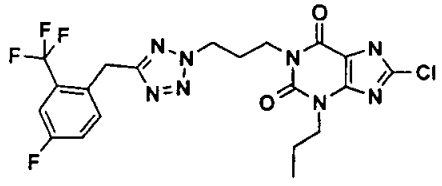
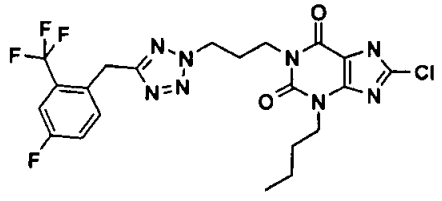
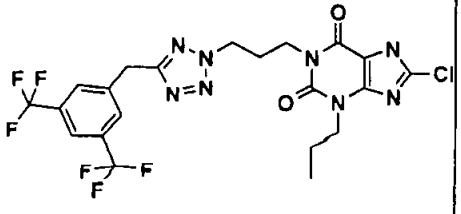
521		8-chloro-1-(3-{5-[(2-methylphenyl)methyl]-1H-tetrazol-1-yl}propyl)-3-propyl-3,7-dihydro-1H-purine-2,6-dione	7.2	m/z 443 $[MH]^+$ RT 2.97min
522		8-chloro-1-(3-{5-[(3-methylphenyl)methyl]-1H-tetrazol-1-yl}propyl)-3-propyl-3,7-dihydro-1H-purine-2,6-dione	5.7	m/z 443 $[MH]^+$ RT 3.01min
523		8-chloro-1-(3-{5-[(4-methylphenyl)methyl]-1H-tetrazol-1-yl}propyl)-3-propyl-3,7-dihydro-1H-purine-2,6-dione	5.5	m/z 443 $[MH]^+$ RT 3.01min
524		8-chloro-3-propyl-1-[3-(5-{[3-(trifluoromethyl)phenyl]methyl}-1H-tetrazol-1-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione	3.3	m/z 497 $[MH]^+$ RT 3.16min
525		8-chloro-1-(3-{5-[(2-methylphenyl)methyl]-2H-tetrazol-2-yl}propyl)-3-propyl-3,7-dihydro-1H-purine-2,6-dione	24.1	m/z 443 $[MH]^+$ RT 3.20min
526		8-chloro-1-(3-{5-[(2-fluorophenyl)methyl]-1H-tetrazol-1-yl}propyl)-3-propyl-3,7-dihydro-1H-purine-2,6-dione	1.3	m/z 447 $[MH]^+$ RT 2.89min

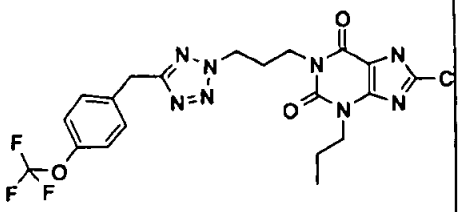
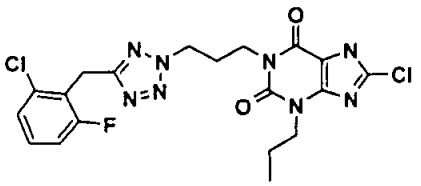
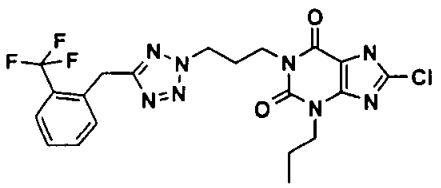
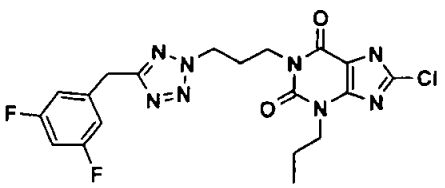
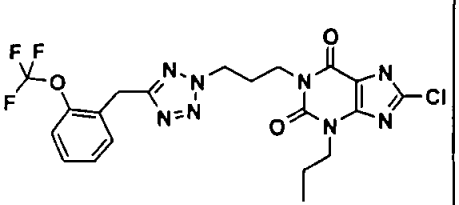
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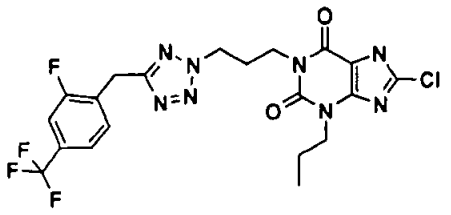
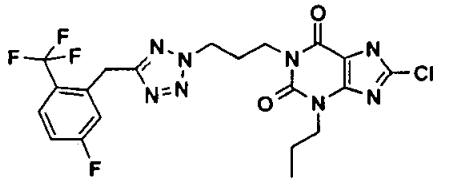
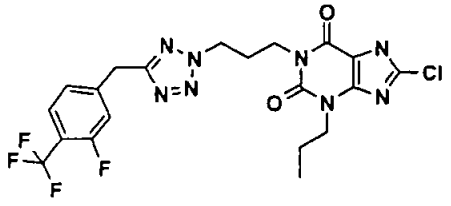
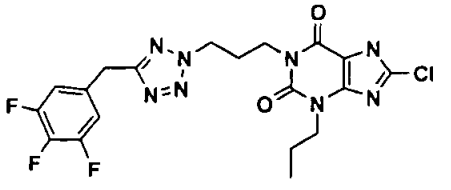
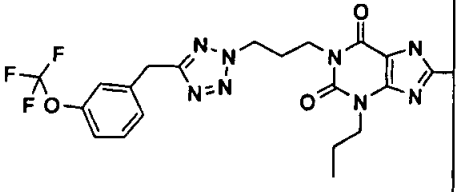
527		8-chloro-3-propyl-1-{3-[5-(2-thienylmethyl)-1H-tetrazol-1-yl]propyl}-3,7-dihydro-1H-purine-2,6-dione	5.2	m/z 435 $[MH]^+$ RT 2.83min
528		8-chloro-1-[3-(5-{[4-(methyloxy)phenyl]methyl}-1H-tetrazol-1-yl)propyl]-3-propyl-3,7-dihydro-1H-purine-2,6-dione	1.2	m/z 459 $[MH]^+$ RT 2.87min
529		8-chloro-1-[3-(5-{[4-(methyloxy)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-3-propyl-3,7-dihydro-1H-purine-2,6-dione	19.7	m/z 459 $[MH]^+$ RT 3.07min
530		8-chloro-1-[3-(5-{[2-(methyloxy)phenyl]methyl}-1H-tetrazol-1-yl)propyl]-3-propyl-3,7-dihydro-1H-purine-2,6-dione	1.9	m/z 459 $[MH]^+$ RT 2.92min
531		3-butyl-8-chloro-1-{2-[5-(2-phenylethyl)-2H-tetrazol-2-yl]ethyl}-3,7-dihydro-1H-purine-2,6-dione	44.0	m/z 443 $[MH]^+$ RT 3.31min
532		3-butyl-8-chloro-1-{2-[5-(2-phenylethyl)-1H-tetrazol-1-yl]ethyl}-3,7-dihydro-1H-purine-2,6-dione	10.4	m/z 443 $[MH]^+$ RT 3.12min

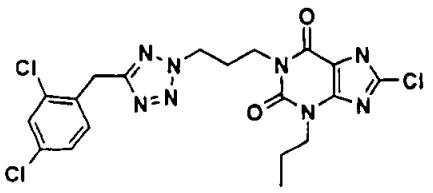
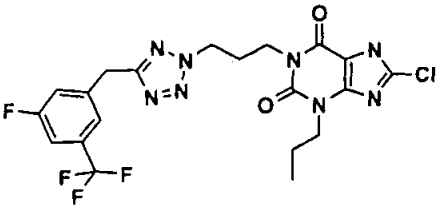
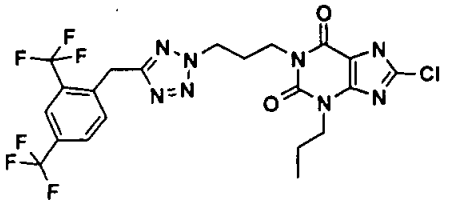
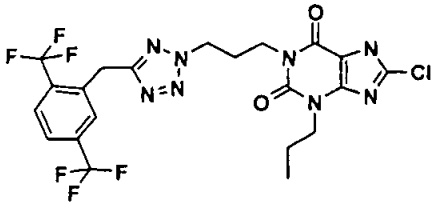
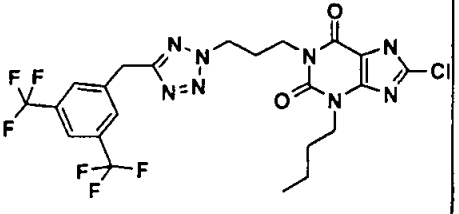
533		3-butyl-8-chloro-1-[3-(5-{[2-fluoro-4-(trifluoromethyl)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione	24.5	m/z 529 $[MH]^+$ RT 3.22min
534		3-butyl-8-chloro-1-[3-(5-{[5-fluoro-2-(trifluoromethyl)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione	25.3	m/z 529 $[MH]^+$ RT 3.51min
535		3-butyl-8-chloro-1-[3-(5-{[3-fluoro-4-(trifluoromethyl)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione	11.5	m/z 529 $[MH]^+$ RT 3.56min
536		3-butyl-8-chloro-1-(3-{5-[(3,4,5-trifluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	19.4	m/z 497 $[MH]^+$ RT 3.45min
537		3-butyl-8-chloro-1-{3-[5-({3-[(trifluoromethyl)oxy]phenyl}methyl)-2H-tetrazol-2-yl]propyl}-3,7-dihydro-1H-purine-2,6-dione	27.2	m/z 527 $[MH]^+$ RT 3.55min

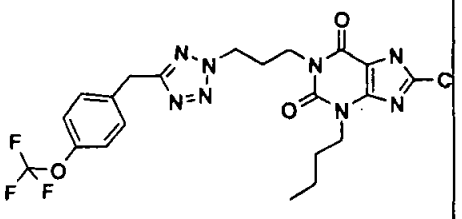
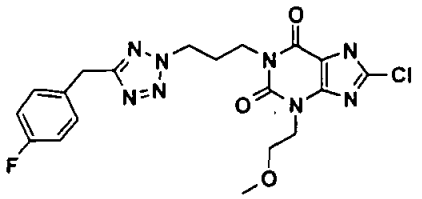
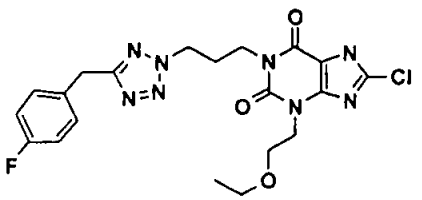
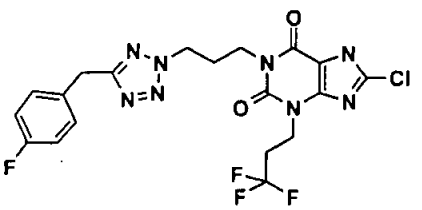
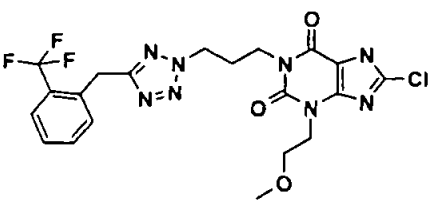
538		3-butyl-8-chloro-1-[3-(5-{[3-fluoro-5-(trifluoromethyl)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione	19.8	m/z 529 $[MH]^+$ RT 3.56min
539		1-[3-(5-{[2,4-bis(trifluoromethyl)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-3-butyl-8-chloro-3,7-dihydro-1H-purine-2,6-dione	36.6	m/z 579 $[MH]^+$ RT 3.72min
540		1-[3-(5-{[2,5-bis(trifluoromethyl)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-3-butyl-8-chloro-3,7-dihydro-1H-purine-2,6-dione	50.3	m/z 579 $[MH]^+$ RT 3.65min
541		8-chloro-1-[3-(5-{[4-fluoro-2-(trifluoromethyl)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-3-(4,4,4-trifluorobutyl)-3,7-dihydro-1H-purine-2,6-dione	25.0	m/z 583 $[MH]^+$ RT 3.50min
542		8-chloro-1-[3-(5-{[4-fluoro-2-(trifluoromethyl)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-3-[2-(methyloxy)ethyl]-3,7-dihydro-1H-purine-2,6-dione	23.0	m/z 531 $[MH]^+$ RT 3.16min

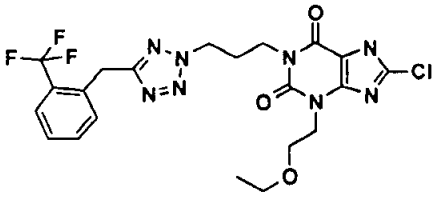
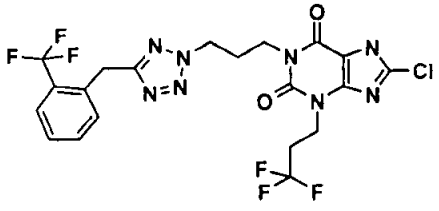
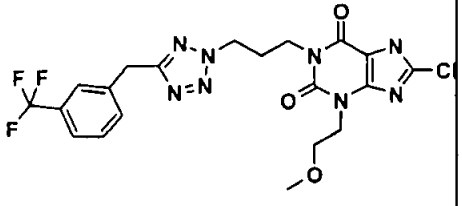
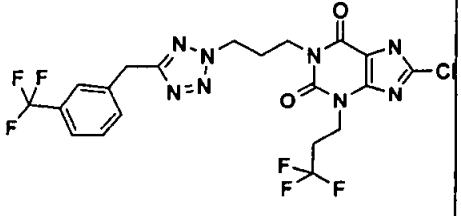
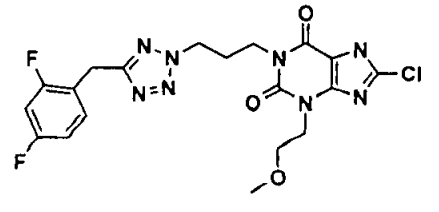
543		8-chloro-3-[2-(ethyloxy)ethyl]-1-[3-(5-{[4-fluoro-2-(trifluoromethyl)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione	13.1	m/z 545 $[MH]^+$ RT 3.30min
544		8-chloro-1-[3-(5-{[4-fluoro-2-(trifluoromethyl)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-3-(3,3,3-trifluoropropyl)-3,7-dihydro-1H-purine-2,6-dione	36.3	m/z 569 $[MH]^+$ RT 3.46min
545		8-chloro-1-[3-(5-{[4-fluoro-2-(trifluoromethyl)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-3-propyl-3,7-dihydro-1H-purine-2,6-dione	32.0	m/z 515 $[MH]^+$ RT 3.37min
546		3-butyl-8-chloro-1-[3-(5-{[4-fluoro-2-(trifluoromethyl)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione	30.3	m/z 529 $[MH]^+$ RT 3.53min
547		1-[3-(5-{[3,5-bis(trifluoromethyl)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-8-chloro-3-propyl-3,7-dihydro-1H-purine-2,6-dione	22.9	m/z 565 $[MH]^+$ RT 3.54min

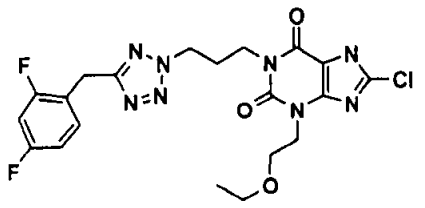
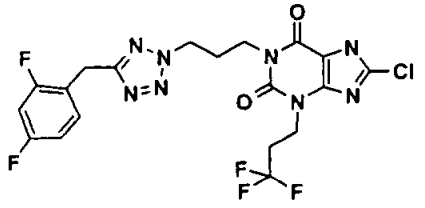
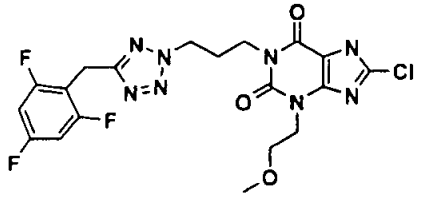
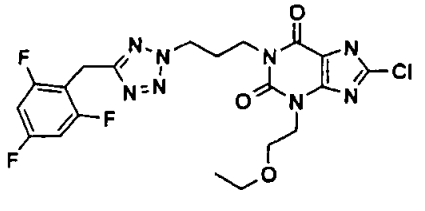
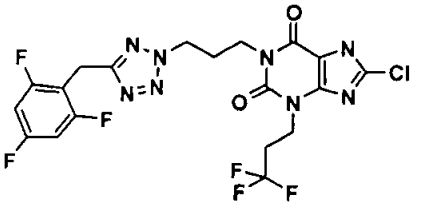
548		8-chloro-3-propyl-1-{3-[5-({4-[(trifluoromethyl)oxy]phenyl}methyl)-2H-tetrazol-2-yl]propyl}-3,7-dihydro-1H-purine-2,6-dione	21.6	m/z 513 $[MH]^+$ RT 3.42min
549		8-chloro-1-(3-{5-[(2-chloro-6-fluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3-propyl-3,7-dihydro-1H-purine-2,6-dione	12.4	m/z 481 $[MH]^+$ RT 3.20min
550		8-chloro-3-propyl-1-[3-(5-{[2-(trifluoromethyl)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione	17.7	m/z 497 $[MH]^+$ RT 3.26min
551		8-chloro-1-(3-{5-[(3,5-difluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3-propyl-3,7-dihydro-1H-purine-2,6-dione	21.6	m/z 465 $[MH]^+$ RT 3.16min
552		8-chloro-3-propyl-1-{3-[5-({2-[(trifluoromethyl)oxy]phenyl}methyl)-2H-tetrazol-2-yl]propyl}-3,7-dihydro-1H-purine-2,6-dione	22.3	m/z 513 $[MH]^+$ RT 3.27min

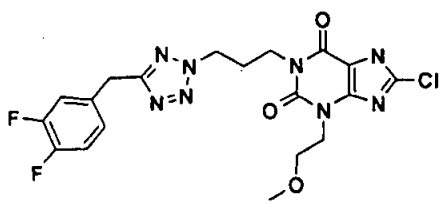
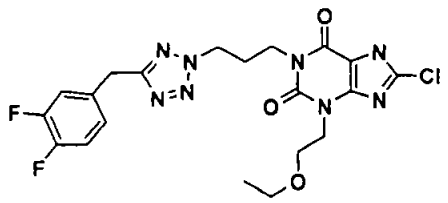
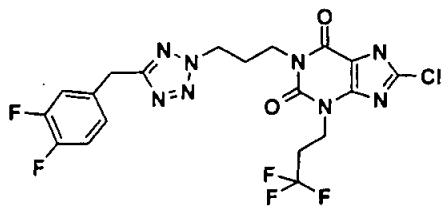
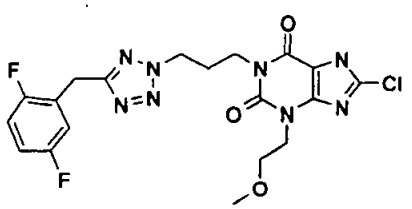
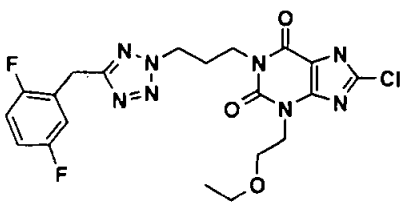
553		8-chloro-1-[3-(5-{[2-fluoro-4-(trifluoromethyl)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-3-propyl-3,7-dihydro-1H-purine-2,6-dione	9.7	m/z 515 $[MH]^+$ RT 3.40min
554		8-chloro-1-[3-(5-{[5-fluoro-2-(trifluoromethyl)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-3-propyl-3,7-dihydro-1H-purine-2,6-dione	26.8	m/z 515 $[MH]^+$ RT 3.26min
555		8-chloro-1-[3-(5-{[3-fluoro-4-(trifluoromethyl)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-3-propyl-3,7-dihydro-1H-purine-2,6-dione	20.7	m/z 515 $[MH]^+$ RT 3.31min
556		8-chloro-3-propyl-1-(3-{5-[(3,4,5-trifluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	10.2	m/z 483 $[MH]^+$ RT 3.23min
557		8-chloro-3-propyl-1-{3-[5-({3-[(trifluoromethyl)oxy]phenyl}methyl)-2H-tetrazol-2-yl]propyl}-3,7-dihydro-1H-purine-2,6-dione	9.8	m/z 513 $[MH]^+$ RT 3.35min

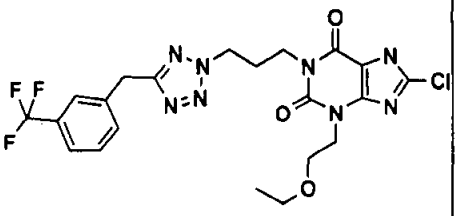
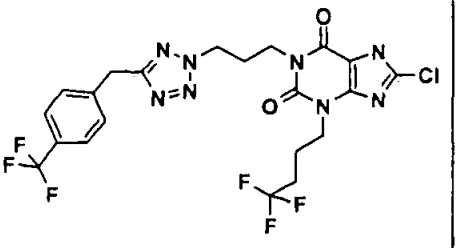
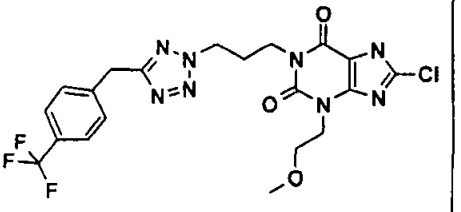
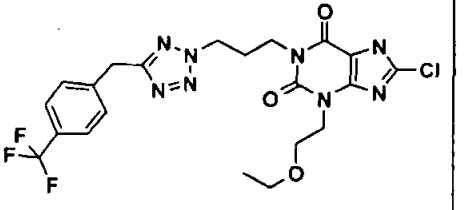
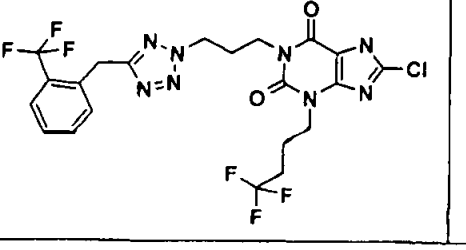
558		8-chloro-1-(3-{5-[(2,4-dichlorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3-propyl-3,7-dihydro-1H-purine-2,6-dione	27.6	m/z 497 $[MH]^+$ RT 3.40min
559		8-chloro-1-[3-(5-{[3-fluoro-5-(trifluoromethyl)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-3-propyl-3,7-dihydro-1H-purine-2,6-dione	17.6	m/z 515 $[MH]^+$ RT 3.23min
560		1-[3-(5-{[2,4-bis(trifluoromethyl)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-8-chloro-3-propyl-3,7-dihydro-1H-purine-2,6-dione	21.0	m/z 565 $[MH]^+$ RT 3.40min
561		1-[3-(5-{[2,5-bis(trifluoromethyl)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-8-chloro-3-propyl-3,7-dihydro-1H-purine-2,6-dione	9.7	m/z 565 $[MH]^+$ RT 3.50min
562		1-[3-(5-{[3,5-bis(trifluoromethyl)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-3-butyl-8-chloro-3,7-dihydro-1H-purine-2,6-dione	28.1	m/z 579 $[MH]^+$ RT 3.68min

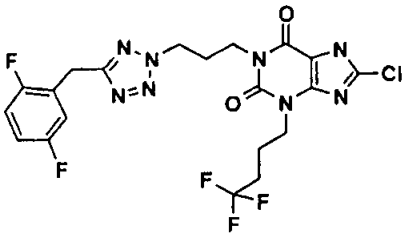
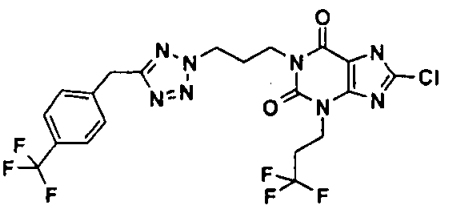
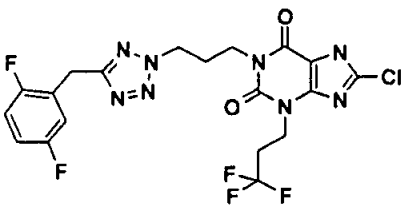
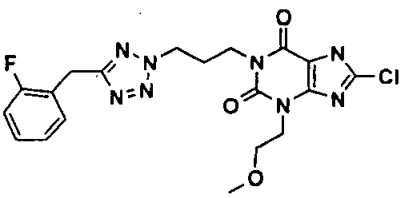
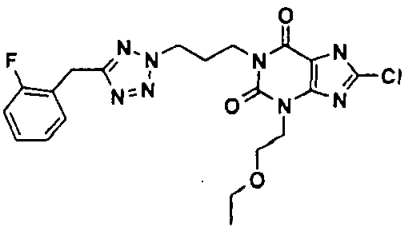
563		3-butyl-8-chloro-1-{3-[5-({4-[(trifluoromethyl)oxy]phenyl}methyl)-2H-tetrazol-2-yl]propyl}-3,7-dihydro-1H-purine-2,6-dione	32.1	m/z 527 $[MH]^+$ RT 3.57min
564		8-chloro-1-(3-{5-[(4-fluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3-[2-(methyloxy)ethyl]-3,7-dihydro-1H-purine-2,6-dione	15.0	m/z 463 $[MH]^+$ RT 2.89min
565		8-chloro-3-[2-(ethyloxy)ethyl]-1-(3-{5-[(4-fluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	12.6	m/z 477 $[MH]^+$ RT 3.03min
566		8-chloro-1-(3-{5-[(4-fluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3-(3,3,3-trifluoropropyl)-3,7-dihydro-1H-purine-2,6-dione	17.8	m/z 501 $[MH]^+$ RT 3.21min
567		8-chloro-3-[2-(methyloxy)ethyl]-1-[3-(5-{[2-(trifluoromethyl)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione	14.2	m/z 513 $[MH]^+$ RT 3.10min

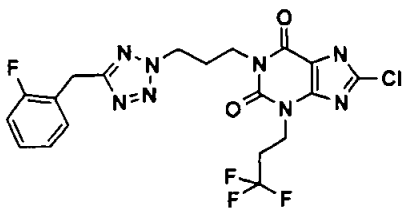
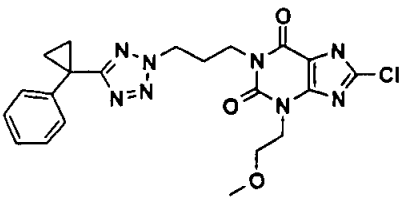
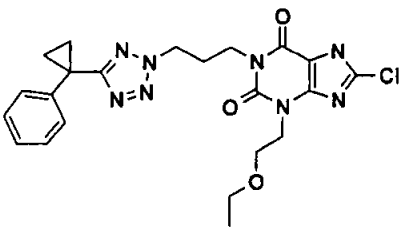
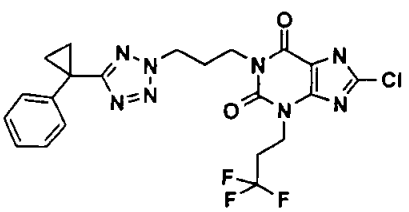
568		8-chloro-3-[2-(ethyloxy)ethyl]-1-[3-(5-{[2-(trifluoromethyl)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione	20.8	m/z 527 $[MH]^+$ RT 3.18min
569		8-chloro-1-[3-(5-{[2-(trifluoromethyl)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-3-(3,3,3-trifluoropropyl)-3,7-dihydro-1H-purine-2,6-dione	35.8	m/z 551 $[MH]^+$ RT 3.35min
570		8-chloro-3-[2-(methyloxy)ethyl]-1-[3-(5-{[3-(trifluoromethyl)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione	15.3	m/z 513 $[MH]^+$ RT 3.14min
571		8-chloro-1-[3-(5-{[3-(trifluoromethyl)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-3-(3,3,3-trifluoropropyl)-3,7-dihydro-1H-purine-2,6-dione	29.4	m/z 551 $[MH]^+$ RT 3.42min
572		8-chloro-1-(3-{5-[(2,4-difluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3-[2-(methyloxy)ethyl]-3,7-dihydro-1H-purine-2,6-dione	17.8	m/z 481 $[MH]^+$ RT 2.96min

573		8-chloro-1-(3-{5-[(2,4-difluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3-[2-(ethyloxy)ethyl]-3,7-dihydro-1H-purine-2,6-dione	14.4	m/z 495 $[MH]^+$ RT 2.86min
574		8-chloro-1-(3-{5-[(2,4-difluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3-(3,3,3-trifluoropropyl)-3,7-dihydro-1H-purine-2,6-dione	29.9	m/z 519 $[MH]^+$ RT 3.19min
575		8-chloro-3-[2-(methyloxy)ethyl]-1-(3-{5-[(2,4,6-trifluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	21.3	m/z 499 $[MH]^+$ RT 2.93min
576		8-chloro-3-[2-(ethyloxy)ethyl]-1-(3-{5-[(2,4,6-trifluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	15.5	m/z 513 $[MH]^+$ RT 2.93min
577		8-chloro-1-(3-{5-[(2,4,6-trifluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3-(3,3,3-trifluoropropyl)-3,7-dihydro-1H-purine-2,6-dione	32.3	m/z 537 $[MH]^+$ RT 3.29min

578		8-chloro-1-(3-{5-[(3,4-difluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3-[2-(methyloxy)ethyl]-3,7-dihydro-1H-purine-2,6-dione	14.5	m/z 481 $[MH]^+$ RT 2.97min
579		8-chloro-1-(3-{5-[(3,4-difluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3-[2-(ethyloxy)ethyl]-3,7-dihydro-1H-purine-2,6-dione	7.2	m/z 495 $[MH]^+$ RT 3.06min
580		8-chloro-1-(3-{5-[(3,4-difluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3-(3,3,3-trifluoropropyl)-3,7-dihydro-1H-purine-2,6-dione	27.8	m/z 519 $[MH]^+$ RT 3.27min
581		8-chloro-1-(3-{5-[(2,5-difluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3-[2-(methyloxy)ethyl]-3,7-dihydro-1H-purine-2,6-dione	17.1	m/z 481 $[MH]^+$ RT 2.89min
582		8-chloro-1-(3-{5-[(2,5-difluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3-[2-(ethyloxy)ethyl]-3,7-dihydro-1H-purine-2,6-dione	13.5	m/z 495 $[MH]^+$ RT 3.05min

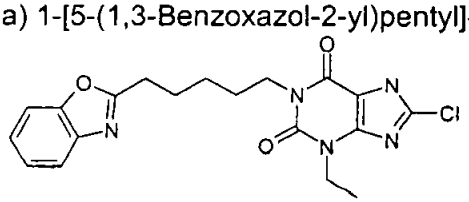
583		8-chloro-3-[2-(ethyloxy)ethyl]-1-[3-(5-{[3-(trifluoromethyl)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione	14.6	m/z 527 $[MH]^+$ RT 3.26min
584		8-chloro-3-(4,4,4-trifluorobutyl)-1-[3-(5-{[4-(trifluoromethyl)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione	12.1	m/z 565 $[MH]^+$ RT 3.51min
585		8-chloro-3-[2-(methyloxy)ethyl]-1-[3-(5-{[4-(trifluoromethyl)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione	17.3	m/z 513 $[MH]^+$ RT 3.17min
586		8-chloro-3-[2-(ethyloxy)ethyl]-1-[3-(5-{[4-(trifluoromethyl)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione	15.2	m/z 527 $[MH]^+$ RT 3.30min
587		8-chloro-3-(4,4,4-trifluorobutyl)-1-[3-(5-{[2-(trifluoromethyl)phenyl]methyl}-2H-tetrazol-2-	5.8	m/z 565 $[MH]^+$ RT 3.46min

		yl)propyl]-3,7-dihydro-1H-purine-2,6-dione		
588		8-chloro-1-(3-{5-[(2,5-difluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3-(4,4,4-trifluorobutyl)-3,7-dihydro-1H-purine-2,6-dione	14.7	m/z 533 $[MH]^+$ RT 3.34min
589		8-chloro-1-[3-(5-{[4-(trifluoromethyl)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-3-(3,3,3-trifluoropropyl)-3,7-dihydro-1H-purine-2,6-dione	26.1	m/z 551 $[MH]^+$ RT 3.46min
590		8-chloro-1-(3-{5-[(2,5-difluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3-(3,3,3-trifluoropropyl)-3,7-dihydro-1H-purine-2,6-dione	18.0	m/z 519 $[MH]^+$ RT 3.29min
591		8-chloro-1-(3-{5-[(2-fluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3-[2-(methyloxy)ethyl]-3,7-dihydro-1H-purine-2,6-dione	3.4	m/z 463 $[MH]^+$ RT 2.84min
592		8-chloro-3-[2-(ethyloxy)ethyl]-1-(3-{5-[(2-fluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	8.2	m/z 477 $[MH]^+$ RT 2.85min

593		8-chloro-1-(3-{5-[(2-fluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3-(3,3,3-trifluoropropyl)-3,7-dihydro-1H-purine-2,6-dione	32.7	m/z 501 $[MH]^+$ RT 3.25min
594		8-chloro-3-[2-(methyloxy)ethyl]-1-{3-[5-(1-phenylcyclopropyl)-2H-tetrazol-2-yl]propyl}-3,7-dihydro-1H-purine-2,6-dione	10.2	m/z 471 $[MH]^+$ RT 2.93min
595		8-chloro-3-[2-(ethyloxy)ethyl]-1-{3-[5-(1-phenylcyclopropyl)-2H-tetrazol-2-yl]propyl}-3,7-dihydro-1H-purine-2,6-dione	15.2	m/z 485 $[MH]^+$ RT 2.96min
596		8-chloro-1-{3-[5-(1-phenylcyclopropyl)-2H-tetrazol-2-yl]propyl}-3-(3,3,3-trifluoropropyl)-3,7-dihydro-1H-purine-2,6-dione	4.6	m/z 509 $[MH]^+$ RT 3.00min

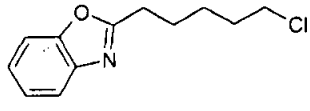
Example 597 : 1-[5-(1,3-Benzoxazol-2-yl)pentyl]-8-chloro-3-ethyl-3,7-dihydro-1*H*-purine-2,6-dione

a) 1-[5-(1,3-Benzoxazol-2-yl)pentyl]-8-chloro-3-ethyl-3,7-dihydro-1*H*-purine-2,6-dione



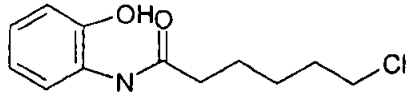
a) A solution of 3-ethyl-8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1H-purine-2,6-dione (0.095g, 0.37mmol) in DMF (10ml) was treated with potassium carbonate (0.0615g, 0.45mmol) and 2-(5-chloropentyl)-1,3-benzoxazole (0.091g, 0.41mmol) and the mixture heated at 70°C for 4.5h. The mixture was cooled and degassed by the repeated application of vacuum to the reaction mixture and subsequent backfilling with nitrogen gas and then treated with tetrakis(triphenylphosphine)palladium(0) (0.043g, 0.037mmol) and morpholine (0.32ml, 3.7mmol) and the mixture stirred for 4h in a nitrogen atmosphere. The mixture was evaporated to dryness and the residue partitioned between 25ml of ethyl acetate and 25ml of brine. The aqueous phase was re-extracted with 25ml of ethyl acetate and the combined organics dried over magnesium sulfate, filtered and evaporated. The residue was dissolved in 5ml of methanol and added to a 5g aminopropyl SPE which was subsequently washed with methanol and the product eluted with a 5% solution of acetic acid in methanol. Product-containing fractions were pooled and evaporated to reveal a colourless gum which was triturated with diethyl ether and dried to give the title compound as a white solid (0.0538g, 36%).
LC/MS: m/z 402 $[MH]^+$, RT 3.06min

b) 2-(5-Chloropentyl)-1,3-benzoxazole



6-Chloro-*N*-(2-hydroxyphenyl)hexanamide (0.95g, 3.9mmol) was treated with toluene (20ml) and 4-toluenesulfonic acid monohydrate (0.05g, 0.26mmol) and the mixture heated in the microwave at 160°C for 1h then cooled and evaporated. The residue was partition between 25ml of ethyl acetate and 25ml of saturates aqueous sodium bicarbonate. The aqueous phase was extracted twice more with 25ml ethyl acetate and the combined organics dried over magnesium sulfate, filtered and evaporated to dryness. The product was then purified by flash chromatography (gradient elution: cyclohexane to cyclohexane/ethyl acetate 1:1) to give 2-(5-chloropentyl)-1,3-benzoxazole as a colourless oil which solidified upon standing (0.47g, 53%).
LC/MS: m/z 224 $[MH]^+$, RT 3.32min

c) 6-chloro-*N*-(2-hydroxyphenyl)hexanamide

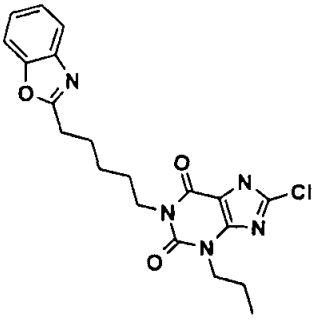
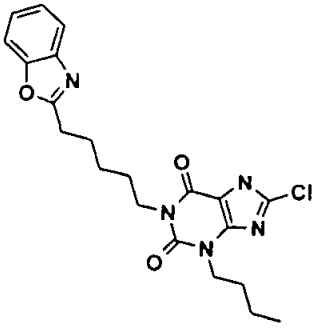
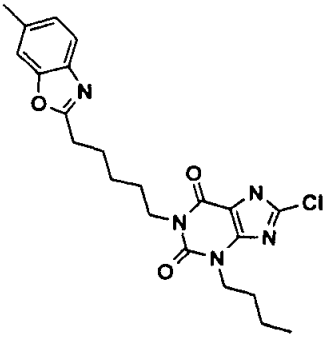


2-Aminophenol (0.5g, 4.6mmol) was stirred in ethyl acetate (15ml) and treated dropwise with 6-chlorohexanoyl chloride (0.664ml, 5.5mmol) and then dropwise with triethylamine (0.95ml, 6.9mmol). After 1h the mixture was washed with 2 x 25ml of

saturated aqueous sodium bicarbonate and the organic phase dried over magnesium sulfate, filterd and evaporated to dryness to give 6-chloro-*N*-(2-hydroxyphenyl)hexanamide as a pale brown solid (0.05g, 86%).
LC/MS: m/z 242 $[MH]^+$, RT 2.95min.

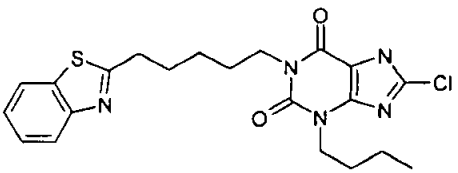
The following compounds (**Table 33**) were prepared using a method analogous to that for **Example 597**.

Table 33

Example	Structure	Name	Yield (mg)	LC/MS
598		1-[5-(1,3-benzoxazol-2-yl)pentyl]-8-chloro-3-propyl-3,7-dihydro-1H-purine-2,6-dione	60.5	m/z 416 $[MH]^+$ RT 3.23mins
599		1-[5-(1,3-benzoxazol-2-yl)pentyl]-3-butyl-8-chloro-3,7-dihydro-1H-purine-2,6-dione	55.1	m/z 428 $[MH]^+$ RT 3.42mins
600		3-butyl-8-chloro-1-[5-(6-methyl-1,3-benzoxazol-2-yl)pentyl]-3,7-dihydro-1H-purine-2,6-dione	68.9	m/z 444 $[MH]^+$ RT 3.56mins

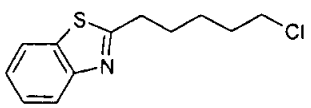
Example 601 : 1-[5-(1,3-Benzothiazol-2-yl)pentyl]-3-butyl-8-chloro-3,7-dihydro-1*H*-purine-2,6-dione

a) 1-[5-(1,3-Benzothiazol-2-yl)pentyl]-3-butyl-8-chloro-3,7-dihydro-1*H*-purine-2,6-dione



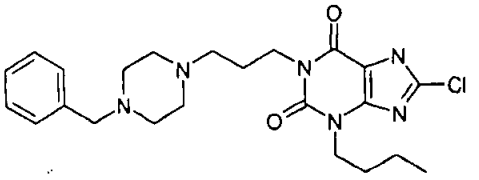
A solution of 3-butyl-8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1H-purine-2,6-dione (0.053g, 0.19mmol) in DMF (5ml) was treated with potassium carbonate (0.026g, 0.19mmol) and 2-(5-chloropentyl)-1,3-benzothiazole (0.0498g, 0.21mmol) and the mixture heated at 60°C for 3 days. The mixture was cooled and degassed by the repeated application of vacuum to the reaction mixture and subsequent backfilling with nitrogen gas and then treated with tetrakis(triphenylphosphine)palladium(0) (0.0294g, 0.025mmol) and morpholine (0.164ml, 1.9mmol) and the mixture stirred for 18 hours in a nitrogen atmosphere. The mixture was evaporated to dryness and the residue partitioned between 25ml of ethyl acetate and 25ml of saturated aqueous sodium bicarbonate. The organic phase was dried over magnesium sulfate, filtered and evaporated. The residue was dissolved in 5ml of methanol and added to a 5g aminopropyl SPE which was subsequently washed with methanol and the product eluted with a 5% solution of acetic acid in methanol. Product-containing fractions were pooled and evaporated and the residue subjected to purification by MDAP to give the title compound as a white solid (0.0101g, 12%).
LC/MS: m/z 446 $[MH]^+$, RT 3.55min.

b) 2-(5-Chloropentyl)-1,3-benzothiazole



An ice-cooled solution of 2-aminothiophenol (0.376ml, 3.54mmol) in anhydrous THF (5ml) was treated with diisopropylethylamine (0.62ml, 3.54mmol) followed by 6-chlorohexanoyl chloride (0.36ml, 2.95mmol). The mixture was stirred at ambient temperature for 2h then heated at reflux for 19h and then cooled and diluted with DCM (10ml). The solution was washed with 10ml of 2M aqueous hydrochloric acid, 10ml of 2M aqueous sodium hydroxide and 10ml of brine; dried over magnesium sulfate, filtered and evaporated to reveal 0.4122g of a pale yellow oil. The product was purified by flash chromatography using a gradient elution from cyclohexane to cylcohexane/ethyl acetate (7:3) to give 2-(5-chloropentyl)-1,3-benzothiazole as a colourless oil (0.0541g, 6%).
LC/MS: m/z 240 $[MH]^+$, RT 3.48min.

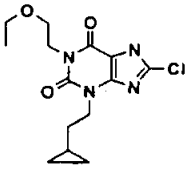
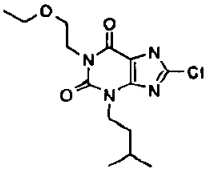
Example 602 : 3-Butyl-8-chloro-1-{3-[4-(phenylmethyl)-1-piperazinyl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione

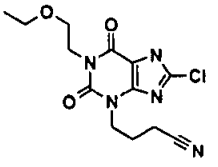
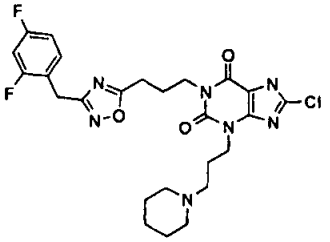
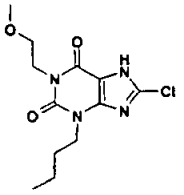
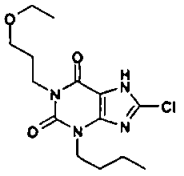
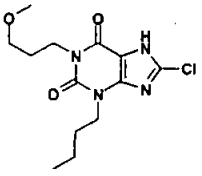
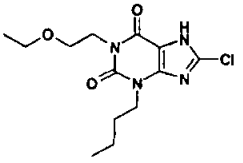
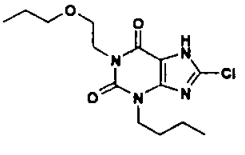


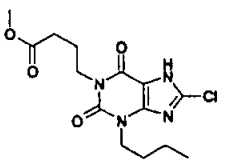
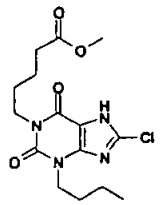
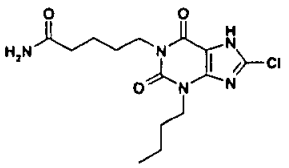
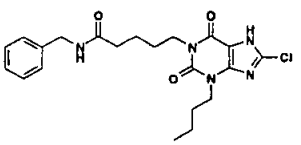
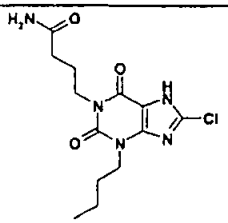
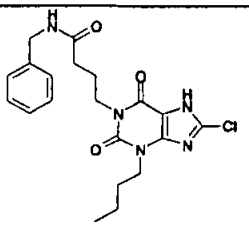
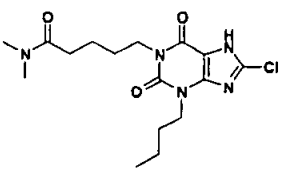
A solution of 3-[3-butyl-8-chloro-2,6-dioxo-7-(2-propen-1-yl)-2,3,6,7-tetrahydro-1*H*-purin-1-yl]propyl methanesulfonate (0.08g, 0.19mmol) in DMF (5ml) was treated with potassium carbonate (0.08g, 0.6mmol) and 1-benzylpiperazine (0.04g, 0.23mmol) and then heated at 70°C for 2h. The mixture was cooled, evaporated to dryness and partitioned between 10ml of DCM and 10ml of water. The organic phase was evaporated to dryness and the residue dissolved in anhydrous THF (5ml). The solution was cautiously degassed by the repeated application of vacuum to the reaction mixture and subsequent backfilling with nitrogen gas and then treated with tetrakis(triphenylphosphine)palladium(0) (0.010g, 0.009mmol) and morpholine (0.200ml, 2.3mmol) and the mixture stirred for 2h in a nitrogen atmosphere. The mixture was evaporated and the residue taken up in 5ml of methanol and added to a 2g aminopropyl SPE cartridge which was then washed with methanol and the product eluted using a 3% solution of acetic acid in methanol. Product-containing fractions were pooled and evaporated to dryness. The product was then purified by flash chromatography using a gradient elution from DCM /2% Acetic acid to DCM /20% MeOH /2% Acetic acid and the final product freeze-dried from 1,4-dioxan to give the title compound as a white solid (0.021g, 24%).
LC/MS: m/z 459 $[MH]^+$, RT 2.37min.

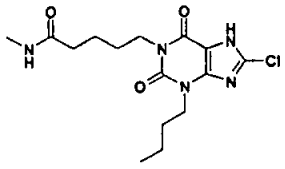
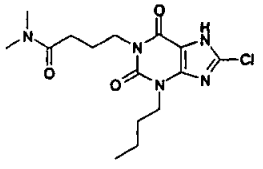
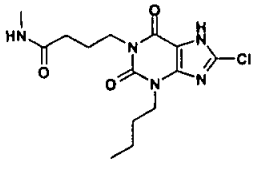
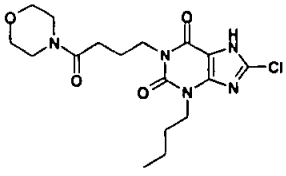
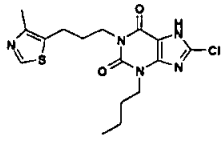
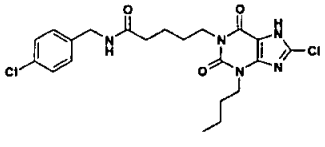
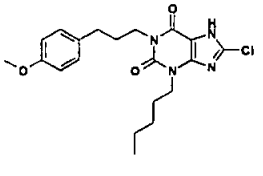
The following compounds (**Table 34**) were prepared by the appropriate general methodology described above.

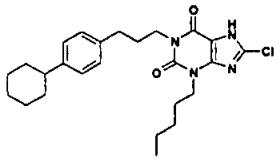
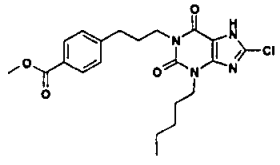
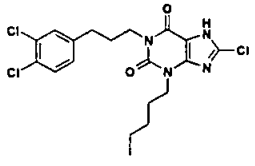
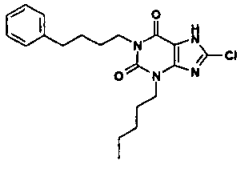
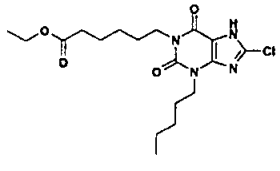
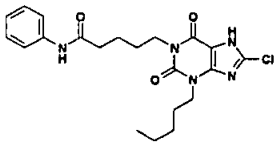
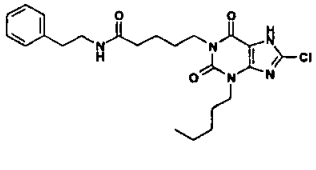
Table 34

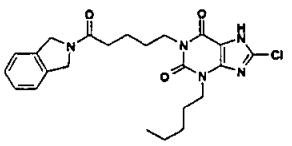
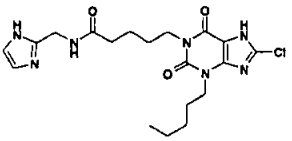
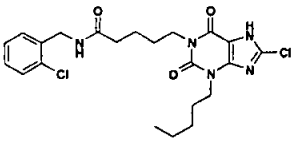
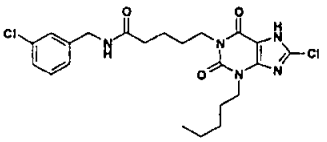
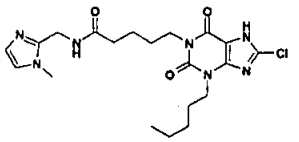
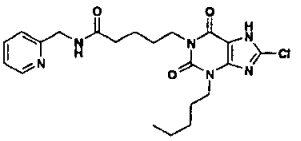
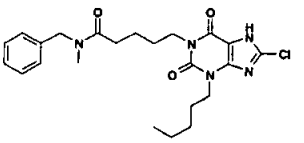
Example	Structure	Name	LC/MS
603		8-chloro-3-(2-cyclopropylethyl)-1-[2-(ethyloxy)ethyl]-3,7-dihydro-1H-purine-2,6-dione	m/z 327 $[MH]^+$ RT 2.80min
604		8-chloro-1-[2-(ethyloxy)ethyl]-3-(3-methylbutyl)-3,7-dihydro-1H-purine-2,6-dione	m/z 329 $[MH]^+$ RT 3.02min

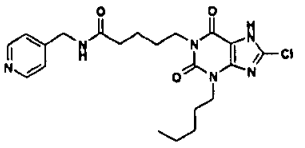
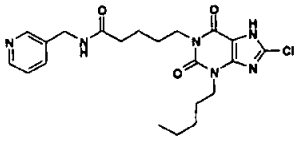
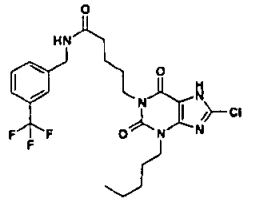
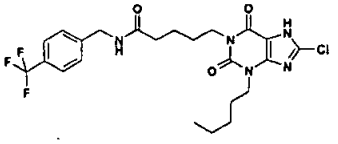
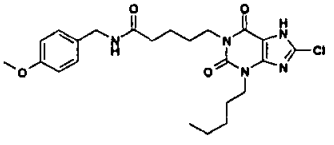
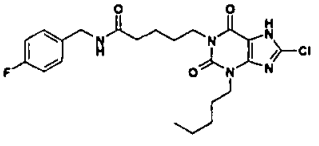
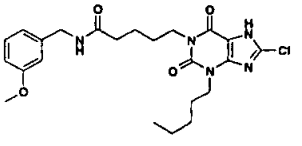
605		4-{8-chloro-1-[2-(ethyloxy)ethyl]-2,6-dioxo-1,2,6,7-tetrahydro-3H-purin-3-yl}butanenitrile	m/z 326 $[MH]^+$ RT 2.33min
606		8-chloro-1-(3-{3-[(2,4-difluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3-[3-(1-piperidinyl)propyl]-3,7-dihydro-1*H*-purine-2,6-dione	m/z 548 $[MH]^+$ RT 2.44min
607		3-butyl-8-chloro-1-[2-(methyloxy)ethyl]-3,7-dihydro-1*H*-purine-2,6-dione	m/z 301 $[MH]^+$ RT 2.31*min*
608		3-butyl-8-chloro-1-[3-(ethyloxy)propyl]-3,7-dihydro-1*H*-purine-2,6-dione	m/z 329 $[MH]^+$ RT 2.95*min*
609		3-butyl-8-chloro-1-[3-(methyloxy)propyl]-3,7-dihydro-1*H*-purine-2,6-dione	m/z 315 $[MH]^+$ RT 2.36*min*
610		3-butyl-8-chloro-1-[2-(ethyloxy)ethyl]-3,7-dihydro-1H-purine-2,6-dione	m/z 315 $[MH]^+$ RT 2.34min
611		3-butyl-8-chloro-1-[2-(propyloxy)ethyl]-3,7-dihydro-1H-purine-2,6-dione	m/z 329 $[MH]^+$ RT 2.71min

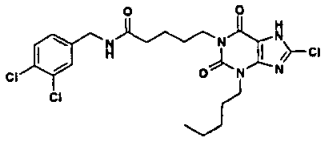
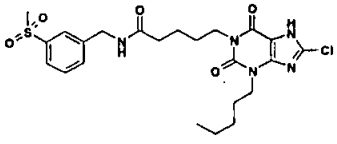
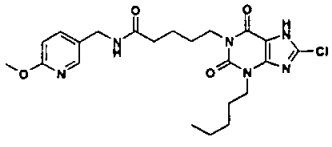
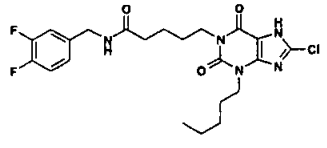
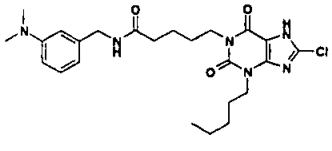
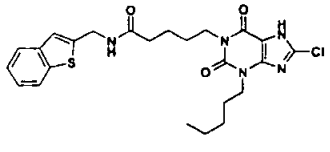
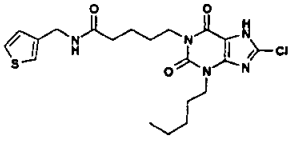
612		methyl 4-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)butanoate	m/z 343 $[MH]^+$ RT 2.56min
613		methyl 5-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)pentanoate	m/z 357 $[MH]^+$ RT 2.66min
614		5-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)pentanamide	m/z 342 $[MH]^+$ RT 2.41min
615		5-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-(phenylmethyl)pentanamide	m/z 432 $[MH]^+$ RT 2.97min
616		4-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)butanamide	m/z 328 $[MH]^+$ RT 2.34min
617		4-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-(phenylmethyl)butanamide	m/z 418 $[MH]^+$ RT 2.93min
618		5-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)-N,N-dimethylpentanamide	m/z 370 $[MH]^+$ RT 2.26min

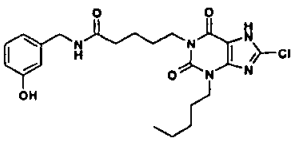
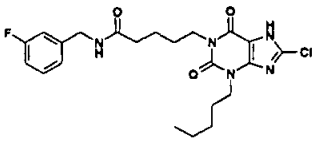
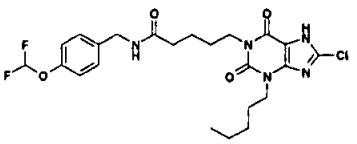
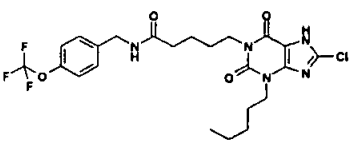
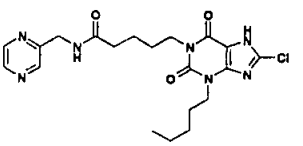
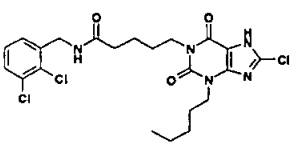
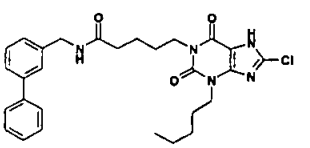
619		5-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-methylpentanamide	m/z 356 $[MH]^+$ RT 2.56min
620		4-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)-N,N-dimethylbutanamide	m/z 356 $[MH]^+$ RT 2.59min
621		4-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-methylbutanamide	m/z 342 $[MH]^+$ RT 2.48min
622		3-butyl-8-chloro-1-(4-morpholin-4-yl-4-oxobutyl)-3,7-dihydro-1H-purine-2,6-dione	m/z 398 $[MH]^+$ RT 2.58min
623		3-butyl-8-chloro-1-[3-(4-methyl-1,3-thiazol-5-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione	m/z 382 $[MH]^+$ RT 3.00min
624		5-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-[(4-chlorophenyl)methyl]pentanamide	m/z 466 $[MH]^+$ RT 3.26min
625		8-chloro-1-{3-[4-(methyloxy)phenyl]propyl}-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	m/z 405 $[MH]^+$ RT 3.65min

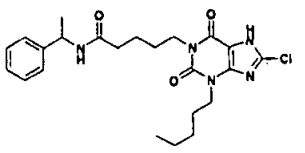
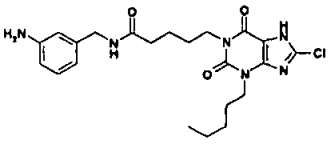
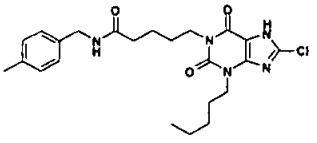
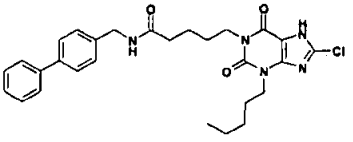
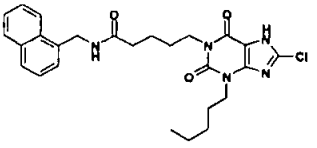
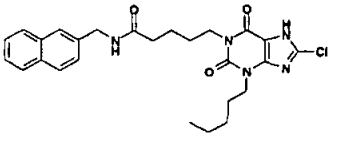
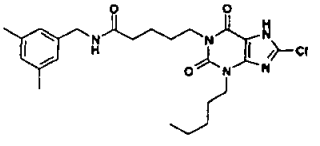
626		8-chloro-1-[3-(4-cyclohexylphenyl)propyl]-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	m/z 457 $[MH]^+$ RT 4.42min
627		methyl 4-[3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)propyl]benzoate	m/z 433 $[MH]^+$ RT 3.59min
628		8-chloro-1-[3-(3,4-dichlorophenyl)propyl]-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	m/z 443 $[MH]^+$ RT 4.03min
629		8-chloro-3-pentyl-1-(4-phenylbutyl)-3,7-dihydro-1H-purine-2,6-dione	m/z 389 $[MH]^+$ RT 3.87min
630		ethyl 6-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)hexanoate	m/z 399 $[MH]^+$ RT 3.47min
631		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-phenylpentanamide	m/z 432 $[MH]^+$ RT 3.36min
632		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-(2-phenylethyl)pentanamide	m/z 460 $[MH]^+$ RT 3.29min

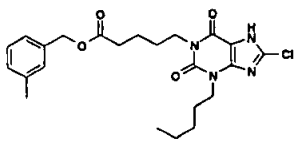
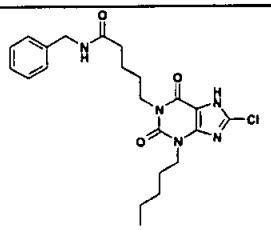
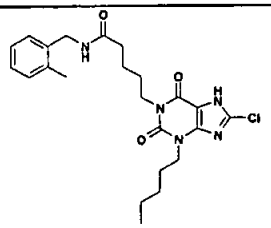
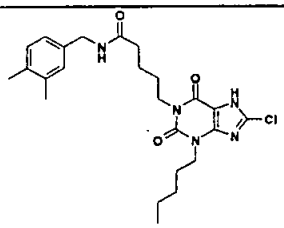
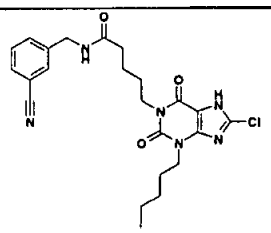
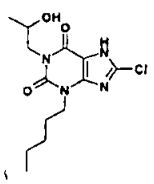
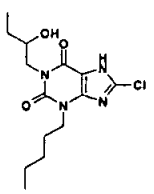
633		8-chloro-1-[5-(1,3-dihydro-2H-isoindol-2-yl)-5-oxopentyl]-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	m/z 458 $[MH]^+$ RT 3.35min
634		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-(1H-imidazol-2-ylmethyl)pentanamide	m/z 436 $[MH]^+$ RT 2.32min
635		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-[(2-chlorophenyl)methyl]pentanamide	m/z 480 $[MH]^+$ RT 2.77min
636		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-[(3-chlorophenyl)methyl]pentanamide	m/z 480 $[MH]^+$ RT 3.42min
637		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-[(1-methyl-1H-imidazol-2-yl)methyl]pentanamide	m/z 450 $[MH]^+$ RT 2.32min
638		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-(pyridin-2-ylmethyl)pentanamide	m/z 447 $[MH]^+$ RT 2.70min
639		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-methyl-N-(phenylmethyl)pentanamide	m/z 460 $[MH]^+$ RT 3.38min

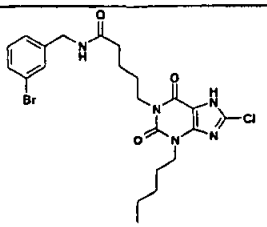
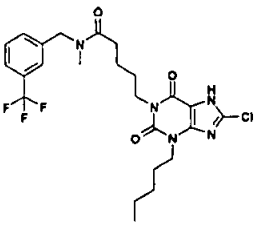
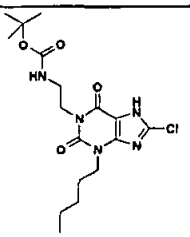
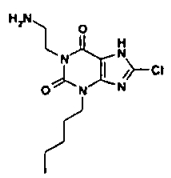
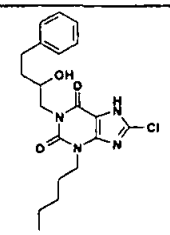
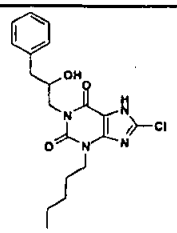
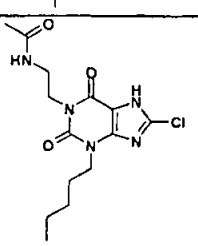
640		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-(pyridin-4-ylmethyl)pentanamide	m/z 447 $[MH]^+$ RT 2.42min
641		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-(pyridin-3-ylmethyl)pentanamide	m/z 447 $[MH]^+$ RT 2.54min
642		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-{[3-(trifluoromethyl)phenyl]methyl}pentanamide	m/z 514 $[MH]^+$ RT 3.45min
643		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-{[4-(trifluoromethyl)phenyl]methyl}pentanamide	m/z 514 $[MH]^+$ RT 3.47min
644		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-{[4-(methyloxy)phenyl]methyl}pentanamide	m/z 476 $[MH]^+$ RT 2.67min
645		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-[(4-fluorophenyl)methyl]pentanamide	m/z 464 $[MH]^+$ RT 3.26min
646		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-{[3-(methyloxy)phenyl]methyl}pentanamide	m/z 476 $[MH]^+$ RT 3.21min

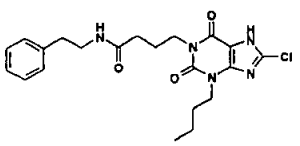
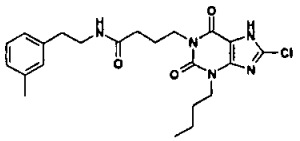
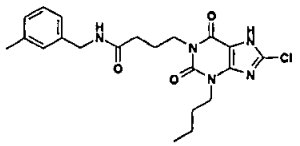
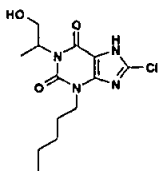
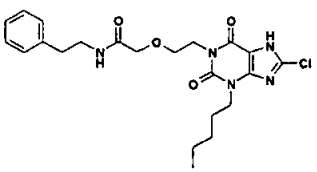
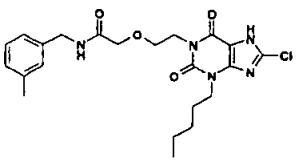
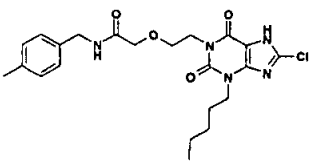
647		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-[(3,4-dichlorophenyl)methyl]pentanamide	m/z 514 $[MH]^+$ RT 3.56min
648		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-{[3-(methylsulfonyl)phenyl]methyl}pentanamide	m/z 524 $[MH]^+$ RT 2.97min
649		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-{[6-(methyloxy)pyridin-3-yl]methyl}pentanamide	m/z 477 $[MH]^+$ RT 3.01min
650		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-[(3,4-difluorophenyl)methyl]pentanamide	m/z 482 $[MH]^+$ RT 3.33min
651		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-{[3-(dimethylamino)phenyl]methyl}pentanamide	m/z 489 $[MH]^+$ RT 3.01min
652		N-(1-benzothien-2-ylmethyl)-5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)pentanamide	m/z 502 $[MH]^+$ RT 3.48min
653		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-(3-thienylmethyl)pentanamide	m/z 452 $[MH]^+$ RT 3.18min

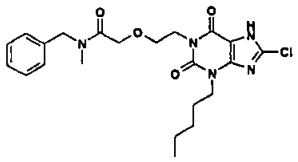
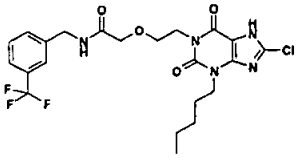
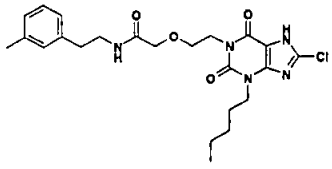
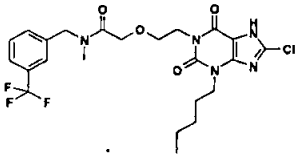
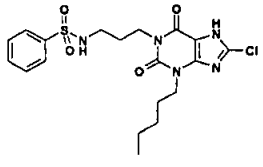
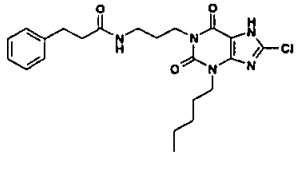
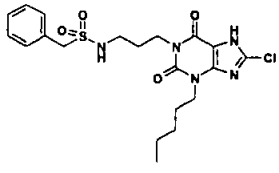
654		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-[(3-hydroxyphenyl)methyl]pentanamide	m/z 462 $[MH]^+$ RT 3.04min
655		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-[(3-fluorophenyl)methyl]pentanamide	m/z 464 $[MH]^+$ RT 3.28min
656		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-({4-[(difluoromethyl)oxy]phenyl}methyl)pentanamide	m/z 512 $[MH]^+$ RT 3.34min
657		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-({4-[(trifluoromethyl)oxy]phenyl}methyl)pentanamide	m/z 530 $[MH]^+$ RT 3.50min
658		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-(pyrazin-2-ylmethyl)pentanamide	m/z 448 $[MH]^+$ RT 2.74min
659		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-[(2,3-dichlorophenyl)methyl]pentanamide	m/z 514 $[MH]^+$ RT 3.55min
660		N-(biphenyl-3-ylmethyl)-5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)pentanamide	m/z 522 $[MH]^+$ RT 3.61min

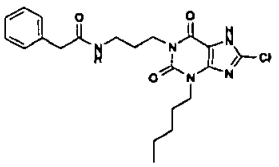
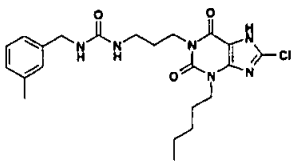
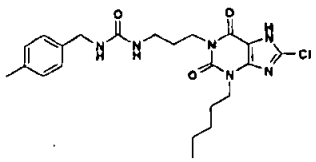
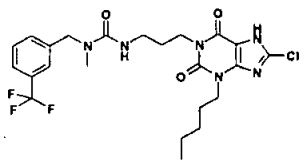
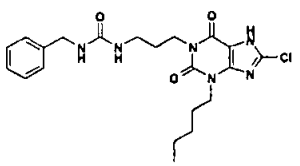
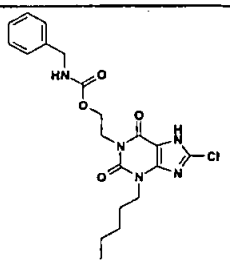
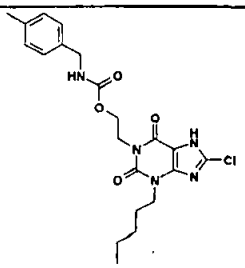
661		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-(1-phenylethyl)pentanamide	m/z 460 $[MH]^+$ RT 3.30min
662		N-[(3-aminophenyl)methyl]-5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)pentanamide	m/z 461 $[MH]^+$ RT 2.79min
663		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-[(4-methylphenyl)methyl]pentanamide	m/z 460 $[MH]^+$ RT 3.36min
664		N-(biphenyl-4-ylmethyl)-5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)pentanamide	m/z 522 $[MH]^+$ RT 3.63min
665		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-(naphthalen-1-ylmethyl)pentanamide	m/z 496 $[MH]^+$ RT 3.48min
666		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-(naphthalen-2-ylmethyl)pentanamide	m/z 496 $[MH]^+$ RT 3.50min
667		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-[(3,5-dimethylphenyl)methyl]pentanamide	m/z 474 $[MH]^+$ RT 3.48min

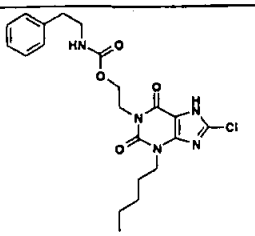
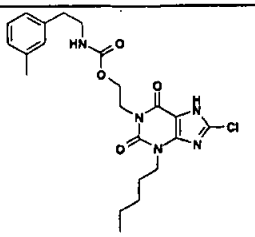
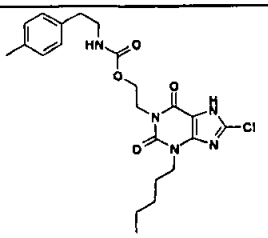
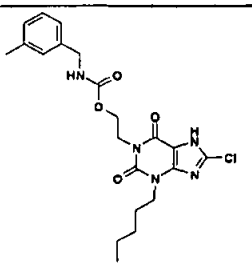
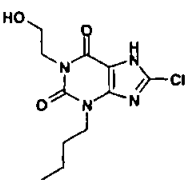
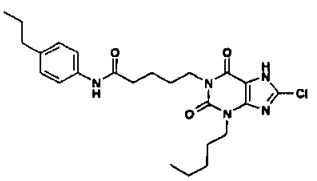
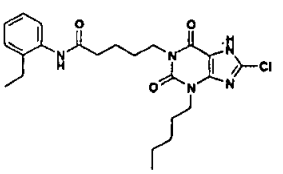
668		(3-methylphenyl)methyl 5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)pentanoate	m/z 461 $[MH]^+$ RT 3.78min
669		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-(phenylmethyl)pentanamide	m/z 446 $[MH]^+$ RT 3.12min
670		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-[(2-methylphenyl)methyl]pentanamide	m/z 460 $[MH]^+$ RT 3.22min
671		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-[(3,4-dimethylphenyl)methyl]pentanamide	m/z 474 $[MH]^+$ RT 3.34min
672		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-[(3-cyanophenyl)methyl]pentanamide	m/z 471 $[MH]^+$ RT 3.14min
673		8-chloro-1-(2-hydroxypropyl)-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	m/z 315 $[MH]^+$ RT 2.73min
674		8-chloro-1-(2-hydroxybutyl)-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	m/z 329 $[MH]^+$ RT 2.91min

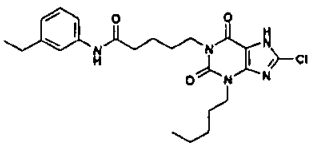
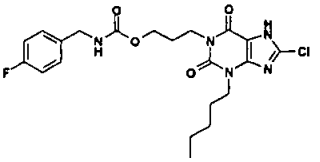
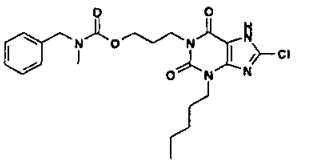
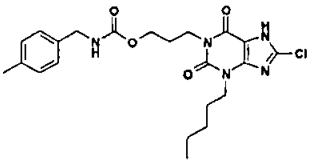
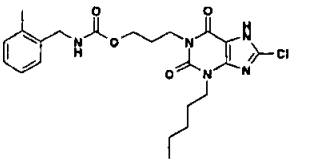
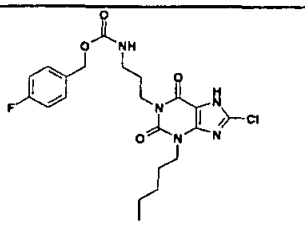
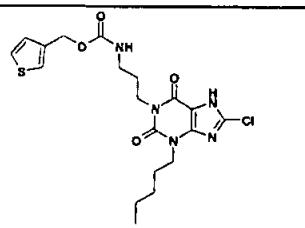
675		N-[(3-bromophenyl)methyl]-5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)pentanamide	m/z 524 $[MH]^+$ RT 3.43min
676		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-methyl-N-{[3-(trifluoromethyl)phenyl]methyl}pentanamide	m/z 528 $[MH]^+$ RT 3.55min
677		1,1-dimethylethyl [2-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)ethyl]carbamate	m/z 400 $[MH]^+$ RT 3.21min
678		1-(2-aminoethyl)-8-chloro-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	m/z 300 $[MH]^+$ RT 2.14min
679		8-chloro-1-(2-hydroxy-4-phenylbutyl)-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	m/z 405 $[MH]^+$ RT 3.43min
680		8-chloro-1-(2-hydroxy-3-phenylpropyl)-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	m/z 391 $[MH]^+$ RT 3.17min
681		N-[2-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)ethyl]acetamide	m/z 342 $[MH]^+$ RT 2.61min

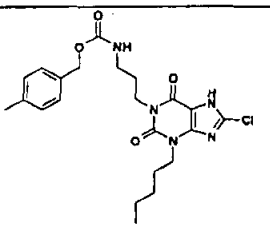
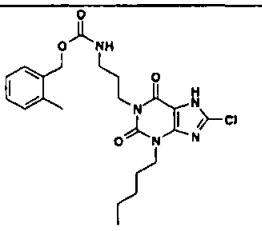
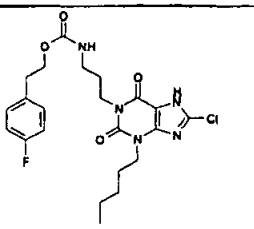
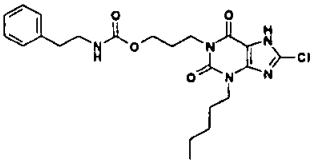
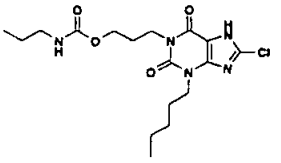
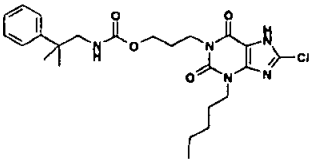
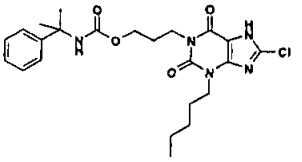
682		4-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-(2-phenylethyl)butanamide	m/z 432 $[MH]^+$ RT 3.06min
683		4-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-[2-(3-methylphenyl)ethyl]butanamide	m/z 446 $[MH]^+$ RT 3.19min
684		4-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-[(3-methylphenyl)methyl]butanamide	m/z 432 $[MH]^+$ RT 3.14min
685		8-chloro-1-(2-hydroxy-1-methylethyl)-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	m/z 315 $[MH]^+$ RT 2.80min
686		2-{[2-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)ethyl]oxy}-N-(2-phenylethyl)acetamide	m/z 462 $[MH]^+$ RT 3.23min
687		2-{[2-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)ethyl]oxy}-N-[(3-methylphenyl)methyl]acetamide	m/z 462 $[MH]^+$ RT 3.28min
688		2-{[2-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)ethyl]oxy}-N-[(4-methylphenyl)methyl]acetamide	m/z 462 $[MH]^+$ RT 3.27min

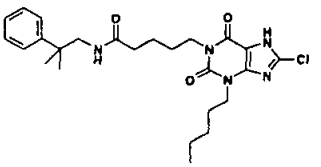
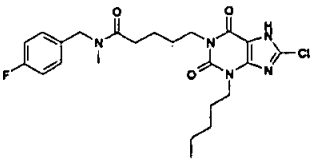
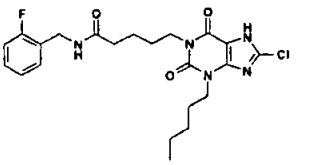
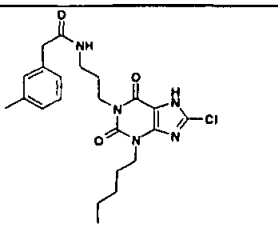
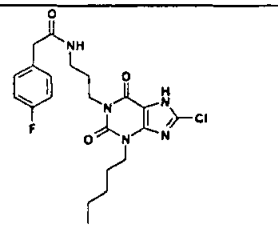
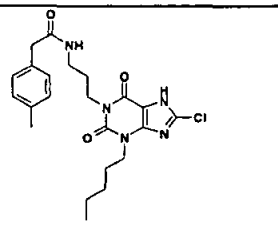
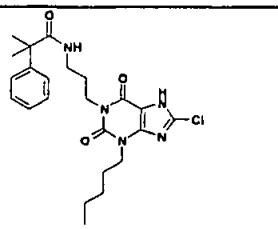
689		2-{[2-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)ethyl]oxy}-N-methyl-N-(phenylmethyl)acetamide	m/z 462 $[MH]^+$ RT 3.27min
690		2-{[2-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)ethyl]oxy}-N-{[3-(trifluoromethyl)phenyl]methyl}acetamide	m/z 516 $[MH]^+$ RT 3.39min
691		2-{[2-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)ethyl]oxy}-N-[2-(3-methylphenyl)ethyl]acetamide	m/z 476 $[MH]^+$ RT 3.36min
692		2-{[2-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)ethyl]oxy}-N-methyl-N-{[3-(trifluoromethyl)phenyl]methyl}acetamide	m/z 530 $[MH]^+$ RT 3.41min
693		N-[3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)propyl]benzenesulfonamide	m/z 454 $[MH]^+$ RT 3.29min
694		N-[3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)propyl]-3-phenylpropanamide	m/z 446 $[MH]^+$ RT 3.27min
695		N-[3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)propyl]-1-phenylmethanesulfonamide	m/z 468 $[MH]^+$ RT 3.29min

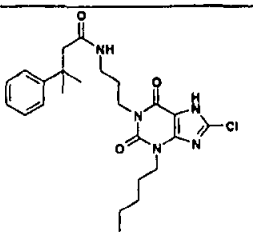
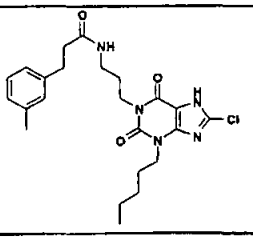
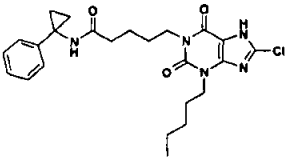
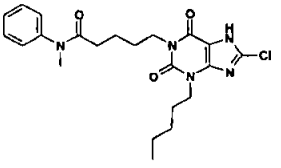
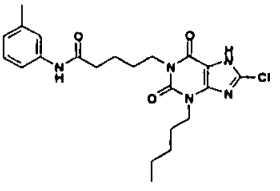
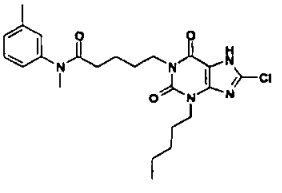
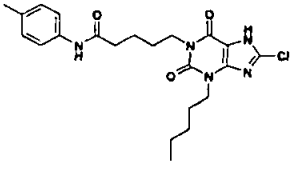
696		N-[3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)propyl]-2-phenylacetamide	m/z 432 $[MH]^+$ RT 3.18min
697		1-[3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)propyl]-3-[(3-methylphenyl)methyl]urea	m/z 461 $[MH]^+$ RT 3.29min
698		1-[3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)propyl]-3-[(4-methylphenyl)methyl]urea	m/z 461 $[MH]^+$ RT 3.29min
699		3-[3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)propyl]-1-methyl-1-{[3-(trifluoromethyl)phenyl]methyl}urea	m/z 529 $[MH]^+$ RT 3.51min
700		1-[3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)propyl]-3-(phenylmethyl)urea	m/z 447 $[MH]^+$ RT 3.17min
701		2-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)ethyl (phenylmethyl)carbamate	m/z 434 $[MH]^+$ RT 3.24min
702		2-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)ethyl [(4-methylphenyl)methyl]carbamate	m/z 448 $[MH]^+$ RT 3.34min

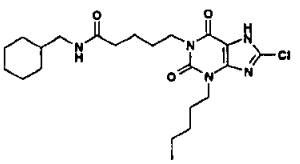
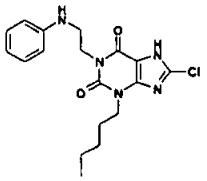
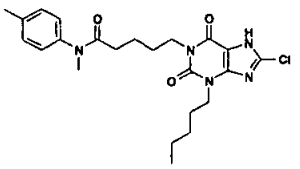
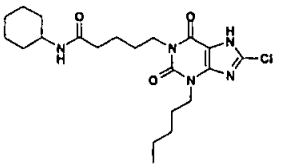
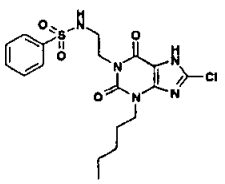
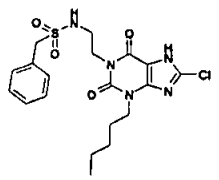
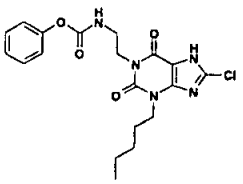
703		2-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)ethyl (2-phenylethyl)carbamate	m/z 448 $[MH]^+$ RT 3.34min
704		2-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)ethyl [2-(3-methylphenyl)ethyl]carbamate	m/z 462 $[MH]^+$ RT 3.48min
705		2-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)ethyl [2-(4-methylphenyl)ethyl]carbamate	m/z 462 $[MH]^+$ RT 3.48min
706		2-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)ethyl [(3-methylphenyl)methyl]carbamate	m/z 448 $[MH]^+$ RT 3.37min
707		3-butyl-8-chloro-1-(2-hydroxyethyl)-3,7-dihydro-1H-purine-2,6-dione	m/z 287 $[MH]^+$ RT 2.42min
708		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-(4-propylphenyl)pentanamide	m/z 474 $[MH]^+$ RT 3.73min
709		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-(2-ethylphenyl)pentanamide	m/z 460 $[MH]^+$ RT 3.41min

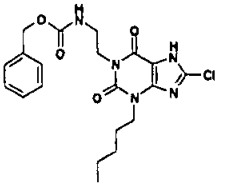
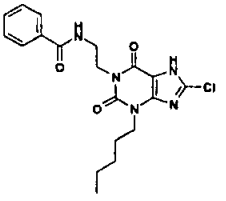
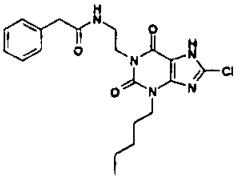
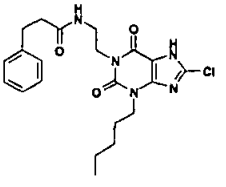
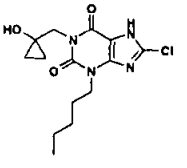
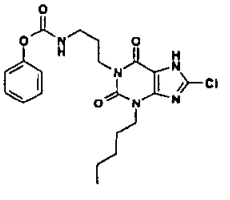
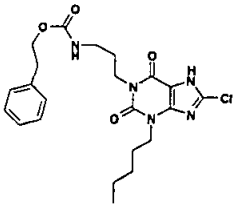
710		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-(3-ethylphenyl)pentanamide	m/z 460 $[MH]^+$ RT 3.58min
711		3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)propyl [(4-fluorophenyl)methyl]carbamate	m/z 466 $[MH]^+$ RT 3.43min
712		3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)propyl methyl(phenylmethyl)carbamate	m/z 462 $[MH]^+$ RT 3.54min
713		3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)propyl [(4-methylphenyl)methyl]carbamate	
714		3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)propyl [(2-methylphenyl)methyl]carbamate	m/z 462 $[MH]^+$ RT 3.50min
715		(4-fluorophenyl)methyl [3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)propyl]carbamate	m/z 466 $[MH]^+$ RT 3.36min
716		3-thienylmethyl [3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)propyl]carbamate	m/z 454 $[MH]^+$ RT 3.27min

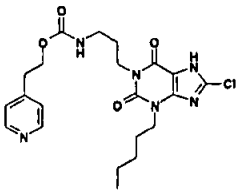
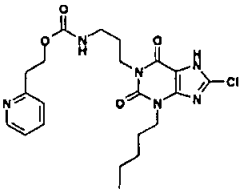
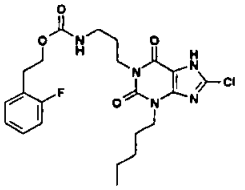
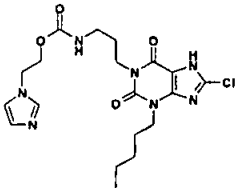
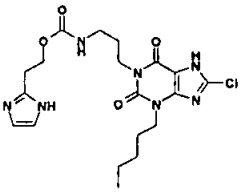
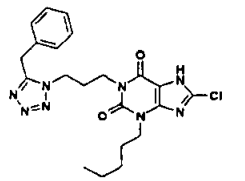
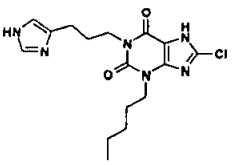
717		(4-methylphenyl)methyl [3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)propyl]carbamate	m/z 462 $[MH]^+$ RT 3.45min
718		(2-methylphenyl)methyl [3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)propyl]carbamate	m/z 462 $[MH]^+$ RT 3.42min
719		2-(4-fluorophenyl)ethyl [3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)propyl]carbamate	m/z 480 $[MH]^+$ RT 3.49min
720		3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)propyl (2-phenylethyl)carbamate	m/z 462 $[MH]^+$ RT 3.50min
721		3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)propyl propylcarbamate	m/z 400 $[MH]^+$ RT 3.20min
722		3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)propyl (2-methyl-2-phenylpropyl)carbamate	m/z 490 $[MH]^+$ RT 3.66min
723		3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)propyl (1-methyl-1-phenylethyl)carbamate	m/z 476 $[MH]^+$ RT 3.59min

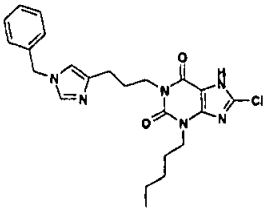
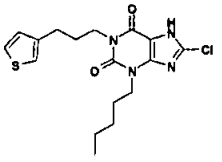
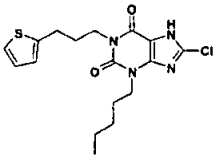
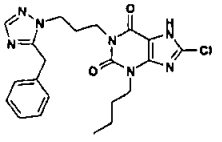
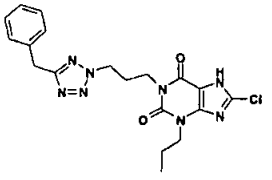
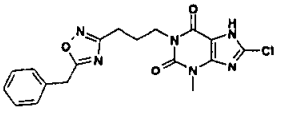
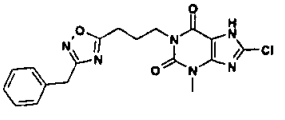
724		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-(2-methyl-2-phenylpropyl)pentanamide	m/z 488 $[MH]^+$ RT 3.53min
725		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-[(4-fluorophenyl)methyl]-N-methylpentanamide	m/z 478 $[MH]^+$ RT 3.46min
726		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-[(2-fluorophenyl)methyl]pentanamide	m/z 464 $[MH]^+$ RT 3.32min
727		N-[3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)propyl]-2-(3-methylphenyl)acetamide	m/z 446 $[MH]^+$ RT 3.37min
728		N-[3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)propyl]-2-(4-fluorophenyl)acetamide	m/z 450 $[MH]^+$ RT 3.28min
729		N-[3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)propyl]-2-(4-methylphenyl)acetamide	m/z 446 $[MH]^+$ RT 3.36min
730		N-[3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)propyl]-2-methyl-2-phenylpropanamide	m/z 460 $[MH]^+$ RT 3.50min

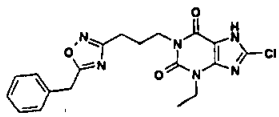
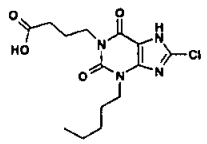
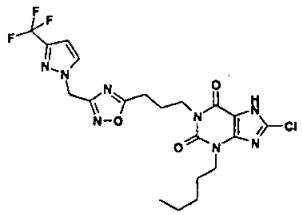
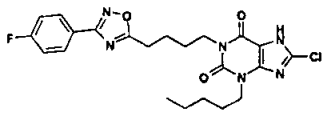
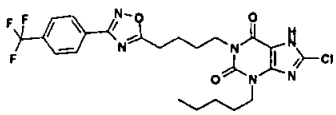
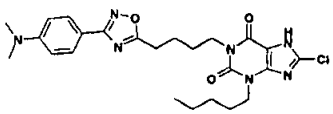
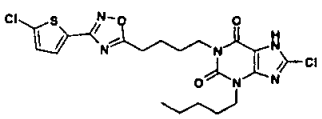
731		N-[3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)propyl]-3-methyl-3-phenylbutanamide	m/z 474 $[MH]^+$ RT 3.51min
732		N-[3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)propyl]-3-(3-methylphenyl)propanamide	m/z 460 $[MH]^+$ RT 3.45min
733		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-(1-phenylcyclopropyl)pentanamide	m/z 472 $[MH]^+$ RT 3.29min
734		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-methyl-N-phenylpentanamide	m/z 446 $[MH]^+$ RT 3.27min
735		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-(3-methylphenyl)pentanamide	m/z 446 $[MH]^+$ RT 3.41min
736		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-methyl-N-(3-methylphenyl)pentanamide	m/z 460 $[MH]^+$ RT 3.41min
737		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-(4-methylphenyl)pentanamide	m/z 446 $[MH]^+$ RT 3.40min

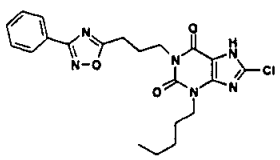
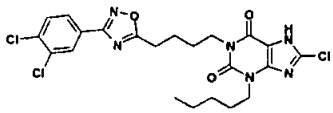
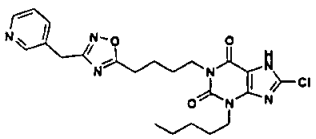
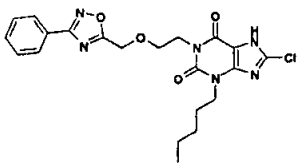
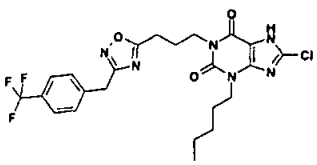
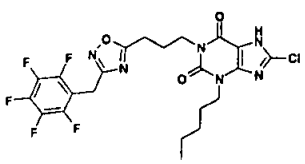
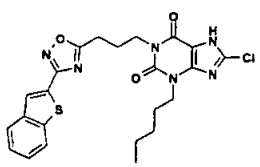
738		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-(cyclohexylmethyl)pentanamide	m/z 452 $[MH]^+$ RT 3.40min
739		8-chloro-3-pentyl-1-[2-(phenylamino)ethyl]-3,7-dihydro-1H-purine-2,6-dione	m/z 376 $[MH]^+$ RT 3.55min
740		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-methyl-N-(4-methylphenyl)pentanamide	m/z 460 $[MH]^+$ RT 3.41min
741		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-cyclohexylpentanamide	m/z 438 $[MH]^+$ RT 3.25min
742		N-[2-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)ethyl]benzenesulfonamide	m/z 440 $[MH]^+$ RT 3.08min
743		N-[2-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)ethyl]-1-phenylmethanesulfonamide	m/z 454 $[MH]^+$ RT 3.15min
744		phenyl [2-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)ethyl]carbamate	m/z 420 $[MH]^+$ RT 3.18min

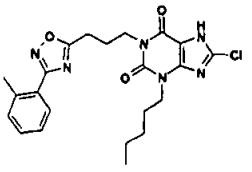
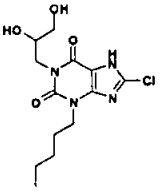
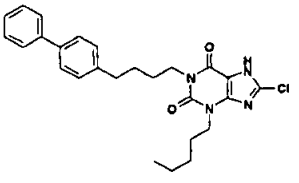
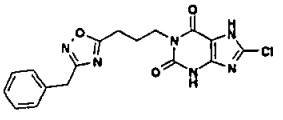
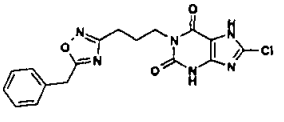
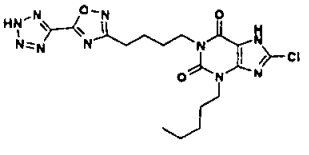
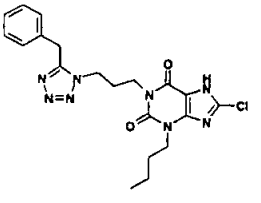
745		phenylmethyl [2-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)ethyl]carbamate	m/z 434 $[MH]^+$ RT 3.23min
746		N-[2-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)ethyl]benzamide	m/z 404 $[MH]^+$ RT 3.04min
747		N-[2-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)ethyl]-2-phenylacetamide	m/z 418 $[MH]^+$ RT 2.99min
748		N-[2-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)ethyl]-3-phenylpropanamide	m/z 432 $[MH]^+$ RT 3.14min
749		8-chloro-1-[(1-hydroxycyclopropyl)methyl]-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	m/z 327 $[MH]^+$ RT 2.82min
750		phenyl [3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)propyl]carbamate	m/z 434 $[MH]^+$ RT 3.31min
751		2-phenylethyl [3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)propyl]carbamate	m/z 462 $[MH]^+$ RT 3.48min

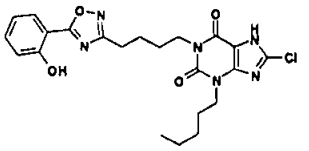
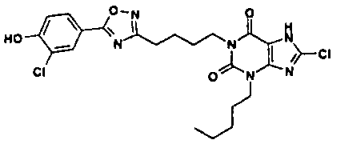
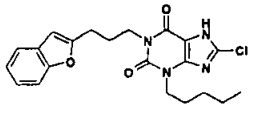
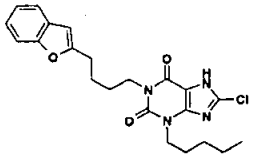
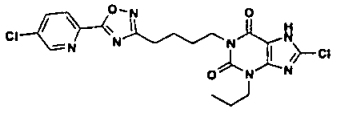
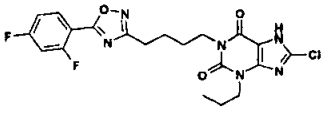
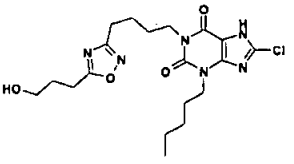
752		2-pyridin-4-ylethyl [3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)propyl]carbamate	m/z 463 $[MH]^+$ RT 2.44min
753		2-pyridin-2-ylethyl [3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)propyl]carbamate	m/z 463 $[MH]^+$ RT 2.44min
754		2-(2-fluorophenyl)ethyl [3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)propyl]carbamate	m/z 480 $[MH]^+$ RT 3.46min
755		2-(1H-imidazol-1-yl)ethyl [3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)propyl]carbamate	m/z 452 $[MH]^+$ RT 2.30min
756		2-(1H-imidazol-2-yl)ethyl [3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)propyl]carbamate	m/z 452 $[MH]^+$ RT 2.31min
757		8-chloro-3-pentyl-1-{3-[5-(phenylmethyl)-1H-tetrazol-1-yl]propyl}-3,7-dihydro-1H-purine-2,6-dione	m/z 457 $[MH]^+$ RT 3.32min
758		8-chloro-1-[3-(1H-imidazol-4-yl)propyl]-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	m/z 365 $[MH]^+$ RT 2.27min

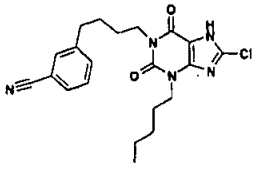
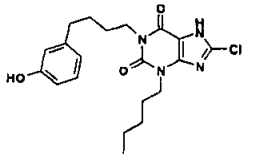
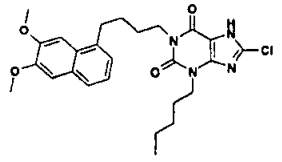
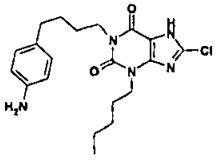
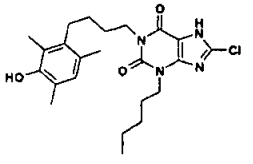
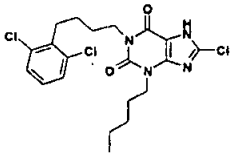
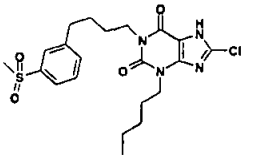
759		8-chloro-3-pentyl-1-{3-[1-(phenylmethyl)-1H-imidazol-4-yl]propyl}-3,7-dihydro-1H-purine-2,6-dione	m/z 455 $[MH]^+$ RT 2.61min
760		8-chloro-3-pentyl-1-[3-(3-thienyl)propyl]-3,7-dihydro-1H-purine-2,6-dione	m/z 381 $[MH]^+$ RT 3.61min
761		8-chloro-3-pentyl-1-[3-(2-thienyl)propyl]-3,7-dihydro-1H-purine-2,6-dione	m/z 381 $[MH]^+$ RT 3.69min
762		3-butyl-8-chloro-1-{3-[5-(phenylmethyl)-1H-1,2,4-triazol-1-yl]propyl}-3,7-dihydro-1H-purine-2,6-dione	m/z 442 $[MH]^+$ RT 2.94min
763		8-chloro-1-{3-[5-(phenylmethyl)-2H-tetrazol-2-yl]propyl}-3-propyl-3,7-dihydro-1H-purine-2,6-dione	m/z 429 $[MH]^+$ RT 3.14min
764		8-chloro-3-methyl-1-{3-[5-(phenylmethyl)-1,2,4-oxadiazol-3-yl]propyl}-3,7-dihydro-1H-purine-2,6-dione	m/z 401 $[MH]^+$ RT 2.88min
765		8-chloro-3-methyl-1-{3-[3-(phenylmethyl)-1,2,4-oxadiazol-5-yl]propyl}-3,7-dihydro-1H-purine-2,6-dione	m/z 401 $[MH]^+$ RT 2.89min

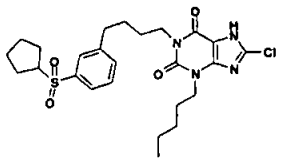
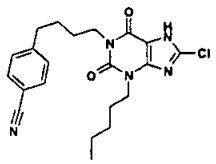
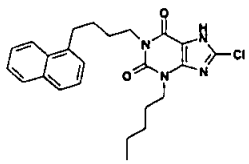
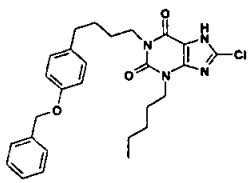
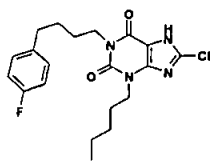
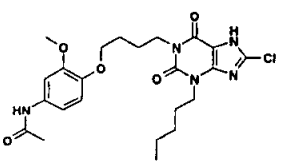
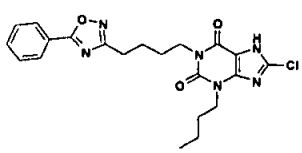
766		8-chloro-3-ethyl-1-{3-[5-(phenylmethyl)-1,2,4-oxadiazol-3-yl]propyl}-3,7-dihydro-1H-purine-2,6-dione	m/z 415 $[MH]^+$ RT 2.97min
767		4-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)butanoic acid	m/z 343 $[MH]^+$ RT 2.81min
768		8-chloro-3-pentyl-1-[3-(3-{[3-(trifluoromethyl)-1H-pyrazol-1-yl]methyl}-1,2,4-oxadiazol-5-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione	m/z 515 $[MH]^+$ RT 3.43min
769		8-chloro-1-{4-[3-(4-fluorophenyl)-1,2,4-oxadiazol-5-yl]butyl}-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	m/z 475 $[MH]^+$ RT 3.71min
770		8-chloro-3-pentyl-1-(4-{3-[4-(trifluoromethyl)phenyl]-1,2,4-oxadiazol-5-yl}butyl)-3,7-dihydro-1H-purine-2,6-dione	m/z 525 $[MH]^+$ RT 3.92min
771		8-chloro-1-(4-{3-[4-(dimethylamino)phenyl]-1,2,4-oxadiazol-5-yl}butyl)-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	m/z 500 $[MH]^+$ RT 3.73min
772		8-chloro-1-{4-[3-(5-chloro-2-thienyl)-1,2,4-oxadiazol-5-yl]butyl}-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	m/z 497 $[MH]^+$ RT 3.88min

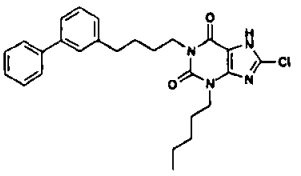
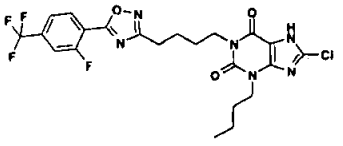
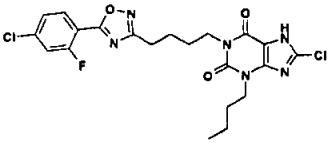
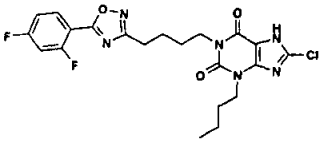
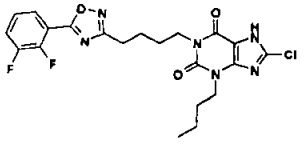
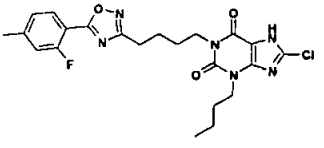
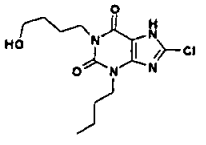
773		8-chloro-3-pentyl-1-[3-(3-phenyl-1,2,4-oxadiazol-5-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione	m/z 443 $[MH]^+$ RT 3.51min
774		8-chloro-1-{4-[3-(3,4-dichlorophenyl)-1,2,4-oxadiazol-5-yl]butyl}-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	m/z 525 $[MH]^+$ RT 4.12min
775		8-chloro-3-pentyl-1-{4-[3-(pyridin-3-ylmethyl)-1,2,4-oxadiazol-5-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione	m/z 472 $[MH]^+$ RT 2.90min
776		8-chloro-3-pentyl-1-(2-{[(3-phenyl-1,2,4-oxadiazol-5-yl)methyl]oxy}ethyl)-3,7-dihydro-1H-purine-2,6-dione	m/z 459 $[MH]^+$ RT 3.45min
777		8-chloro-3-pentyl-1-[3-(3-{[4-(trifluoromethyl)phenyl]methyl}-1,2,4-oxadiazol-5-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione	m/z 525 $[MH]^+$ RT 3.69min
778		8-chloro-1-(3-{3-[(pentafluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	m/z 547 $[MH]^+$ RT 3.66min
779		1-{3-[3-(1-benzothien-2-yl)-1,2,4-oxadiazol-5-yl]propyl}-8-chloro-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	m/z 499 $[MH]^+$ RT 3.77min

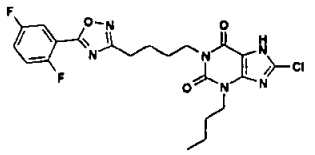
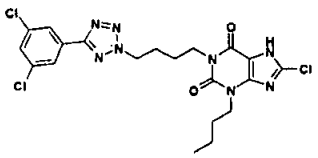
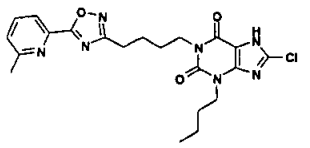
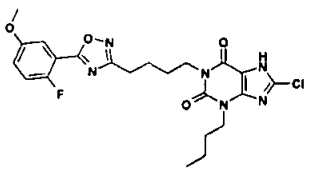
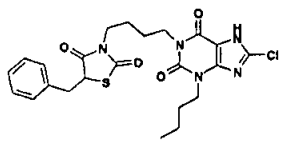
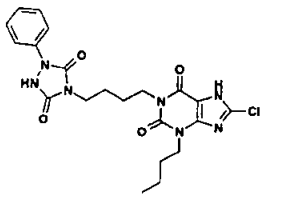
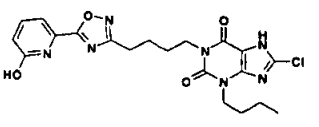
780		8-chloro-1-{3-[3-(2-methylphenyl)-1,2,4-oxadiazol-5-yl]propyl}-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	m/z 457 $[MH]^+$ RT 3.62min
781		8-chloro-1-(2,3-dihydroxypropyl)-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	m/z 331 $[MH]^+$ RT 2.48min
782		1-(4-biphenyl-4-ylbutyl)-8-chloro-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	m/z 465 $[MH]^+$ RT 4.18min
783		8-chloro-1-{3-[3-(phenylmethyl)-1,2,4-oxadiazol-5-yl]propyl}-3,7-dihydro-1H-purine-2,6-dione	m/z 387 $[MH]^+$ RT 2.63min
784		8-chloro-1-{3-[5-(phenylmethyl)-1,2,4-oxadiazol-3-yl]propyl}-3,7-dihydro-1H-purine-2,6-dione	m/z 387 $[MH]^+$ RT 2.65min
785		8-chloro-3-pentyl-1-{4-[5-(1H-tetrazol-5-yl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione	m/z 449 $[MH]^+$ RT 4.03min
786		3-butyl-8-chloro-1-{3-[5-(phenylmethyl)-1H-tetrazol-1-yl]propyl}-3,7-dihydro-1H-purine-2,6-dione	m/z 443 $[MH]^+$ RT 3.11min

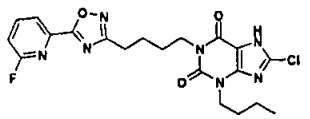
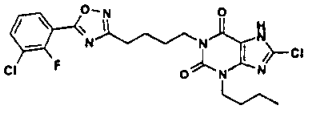
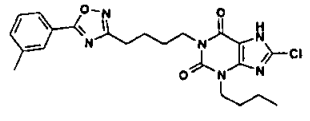
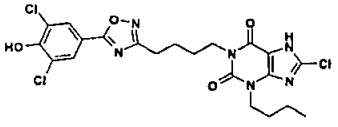
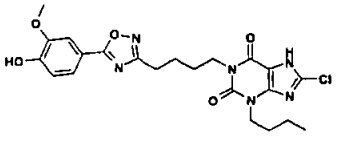
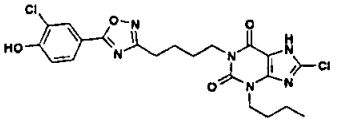
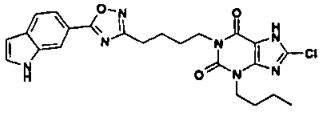
787		8-chloro-1-{4-[5-(2-hydroxyphenyl)-1,2,4-oxadiazol-3-yl]butyl}-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	m/z 473 $[MH]^+$ RT 3.84min
788		8-chloro-1-{4-[5-(3-chloro-4-hydroxyphenyl)-1,2,4-oxadiazol-3-yl]butyl}-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	m/z 507 $[MH]^+$ RT 3.74min
789		1-[3-(1-benzofuran-2-yl)propyl]-8-chloro-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	m/z 415 $[MH]^+$ RT 5.10min
790		1-[4-(1-benzofuran-2-yl)butyl]-8-chloro-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	m/z 429 $[MH]^+$ RT 3.88min
791		8-chloro-1-{4-[5-(5-chloropyridin-2-yl)-1,2,4-oxadiazol-3-yl]butyl}-3-propyl-3,7-dihydro-1H-purine-2,6-dione	m/z 464 $[MH]^+$ RT 3.30min
792		8-chloro-1-{4-[5-(2,4-difluorophenyl)-1,2,4-oxadiazol-3-yl]butyl}-3-propyl-3,7-dihydro-1H-purine-2,6-dione	m/z 465 $[MH]^+$ RT 3.48min
793		8-chloro-1-{4-[5-(3-hydroxypropyl)-1,2,4-oxadiazol-3-yl]butyl}-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	m/z 439 $[MH]^+$ RT 2.93min

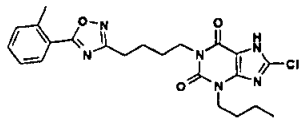
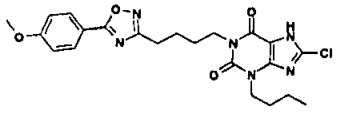
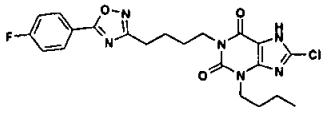
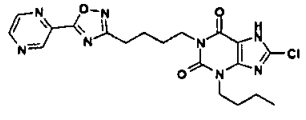
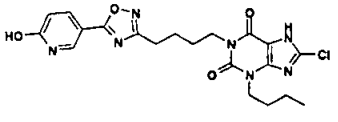
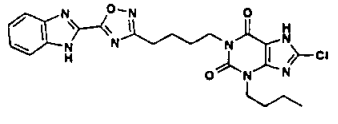
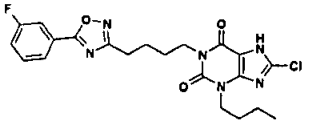
794		3-[4-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)butyl]benzonitrile	m/z 414 $[MH]^+$ RT 3.62min
795		8-chloro-1-[4-(3-hydroxyphenyl)butyl]-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	m/z 405 $[MH]^+$ RT 3.48min
796		1-{4-[6,7-bis(methyloxy)naphthalen-1-yl]butyl}-8-chloro-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	m/z 499 $[MH]^+$ RT 3.78min
797		1-[4-(4-aminophenyl)butyl]-8-chloro-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	m/z 404 $[MH]^+$ RT 3.02min
798		8-chloro-1-[4-(3-hydroxy-2,4,6-trimethylphenyl)butyl]-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	m/z 447 $[MH]^+$ RT 3.78min
799		8-chloro-1-[4-(2,6-dichlorophenyl)butyl]-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	m/z 457 $[MH]^+$ RT 4.10min
800		8-chloro-1-{4-[3-(methylsulfonyl)phenyl]butyl}-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	m/z 467 $[MH]^+$ RT 3.33min

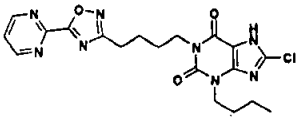
801		8-chloro-1-{4-[3-(cyclopentylsulfonyl)phenyl]butyl}-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	m/z 521 $[MH]^+$ RT 3.65min
802		4-[4-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)butyl]benzonitrile	m/z 414 $[MH]^+$ RT 3.61min
803		8-chloro-1-(4-naphthalen-1-ylbutyl)-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	m/z 439 $[MH]^+$ RT 4.00min
804		8-chloro-3-pentyl-1-(4-{4-[(phenylmethyl)oxy]phenyl}butyl)-3,7-dihydro-1H-purine-2,6-dione	m/z 495 $[MH]^+$ RT 4.06min
805		8-chloro-1-[4-(4-fluorophenyl)butyl]-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	m/z 407 $[MH]^+$ RT 3.78min
806		N-[4-{[4-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)butyl]oxy}-3-(methyloxy)phenyl]acetamide	m/z 492 $[MH]^+$ RT 3.09min
807		3-butyl-8-chloro-1-[4-(5-phenyl-1,2,4-oxadiazol-3-yl)butyl]-3,7-dihydro-1H-purine-2,6-dione	m/z 443 $[MH]^+$ RT 3.49min

808		1-(4-biphenyl-3-ylbutyl)-8-chloro-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	m/z 465 $[MH]^+$ RT 4.13min
809		3-butyl-8-chloro-1-(4-{5-[2-fluoro-4-(trifluoromethyl)phenyl]-1,2,4-oxadiazol-3-yl}butyl)-3,7-dihydro-1H-purine-2,6-dione	m/z 529 $[MH]^+$ RT 3.71min
810		3-butyl-8-chloro-1-{4-[5-(4-chloro-2-fluorophenyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione	m/z 495 $[MH]^+$ RT 3.64min
811		3-butyl-8-chloro-1-{4-[5-(2,4-difluorophenyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione	m/z 479 $[MH]^+$ RT 3.49min
812		3-butyl-8-chloro-1-{4-[5-(2,3-difluorophenyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione	m/z 479 $[MH]^+$ RT 3.53min
813		3-butyl-8-chloro-1-{4-[5-(2-fluoro-4-methylphenyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione	m/z 475 $[MH]^+$ RT 3.51min
814		3-butyl-8-chloro-1-(4-hydroxybutyl)-3,7-dihydro-1H-purine-2,6-dione	m/z 315 $[MH]^+$ RT 2.54min

815		3-butyl-8-chloro-1-{4-[5-(2,5-difluorophenyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione	m/z 479 $[MH]^+$ RT 3.50min
816		3-butyl-8-chloro-1-{4-[5-(3,5-dichlorophenyl)-2H-tetrazol-2-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione	m/z 511 $[MH]^+$ RT 3.92min
817		3-butyl-8-chloro-1-{4-[5-(6-methylpyridin-2-yl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione	m/z 458 $[MH]^+$ RT 3.12min
818		3-butyl-8-chloro-1-(4-{5-[2-fluoro-5-(methyloxy)phenyl]-1,2,4-oxadiazol-3-yl}butyl)-3,7-dihydro-1H-purine-2,6-dione	m/z 491 $[MH]^+$ RT 3.51min
819		3-butyl-8-chloro-1-{4-[2,4-dioxo-5-(phenylmethyl)-1,3-thiazolidin-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione	m/z 504 $[MH]^+$ RT 3.36min
820		3-butyl-8-chloro-1-[4-(3,5-dioxo-1-phenyl-1,2,4-triazolidin-4-yl)butyl]-3,7-dihydro-1H-purine-2,6-dione	m/z 474 $[MH]^+$ RT 2.91min
821		3-butyl-8-chloro-1-{4-[5-(6-oxo-1,6-dihydropyridin-2-yl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione	m/z 460 $[MH]^+$ RT 2.86min

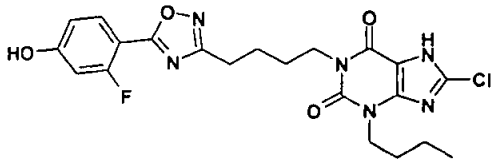
822		3-butyl-8-chloro-1-{4-[5-(6-fluoropyridin-2-yl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione	m/z 462 $[MH]^+$ RT 3.23min
823		3-butyl-8-chloro-1-{4-[5-(3-chloro-2-fluorophenyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione	m/z 495 $[MH]^+$ RT 3.69min
824		3-butyl-8-chloro-1-{4-[5-(3-methylphenyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione	m/z 457 $[MH]^+$ RT 3.67min
825		3-butyl-8-chloro-1-{4-[5-(3,5-dichloro-4-hydroxyphenyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione	m/z 527 $[MH]^+$ RT 3.92min
826		3-butyl-8-chloro-1-(4-{5-[4-hydroxy-3-(methyloxy)phenyl]-1,2,4-oxadiazol-3-yl}butyl)-3,7-dihydro-1H-purine-2,6-dione	m/z 489 $[MH]^+$ RT 3.27min
827		3-butyl-8-chloro-1-{4-[5-(3-chloro-4-hydroxyphenyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione	m/z 493 $[MH]^+$ RT 3.61min
828		3-butyl-8-chloro-1-{4-[5-(1H-indol-6-yl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione	m/z 482 $[MH]^+$ RT 3.55min

829		3-butyl-8-chloro-1-{4-[5-(2-methylphenyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione	m/z 457 $[MH]^+$ RT 3.67min
830		3-butyl-8-chloro-1-(4-{5-[4-(methyloxy)phenyl]-1,2,4-oxadiazol-3-yl}butyl)-3,7-dihydro-1H-purine-2,6-dione	m/z 473 $[MH]^+$ RT 3.51min
831		3-butyl-8-chloro-1-{4-[5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione	m/z 461 $[MH]^+$ RT 3.54min
832		3-butyl-8-chloro-1-[4-(5-pyrazin-2-yl-1,2,4-oxadiazol-3-yl)butyl]-3,7-dihydro-1H-purine-2,6-dione	m/z 445 $[MH]^+$ RT 2.96min
833		3-butyl-8-chloro-1-{4-[5-(6-oxo-1,6-dihydropyridin-3-yl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione	m/z 460 $[MH]^+$ RT 2.78min
834		1-{4-[5-(1H-benzimidazol-2-yl)-1,2,4-oxadiazol-3-yl]butyl}-3-butyl-8-chloro-3,7-dihydro-1H-purine-2,6-dione	m/z 483 $[MH]^+$ RT 3.22min
835		3-butyl-8-chloro-1-{4-[5-(3-fluorophenyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione	m/z 461 $[MH]^+$ RT 3.58min

836		3-butyl-8-chloro-1-[4-(5-pyrimidin-2-yl-1,2,4-oxadiazol-3-yl)butyl]-3,7-dihydro-1H-purine-2,6-dione	m/z 445 $[MH]^+$ RT 2.84min

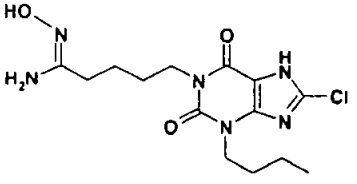
Example 837: 3-Butyl-8-chloro-1-{4-[5-(2-fluoro-4-hydroxyphenyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione

a) 3-Butyl-8-chloro-1-{4-[5-(2-fluoro-4-hydroxyphenyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione



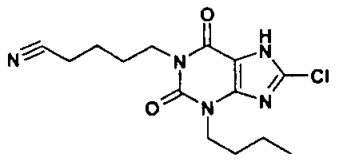
CDI (45mg, 0.28mmol) in anhydrous DMSO (0.5ml) was added to 2-fluoro-4-hydroxybenzoic acid (40mg, 0.25mmol) and stirred at rt for 2h. 5-(3-Butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)-*N*-hydroxypentanimidamide (100mg, 0.28mmol) in DMSO (0.4ml) was added and the resulting mixture heated at 90°C for 18h. Purification by MDAP afforded the title compound as a solid (38mg, 28%).
LC/MS: m/z 477 $[MH]^+$, RT 3.39min.
^{1}H NMR (DMSO-d_6) δ: 0.87 (t, 3H, J = 7Hz), 1.27 (m, 2H), 1.56-1.78 (m, 6H), 2.77 (t, 2H, J = 7Hz), 3.90 (m, 4H), 6.80 (m, 2H), 7.91 (t, 1H, J = 9Hz), 11.01 (s, 1H), 14.45 (br s, 1H).

b) 5-(3-Butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)-*N*-hydroxypentanimidamide



5-(3-Butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)pentanenitrile (8.5g, 26mmol) was dissolved in EtOH (100ml). Hydroxylamine (50% in water; 2.6ml, 39mmol) was added and the mixture heated at 80°C for 48h under nitrogen. The reaction mixture was concentrated *in vacuo*, the resultant solid washed with methanol and dried to give the title compound as a solid (5.9g, 47%).
LC/MS: m/z 357 $[MH]^+$, RT 2.17min.

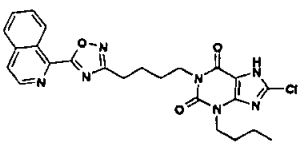
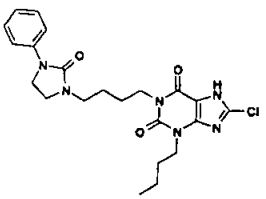
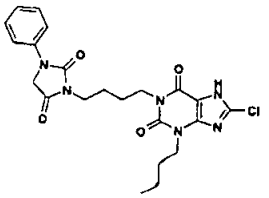
c) 5-(3-Butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)pentanenitrile

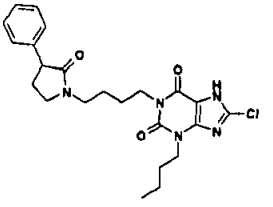
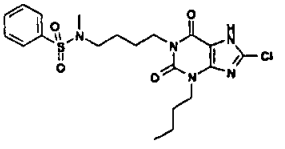
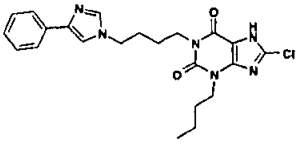
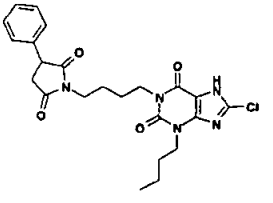
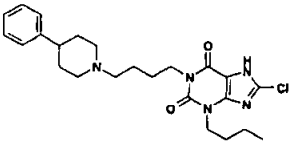
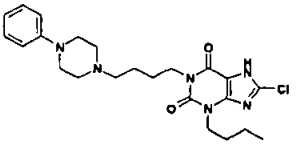
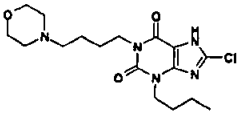


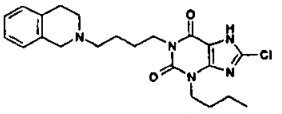
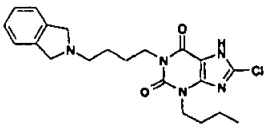
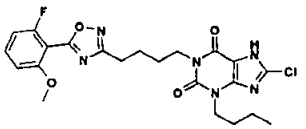
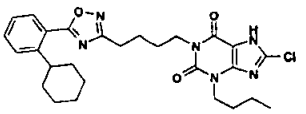
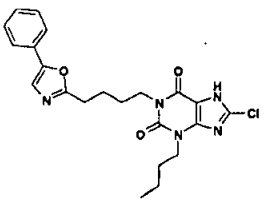
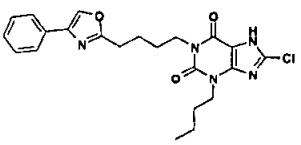
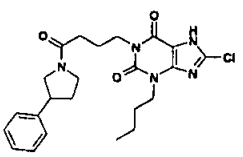
5-Bromopentanenitrile (4.54ml, 39mmol) and cesium carbonate (12.7g) were added to a solution of 3-butyl-8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (10g, 35mmol) in DMF (100ml) and the mixture stirred under nitrogen at 40°C overnight and allowed to cool.

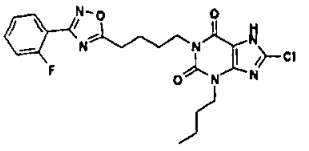
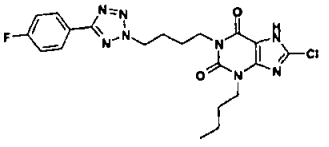
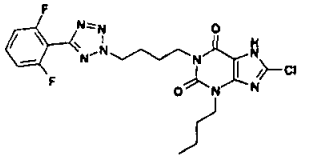
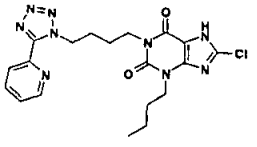
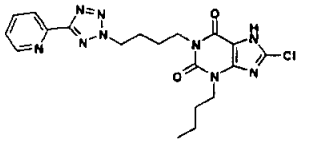
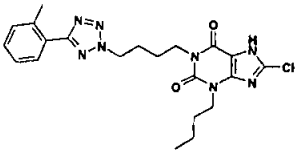
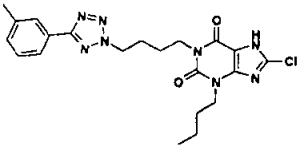
The mixture was then degassed by the repeated successive application of a vacuum and then nitrogen pressure. The mixture was then treated with tetrakis(triphenylphosphine)palladium(0) (2.86g, 2.5mmol) and morpholine (30.8ml, 350mmol). The mixture was stirred in a nitrogen atmosphere for 3h and then partitioned between EtOAc and 2M aqueous hydrochloric acid. The aqueous layer was separated and extracted with EtOAc (x2). The combined organic phases were concentrated *in vacuo* to give a solid that was washed with ether, filtered and dried. The filtrate was concentrated and purified on an aminopropyl column eluting with MeOH followed by 3% AcOH/MeOH. The product-containing fractions were combined and concentrated to give a solid, which was combined with the filtered product. The title compound was obtained as a solid (10.5g, 93%).
LC/MS: m/z 324 $[MH]^+$, RT 2.75min.

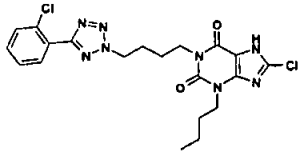
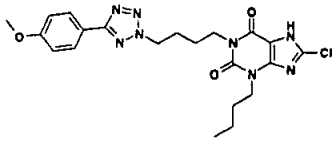
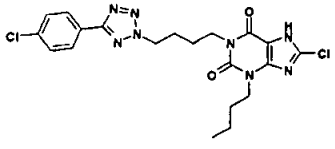
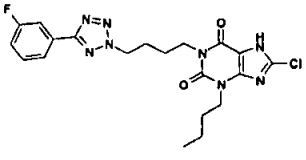
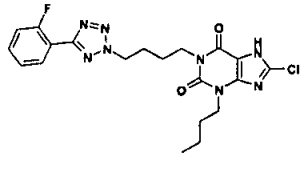
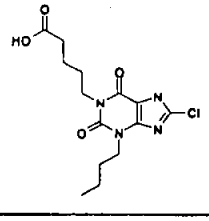
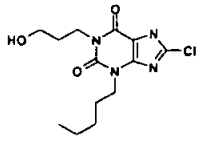
The following compounds (**Table 35**) were prepared using a method analogous to that for **Example 837**, using the appropriate carboxylic acid.

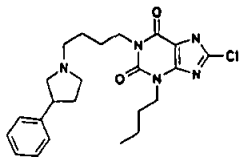
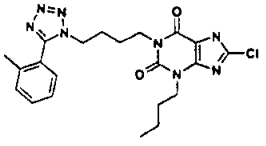
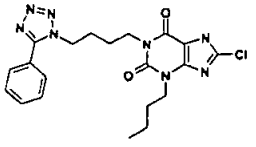
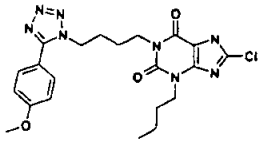
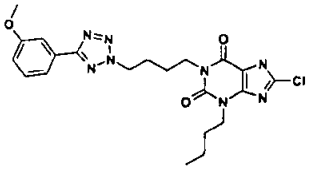
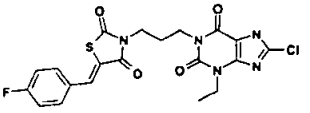
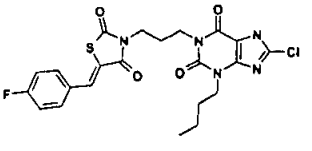
844		3-butyl-8-chloro-1-[4-(5-isoquinolin-1-yl-1,2,4-oxadiazol-3-yl)butyl]-3,7-dihydro-1H-purine-2,6-dione	m/z 494 $[MH]^+$ RT 3.49min
845		3-butyl-8-chloro-1-[4-(2-oxo-3-phenylimidazolidin-1-yl)butyl]-3,7-dihydro-1H-purine-2,6-dione	m/z 459 $[MH]^+$ RT 3.23min
846		3-butyl-8-chloro-1-[4-(2,5-dioxo-3-phenylimidazolidin-1-yl)butyl]-3,7-dihydro-1H-purine-2,6-dione	m/z 473 $[MH]^+$ RT 3.19min

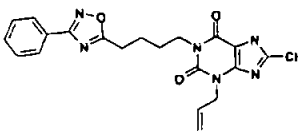
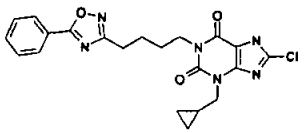
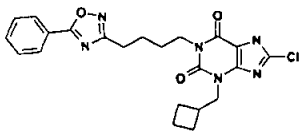
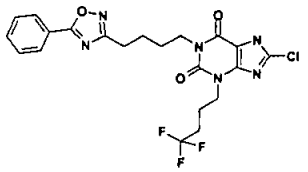
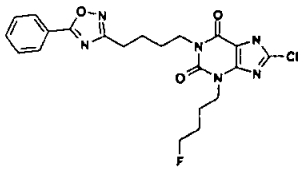
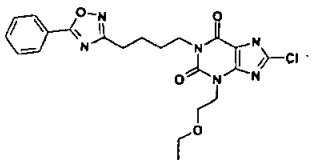
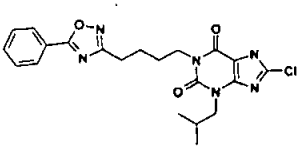
847		3-butyl-8-chloro-1-[4-(2-oxo-3-phenylpyrrolidin-1-yl)butyl]-3,7-dihydro-1H-purine-2,6-dione	m/z 458 $[MH]^+$ RT 3.12min
848		N-[4-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)butyl]-N-methylbenzenesulfonamide	m/z 468 $[MH]^+$ RT 3.28min
849		3-butyl-8-chloro-1-[4-(4-phenyl-1H-imidazol-1-yl)butyl]-3,7-dihydro-1H-purine-2,6-dione	m/z 441 $[MH]^+$ RT 2.60min
850		3-butyl-8-chloro-1-[4-(2,5-dioxo-3-phenylpyrrolidin-1-yl)butyl]-3,7-dihydro-1H-purine-2,6-dione	m/z 472 $[MH]^+$ RT 3.20min
851		3-butyl-8-chloro-1-[4-(4-phenylpiperidin-1-yl)butyl]-3,7-dihydro-1H-purine-2,6-dione	m/z 458 $[MH]^+$ RT 2.56min
852		3-butyl-8-chloro-1-[4-(4-phenylpiperazin-1-yl)butyl]-3,7-dihydro-1H-purine-2,6-dione	m/z 459 $[MH]^+$ RT 2.49min
853		3-butyl-8-chloro-1-(4-morpholin-4-ylbutyl)-3,7-dihydro-1H-purine-2,6-dione	m/z 384 $[MH]^+$ RT 2.11min

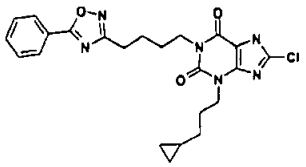
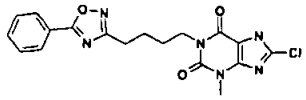
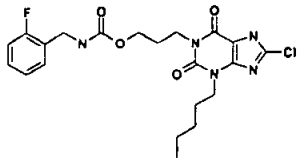
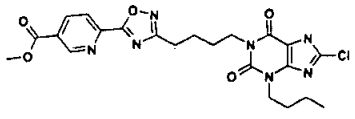
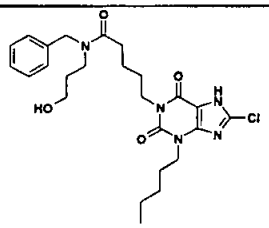
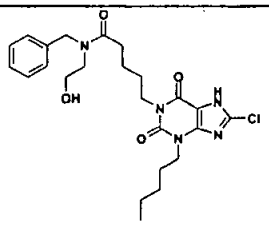
854		3-butyl-8-chloro-1-[4-(3,4-dihydroisoquinolin-2(1H)-yl)butyl]-3,7-dihydro-1H-purine-2,6-dione	m/z 430 $[MH]^+$ RT 2.40min
855		3-butyl-8-chloro-1-[4-(1,3-dihydro-2H-isoindol-2-yl)butyl]-3,7-dihydro-1H-purine-2,6-dione	m/z 416 $[MH]^+$ RT 2.33min
856		3-butyl-8-chloro-1-(4-{5-[2-fluoro-6-(methyloxy)phenyl]-1,2,4-oxadiazol-3-yl}butyl)-3,7-dihydro-1H-purine-2,6-dione	m/z 491 $[MH]^+$ RT 3.33min
857		3-butyl-8-chloro-1-{4-[5-(2-cyclohexylphenyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione	m/z 525 $[MH]^+$ RT 4.18min
858		3-butyl-8-chloro-1-[4-(5-phenyl-1,3-oxazol-2-yl)butyl]-3,7-dihydro-1H-purine-2,6-dione	m/z 442 $[MH]^+$ RT 3.46min
859		3-butyl-8-chloro-1-[4-(4-phenyl-1,3-oxazol-2-yl)butyl]-3,7-dihydro-1H-purine-2,6-dione	m/z 442 $[MH]^+$ RT 3.48min
860		3-butyl-8-chloro-1-[4-oxo-4-(3-phenylpyrrolidin-1-yl)butyl]-3,7-dihydro-1H-purine-2,6-dione	m/z 458 $[MH]^+$ RT 3.16min

861		3-butyl-8-chloro-1-{4-[3-(2-fluorophenyl)-1,2,4-oxadiazol-5-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione	m/z 461 $[MH]^+$ RT 3.45min
862		3-butyl-8-chloro-1-{4-[5-(4-fluorophenyl)-2H-tetrazol-2-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione	m/z 461 $[MH]^+$ RT 3.47min
863		3-butyl-8-chloro-1-{4-[5-(2,6-difluorophenyl)-2H-tetrazol-2-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione	m/z 479 $[MH]^+$ RT 3.32min
864		3-butyl-8-chloro-1-[4-(5-pyridin-2-yl-1H-tetrazol-1-yl)butyl]-3,7-dihydro-1H-purine-2,6-dione	m/z 444 $[MH]^+$ RT 2.94min
865		3-butyl-8-chloro-1-[4-(5-pyridin-2-yl-2H-tetrazol-2-yl)butyl]-3,7-dihydro-1H-purine-2,6-dione	m/z 444 $[MH]^+$ RT 3.07min
866		3-butyl-8-chloro-1-{4-[5-(2-methylphenyl)-2H-tetrazol-2-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione	m/z 457 $[MH]^+$ RT 3.54min
867		3-butyl-8-chloro-1-{4-[5-(3-methylphenyl)-2H-tetrazol-2-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione	m/z 457 $[MH]^+$ RT 3.56min

868		3-butyl-8-chloro-1-{4-[5-(2-chlorophenyl)-2H-tetrazol-2-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione	m/z 477 $[MH]^+$ RT 3.68min
869		3-butyl-8-chloro-1-(4-{5-[4-(methyloxy)phenyl]-2H-tetrazol-2-yl}butyl)-3,7-dihydro-1H-purine-2,6-dione	m/z 473 $[MH]^+$ RT 3.40min
870		3-butyl-8-chloro-1-{4-[5-(4-chlorophenyl)-2H-tetrazol-2-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione	m/z 477 $[MH]^+$ RT 3.68min
871		3-butyl-8-chloro-1-{4-[5-(3-fluorophenyl)-2H-tetrazol-2-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione	m/z 461 $[MH]^+$ RT 3.51min
872		3-butyl-8-chloro-1-{4-[5-(2-fluorophenyl)-2H-tetrazol-2-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione	m/z 461 $[MH]^+$ RT 3.34min
873		5-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)pentanoic acid	m/z 343 $[MH]^+$ RT 2.76min
874		5-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)pentanoic acid	m/z 315 $[MH]^+$ RT 2.74min

875		3-butyl-8-chloro-1-[4-(3-phenyl-1-pyrrolidinyl)butyl]-3,7-dihydro-1*H*-purine-2,6-dione	m/z 444 $[MH]^+$ RT 2.51min
876		3-butyl-8-chloro-1-{4-[5-(2-methylphenyl)-1*H*-tetrazol-1-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	m/z 457 $[MH]^+$ RT 3.16min
877		3-butyl-8-chloro-1-[4-(5-phenyl-1*H*-tetrazol-1-yl)butyl]-3,7-dihydro-1*H*-purine-2,6-dione	m/z 443 $[MH]^+$ RT 3.08min
878		3-butyl-8-chloro-1-(4-{5-[4-(methyloxy)phenyl]-1*H*-tetrazol-1-yl}butyl)-3,7-dihydro-1*H*-purine-2,6-dione	m/z 473 $[MH]^+$ RT 3.10min
879		3-butyl-8-chloro-1-(4-{5-[3-(methyloxy)phenyl]-2*H*-tetrazol-2-yl}butyl)-3,7-dihydro-1*H*-purine-2,6-dione	m/z 473 $[MH]^+$ RT 3.40min
880		8-chloro-3-ethyl-1-(3-{(5*Z*)-5-[(4-fluorophenyl)methylidene]-2,4-dioxo-1,3-thiazolidin-3-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione	m/z 478 $[MH]^+$ RT 3.31min
881		3-butyl-8-chloro-1-(3-{(5*Z*)-5-[(4-fluorophenyl)methylidene]-2,4-dioxo-1,3-thiazolidin-3-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione	m/z 506 $[MH]^+$ RT 3.63min

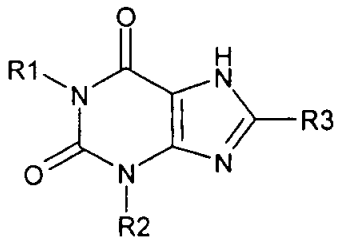
882		8-chloro-1-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)butyl]-3-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione	m/z 427 $[MH]^+$ RT 3.20min
883		8-chloro-3-(cyclopropylmethyl)-1-[4-(5-phenyl-1,2,4-oxadiazol-3-yl)butyl]-3,7-dihydro-1*H*-purine-2,6-dione	m/z 441 $[MH]^+$ RT 3.38min
884		8-chloro-3-(cyclobutylmethyl)-1-[4-(5-phenyl-1,2,4-oxadiazol-3-yl)butyl]-3,7-dihydro-1*H*-purine-2,6-dione	m/z 455 $[MH]^+$ RT 3.53min
885		8-chloro-1-[4-(5-phenyl-1,2,4-oxadiazol-3-yl)butyl]-3-(4,4,4-trifluorobutyl)-3,7-dihydro-1*H*-purine-2,6-dione	m/z 497 $[MH]^+$ RT 3.46min
886		8-chloro-3-(4-fluorobutyl)-1-[4-(5-phenyl-1,2,4-oxadiazol-3-yl)butyl]-3,7-dihydro-1*H*-purine-2,6-dione	m/z 461 $[MH]^+$ RT 3.26min
887		8-chloro-3-[2-(ethyloxy)ethyl]-1-[4-(5-phenyl-1,2,4-oxadiazol-3-yl)butyl]-3,7-dihydro-1*H*-purine-2,6-dione	m/z 459 $[MH]^+$ RT 3.16min
888		8-chloro-3-(2-methylpropyl)-1-[4-(5-phenyl-1,2,4-oxadiazol-3-yl)butyl]-3,7-dihydro-1*H*-purine-2,6-dione	m/z 443 $[MH]^+$ RT 3.44min

889		8-chloro-3-(3-cyclopropylpropyl)-1-[4-(5-phenyl-1,2,4-oxadiazol-3-yl)butyl]-3,7-dihydro-1*H*-purine-2,6-dione	m/z 469 $[MH]^+$ RT 3.63min
890		8-chloro-3-methyl-1-[4-(5-phenyl-1,2,4-oxadiazol-3-yl)butyl]-3,7-dihydro-1*H*-purine-2,6-dione	m/z 401 $[MH]^+$ RT 2.98min
891		3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)propyl [(2-fluorophenyl)methyl]carbamate	m/z 466 $[MH]^+$ RT 3.44min
892		methyl 6-{3-[4-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)butyl]-1,2,4-oxadiazol-5-yl}-3-pyridinecarboxylate	m/z 502 $[MH]^+$ RT 3.22min
893		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-(3-hydroxypropyl)-N-(phenylmethyl)pentanamide	m/z 504 $[MH]^+$ RT 2.64min
894		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-(2-hydroxyethyl)-N-(phenylmethyl)pentanamide	m/z 490 $[MH]^+$ RT 3.13min

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

Claims

1. At least one chemical entity selected from compounds of formula (I)



(I)

and pharmaceutically acceptable derivatives thereof, wherein

R^1 represents $-(alkylene)_m-X-(alkylene)_n-Y$;

Wherein X represents A, A1, A2 or a direct link;

A represents a group selected from
cycloalkylene, cycloalkenylene, aryl, heteroaryl, heterocyclyl, and $-CH_2-OC(O)-$;

A1 represents a group selected from
$-CH_2-O-(CH_2)_q$aryl$-O-$, $-CH_2-O-(CH_2)_wN(R^5)C(O)O-$, $-CH_2-N(R^5)C(O)O-$,
$-CH_2-N(R^5)C(O)-$, $-CH_2-(O)_p-(CH_2)_qC(O)NR^5-$, $-CH_2-N(R^5)C(O)N(R^5)-$,
$-CH_2-C(O)N((CH_2)_wOH)-$, $-CH_2-NR^5-S(O)_2-$, $CH_2-S(O)_2NR^5-$, $-CH_2-C(O)O-$, $-O-$,
$-NR^5-$, and $-S-$;

A2 represents $-CH(OH)-$;

When X is A, A1 or A2, Y represents a group selected from
heteroaryl, heterocyclyl, aryl, cycloalkyl, cycloalkenyl, -NH-aryl, $-O(CH_2)_n$-aryl,
-O-heteroaryl, $-OR^5$, $-C(O)OR^5$, $-C(O)O-C_6$ aryl, $-OC(O)R^4$, $-CH(aryl)_2$,
$-CH(heteroaryl)_2$, and $-C_{1-6}$ haloalkyl;

When X is A1 and Y is selected from
$-O(CH_2)_n$-aryl, -O-heteroaryl, $-OR^5$, $-OC(O)R^4$, and -NH-aryl,
n is an integer selected from 2, 3, 4 and 5;

When X is A1 and Y is $-C_{1-6}$ haloalkyl, or when X is A2, n is an integer selected from 1, 2, 3, 4 and 5;

When X is a direct link, (m + n) is an integer selected from 2 to 10;

When X is a direct link and (m + n) is an integer selected from 3 to 10, Y represents a group selected from
-C(O)$(CH_2)_q$OR^4, -C(O)-aryl, -C(O)-heteroaryl, -C(O)-heterocyclyl, heteroaryl, heterocyclyl, Aryl, 3 or 4 ring fused system, -CH(aryl)$_2$, -CH(heteroaryl)$_2$, -OR^5, -NR^{5}R^6, -NR^{5}C(O)OR^7, -$(O)_p$C(O)NR^{5}R^7, and -NR^{5}C(O)R^7;

When X is a direct link and (m + n) is 2, Y represents a group selected from
-OR^5, -NH_2, and -NR^{5}C(O)OR^8;

When Y incorporates a ring, that ring may be optionally substituted by one or more of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, -$(CH_2)_q$NR^{5}R^7, -$(CH_2)_q$-$(O)_p$-$(CH_2)_q$-N(R^5)C(O)OR^8, -$(CH_2)_q$-N(R^5)C(O)R^8, -$(CH_2)_q$-$(O)_p$-$(CH_2)_q$-C(O)NR^{5}R^6, -$(CH_2)_q$-N(R^5)C(O)N(R^5)R^6, -$(CH_2)_q$-C(O)N($(CH_2)_m$OH)R^5, -$(CH_2)_q$-N(R^5)-S$(O)_2$R^8, -CH_2-S$(O)_2$N(R^5)R^6, -C_{1-6} haloalkyl, -OCF_3, -OCH$(F)_2$, -OCH_2F, -C(O)OR^5, -OR^5, -R^{8}CN, -CN, -SO_2R^9, -$(CH_2)_n$heteroaryl, -$(CH_2)_n$heterocycyl, -$(CH_2)_n$cycloalkyl, -$(CH_2)_n$cycloalkenyl, and -$(CH_2)_n$aryl;

Provided that when X is A1, A1 is -O- and Y is a ring which is substituted by aryl or heteroaryl, then m is an integer selected from 3, 4 and 5;

R^2 is selected from hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, aryl, and heteroaryl, each of which may be optionally substituted by one or more of a group independently selected from: C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, C_{1-6} haloalkyl, halogen, -CN, -OR^4, -$(CH_2)_n$COR^4, -C(O)OR^4, -OCOR^4, -$(CH_2)_n$NR^{5}R^6, -$(NH)_p$CONR^{5}R^6, -OCONR^{5}R^7, and -NR^{5}C(O)OR^7;

R^3 represents a group selected from halogen and CN;

R^4 is selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -$(CH_2)_n$ cycloalkyl, -$(CH_2)_n$ cycloalkenyl, -$(CH_2)_n$ heterocyclyl, -$(CH_2)_n$ aryl, and -$(CH_2)_n$ heteroaryl;

R^5 and R^6 are independently selected from hydrogen and C_{1-4} alkyl;

R^7 represents a group selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -$(CH_2)_t$ cycloalkyl, -$(CH_2)_n$ cycloalkenyl, -$(CH_2)_t$ heterocyclyl, -$(CH_2)_t$ aryl, and -$(CH_2)_t$ heteroaryl;

R^8 represents a group selected from C_{1-4} alkyl;

R^9 represents a group selected from C_{1-6} alkyl C_{2-6} alkenyl, C_{2-6} alkynyl, $-(CH_2)_n$ cycloalkyl, $-(CH_2)_n$cycloalkenyl, $-(CH_2)_n$heterocyclyl, $-(CH_2)_n$ aryl, $-(CH_2)_n$heteroaryl, and CN;

m represents an integer selected from 1, 2, 3, 4 and 5;

n represents an integer selected from 0, 1, 2, 3, 4 and 5;

p represents an integer selected from 0 and 1;

q represents an integer selected from 0, 1 and 2;

t represents an integer selected from 1 and 2; and

w represents an integer selected from 2, 3 and 4.

2. At least one chemical entity according to claim 1 wherein X is selected from A and A1.

3. At least one chemical entity according to claim 1 or 2 wherein R^2 is selected from C_{3-6} alkyl.

4. At least one chemical entity according to any preceding claim wherein X is selected from A and A1, and A represents a group selected from heteroaryl and heterocyclyl, and A1 represents a group selected from CH_2-O-$(CH_2)_w$N(R^5)C(O)O-, CH_2-N(R^5)C(O)O-, CH_2-N(R^5)C(O)-, CH_2-$(O)_p$-$(CH_2)_q$C(O)NR^5-, CH_2-N(R^5)C(O)N(R^5)-, CH_2-C(O)N($(CH_2)_m$OH)-, CH_2-NR^5-S$(O)_2$-, CH_2-S$(O)_2$NR^5-, and CH_2-C(O)O-.

5. At least one chemical entity according to claim 4 wherein X represents A and A represents a group selected from heteroaryl.

6. At least one chemical entity according to claim 5 wherein A represents a group selected from heteroaryl comprising a nitrogen heteroatom.

7. At least one chemical entity according to any preceding claim wherein Y represents a group selected from aryl, heteroaryl and O-aryl.

8. At least one chemical entity according to any preceding claim wherein R^3 represents halogen.

9. At least one chemical entity according to any preceding claim wherein R^3 represents chlorine.

10. At least one chemical entity according to any preceding claim for use in human or veterinary medicine.

11. At least one chemical entity according to any one of claims 1 to 9, for use in the treatment of disorders of lipid metabolism including dyslipidaemia and hyperlipoproteinaemia and/or of inflammatory diseases or conditions.

12. At least one chemical entity according to any one of claims 1 to 9 for use in the treatment of diabetic dyslipidaemia, mixed dyslipidaemia, heart failure, hypercholesteraemia, cardiovascular disease including atherosclerosis, arteriosclerosis, and hypertriglyceridaemia, type II diabetes mellitus, type I diabetes, insulin resistance, hyperlipidaemia, anorexia nervosa, obesity, coronary artery disease, thrombosis, angina, chronic renal failure, peripheral vascular disease or stroke.

13. At least one chemical entity according to any one of claims 1 to 9 for use in the manufacture of a medicament for treating diabetic dyslipidaemia, mixed dyslipidaemia, heart failure, hypercholesteraemia, cardiovascular disease including atherosclerosis, arteriosclerosis, and hypertriglyceridaemia, type II diabetes mellitus, type I diabetes, insulin resistance, hyperlipidaemia, anorexia nervosa, obesity, coronary artery disease, thrombosis, angina, chronic renal failure or stroke.

14. A method for the treatment of a human or animal subject having a condition where under-activation of the HM74A receptor contributes to the condition or where activation of the receptor will be beneficial, which method comprises administering to said human or animal subject an effective amount of at least one chemical entity according to any one of claims 1 to 9.

15. A method according to claim 14 wherein the human or animal subject has a disorder of lipid metabolism including dyslipidaemia or hyperlipoproteinaemia or an inflammatory disease or condition.

16. A pharmaceutical formulation comprising at least one chemical entity according to any one of claims 1 to 9 and at least one pharmaceutically acceptable diluents, excipients or carriers.

17. A combination for administration together or separately, sequentially or simultaneously in separate or combined pharmaceutical formulations, said

combination comprising at least one chemical entity according to any one of claims 1 to 9 together with another therapeutically active agent.

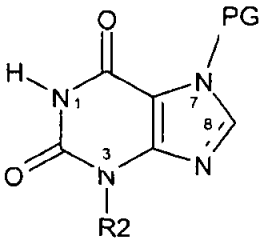
18. A pharmaceutical formulation comprising:

(i) at least one chemical entity according to any one of claims 1 to 9;

(ii) one or more therapeutically active agent selected from statins, fibrates, bile-acid binding resins and nicotinic acid; and

(iii) one or more pharmaceutically acceptable diluent, excipient or carrier.

19. A method for the preparation of at least one chemical entity according to any one of claims 1 to 9 in which R^3 is halogen from an appropriate starting material, for example compound(s) of formula (II):



(II)

wherein PG = protecting group, the method comprising:

(i) alkylation at N1 of an N7 protected xanthine;

(ii) alkylation at N3 of an N7 protected xanthine;

(iii) halogenation at C8; and

(iv) de-protection of N7;

in any order providing de-protection is carried out after alkylation.

Figure 1

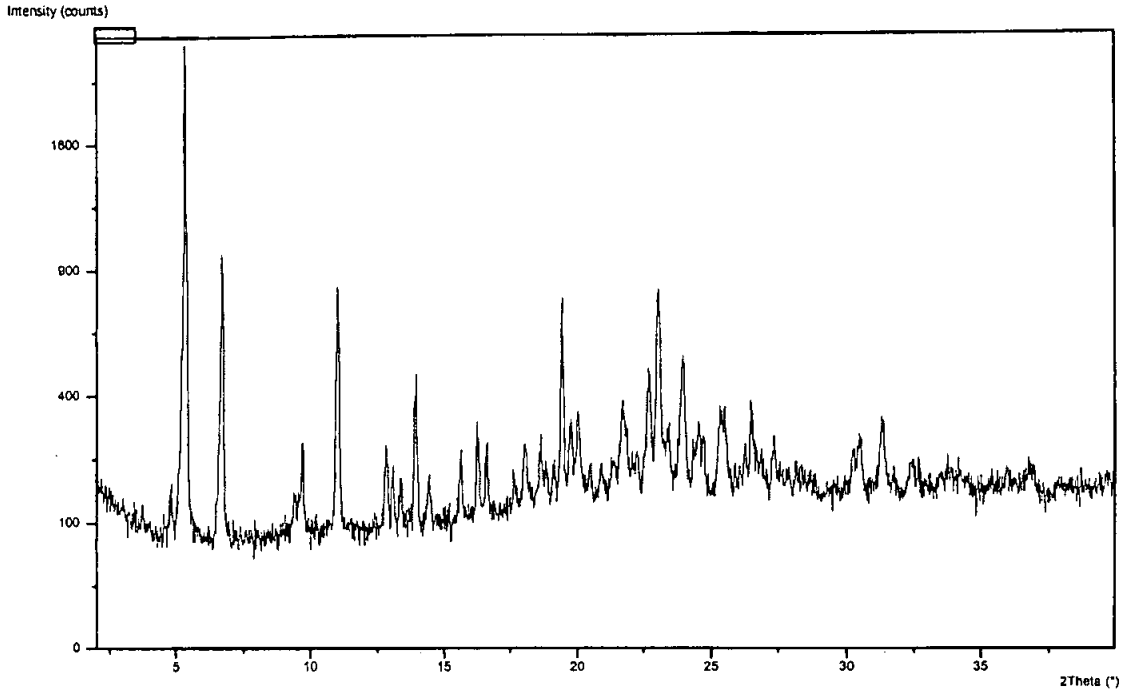


Figure 1: XRPD data of substantially crystalline 3-Butyl-8-chloro-1-{4-[5-(2-pyridinyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione form 1.

Figure 2

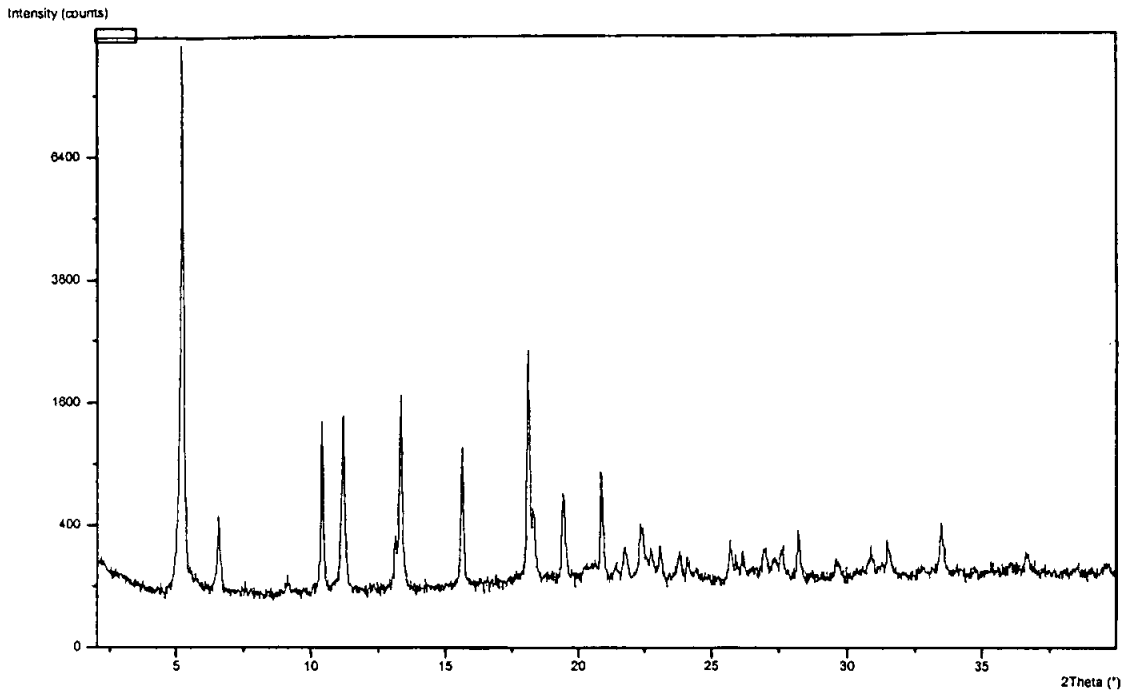


Figure 2: XRPD data of substantially crystalline 3-Butyl-8-chloro-1-{4-[5-(2-pyridinyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione form 2.

Figure 3

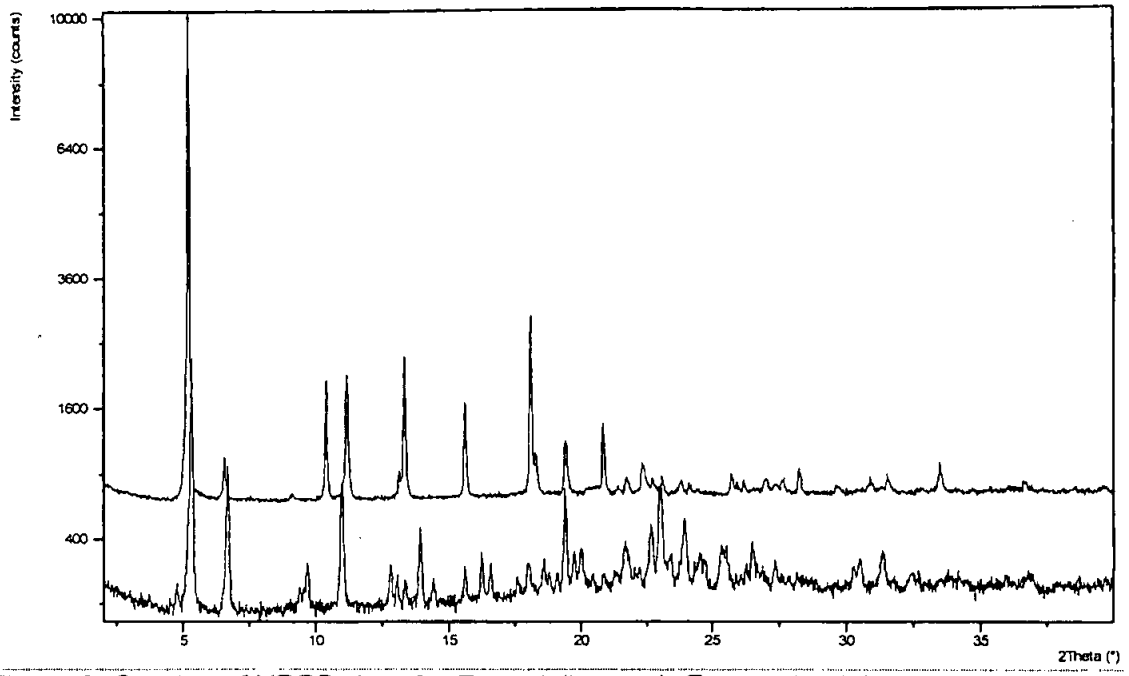


Figure 3 Overlay of XRPD data for Form 1 (bottom), Form 2 (top) (data has been offset for clarity).

DERIVADOS DE XANTINA COMO AGONISTAS DE HM74A SELECTIVOS

MEMORIA DESCRIPTIVA

La presente invención se refiere a compuestos que son derivados de xantina, procedimientos para la fabricación de dichos derivados, formulaciones farmacéuticas que contienen estos compuestos y el uso de los compuestos en terapia, por ejemplo, en el tratamiento de enfermedades en donde la sub-activación del receptor de HM74A contribuye a la enfermedad o en donde la activación del receptor será benéfica.

La dislipidemia es un término general usado para describir a individuos con perfiles de lipoproteína aberrantes. Clínicamente, las clases principales de compuestos usados para el tratamiento de pacientes con dislipidemia, y por lo tanto en riesgo de enfermedad cardiovascular son las estatinas, fibratos, resinas de unión de ácido biliar y ácido nicotínico. El ácido nicotínico (Niacina, una vitamina B) se ha usado clínicamente por más de 40 años en pacientes con varias formas de dislipidemia. El modo de acción primario de ácido nicotínico es mediante inhibición de triglicérido lipasa sensible a hormonas (HSL), que da por resultado una reducción de ácidos grasos no esterificados en el plasma (NEFA) que a su vez altera el metabolismo de grasa hepático para reducir la producción de LDL y VLDL (lipoproteína de baja y muy baja densidad). Se piensa que los niveles reducidos de VLDL reducen la actividad de la proteína de transferencia de

éster de colesterol (CETP) para dar por resultado niveles incrementados de HDL (lipoproteína de alta densidad) que puede ser la causa de los beneficios cardiovasculares observados. Por lo tanto, el ácido nicotínico produce una alteración muy deseable en los perfiles de lipoproteína; reduciendo los niveles de VLDL y LDL mientras incrementa HDL. También se ha demostrado que el ácido nicotínico tiene beneficios modificadores de enfermedad, reduciendo la progresión e incrementando la regresión de lesiones ateroscleróticas y reduciendo el número de eventos cardiovasculares en varios ensayos.

La inhibición observada de HSL por tratamiento con ácido nicotínico es mediada por una disminución en monofosfato de adenosina cíclico celular (AMPc) causada por la inhibición de adenilil ciclasa mediada por proteína G. Recientemente, los receptores acoplados a proteína G HM74 y HM74A han sido identificados como receptores para ácido nicotínico (solicitud de patente del PCT WO02/84298; Wise et. al. J Biol Chem., 2003, 278 (11), 9869-9874). La secuencia de ADN de HM74A humano se puede encontrar en Genbank; número de acceso AY148884. Dos documentos adicionales soportan este descubrimiento, (Tunaru et. al. Nature Medicine, 2003, 9(3), 352-255 y Soga et. al. Biochem Biophys Res Commun., 2003, 303 (1) 364-369), sin embargo, la nomenclatura difiere ligeramente. En el documento de Tunaru lo que ellos denominan HM74 humano los inventores de la presente denominan HM74A y en el documento de Soga el HM74b es idéntico a HM74A. Las células transfectadas para expresar HM74A y/o HM74 ganan la capacidad para inducir respuestas mediadas por proteína G, G1, después de

exponerse a ácido nicotínico. En ratones que carecen del homólogo de HM74A (m-PUMA-G), el ácido nicotínico no reduce los niveles de NEFA en el plasma.

Ciertos derivados de xantina han sido sintetizados y descritos en la técnica anterior. Por ejemplo, el documento EP0389282 describe derivados de xantina como mediadores potenciales de trastornos cerebrovasculares. Una gama de derivados de xantina fueron identificados como antagonistas de receptor de adenosina por Jacobson et. al. in J. Med. Chem., 1993, 36, 2639-2644.

Ahora, los inventores de la presente invención presentan un grupo de derivados de xantina que son agonistas selectivos del receptor de ácido nicotínico HM74A y por lo tanto son de beneficio potencial en el tratamiento, profilaxis y supresión de enfermedades en donde la sub-activación de este receptor ya sea contribuye a la enfermedad o en donde la activación del receptor será benéfica.

BREVE DESCRIPCION DE LA INVENCION

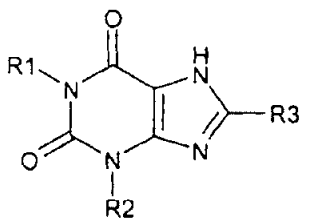
La presente invención provee derivados de xantina y el uso de estos derivados en terapia, por ejemplo, en el tratamiento de enfermedades en donde la sub-activación del receptor de HM74A contribuye a la enfermedad o en donde la activación del receptor será benéfica. Por ejemplo, en el tratamiento de enfermedades de metanolismo de lípidos incluyendo

dislipidemia o hiperlipoproteinemia tal como dislipidemia diabética y dislipidemia mixta, insuficiencia cardiaca, hpercolesteremia, enfermedad cardiovascular incluyendo aterosclerosis, arteriosclerosis e hipertrigliceridemia. Como tales, los compuestos también pueden encontrar ser favorables como terapéuticos para enfermedad de arteria coronaria, trombosis, angina, insuficiencia renal crónica, enfermedad vascular periférica y accidente vascular cerebral, así como las indicaciones cardiovasculares asociadas con diabetes mellitus de tipo II, diabetes de tipo I, resistencia a la insulina, hiperlipidemia, anorexia nerviosa, obesidad. Los compuestos también se pueden usar en el tratamiento de enfermedades o condiciones inflamatorias, como se expone más adelante.

Los intermediarios, formulaciones, métodos y procedimientos descritos aquí forman modalidades adicionales de la invención.

DESCRIPCION DETALLADA DE LA INVENCION

De conformidad con un aspecto de esta invención los inventores de la presente proveen por lo menos una entidad química seleccionada de los compuestos de la fórmula (I)



(I)

y derivados farmacéuticamente aceptables de los mismos, en donde

R^1 representa -(alquileno)$_m$-X-(alquileno)$_n$-Y;

en donde X representa A, A1, A2 o un enlace directo;

A representa un grupo seleccionado de cicloalquileno, cicloalquenileno, arilo, heteroarilo, heterociclilo, y -CH_2-OC(O)-;

A1 representa un grupo seleccionado de

-CH_2-O-$(CH_2)_q$arilo-O-, -CH_2-O-$(CH_2)_w$N(R^5)C(O)O-, -CH_2-N(R^5)C(O)O-, -CH_2-N(R^5)C(O)-, -CH_2-$(O)_p$-$(CH_2)_q$C(O)NR^5-, -CH_2-N(R^5)C(O)N(R^5)-, -CH_2-C(O)N($(CH_2)_w$OH)-, -CH_2-NR^5-S$(O)_2$-, CH_2-S$(O)_2$NR^5-, -CH_2-C(O)O-, -O-, -NR^5-, y -S-;

A2 representa -CH(OH)-;

Cuando X es A, A1 o A2, Y representa un grupo seleccionado de heteroarilo, heterociclilo, arilo, cicloalquilo, cicloalquenilo, -NH-arilo, -O$(CH_2)_n$-arilo, -O-heteroarilo, -OR^5, -C(O)OR^5, -C(O)O-arilo de C_6, -OC(O)R^4, -CH(arilo)$_2$, -CH(heteroarilo)$_2$, y – halogenoalquilo de C_{1-6};

Cuando X es A1 y Y se selecciona de

-O$(CH_2)_n$-arilo, -O-heteroarilo, -OR^5, -OC(O)R^4, y -NH-arilo,

n es un entero seleccionado de 2, 3, 4 y 5;

Cuando X es A1 y Y es -halogenoalquilo de C_{1-6}, o cuando X es A2, n es un entero seleccionado de , 2, 3, 4 y 5;

Cuando X es un enlace directo, (m + n) es un entero seleccionado de 2 a 10;

Cuando X es un enlace directo y (m + n) es un entero seleccionado de 3 a 10, Y representa un grupo seleccionado de

$-C(O)(CH_2)_qOR^4$, -C(O)-arilo, -C(O)-heteroarilo, -C(O)-heterociclilo, heteroarilo, heterociclilo, arilo, sistema fusionado de 3 ó 4 anillos, $-CH(arilo)_2$, $-CH(heteroarilo)_2$, $-OR^5$, $-NR^5R^6$, $-NR^5C(O)OR^7$, $-(O)_pC(O)NR^5R^7$, y $-NR^5C(O)R^7$;

Cuando X es un enlace directo y (m + n) es 2, Y representa un grupo seleccionado de:

$-OR^5$, $-NH_2$, y $-NR^5C(O)OR^8$;

Cuando Y incorpora un anillo, ese anillo puede ser opcionalmente sustituido por uno o más de alquilo de C_{1-6}, alquenilo de C_{2-6}, alquinilo de C_{2-6}, halógeno, $-(CH_2)_q NR^5R^7$, $-(CH_2)_q-(O)_p-(CH_2)_q-N(R^5)C(O)OR^8$, $-(CH_2)_q-N(R^5)C(O)R^8$, $-(CH_2)_q-(O)_p-(CH_2)_q-C(O)NR^5R^6$, $-(CH_2)_q-N(R^5)C(O)N(R^5)R^6$, $-(CH_2)_q-C(O)N((CH_2)_mOH)R^5$, $-(CH_2)_q-N(R^5)-S(O)_2R^8$, $-CH_2-S(O)_2N(R^5)R^6$, halogenoalquilo de C_{1-6}, $-OCF_3$, $-OCH(F)_2$, $-OCH_2F$, $-C(O)OR^5$, $-OR^5$, $-R^8CN$, -CN, $-SO_2R^9$, $-(CH_2)_n$heteroarilo, $-(CH_2)_n$heterociclilo, $-(CH_2)_n$cicloalquilo, $-(CH_2)_n$cicloalquenilo, y $-(CH_2)_n$arilo;

siempre que cuando X es A1, A1 es -O- y Y es un anillo que es sustituido por arilo o heteroarilo, entonces m es un entero seleccionado de 3, 4 y 5;

R^2 se selecciona de hidrógeno, alquilo de C_{1-10}, alquenilo de C_{2-10}, alquinilo de C_{2-10}, cicloalquilo, cicloalquenilo, heterociclilo, arilo y heteroarilo, cada uno de los cuales puede ser opcionalmente sustituido por

uno o más de un grupo independientemente seleccionado de: alquilo de C_{1-10}, alquenilo de C_{2-10}, alquinilo de C_{2-10}, cicloalquilo, heterociclilo, arilo, heteroarilo, halogenoalquilo de C_{1-6}, halógeno, -CN, $-OR^4$, $-(CH_2)_nCOR^4$, $-C(O)OR^4$, $-OCOR^4$, $-(CH_2)_nNR^5R^6$, $-(NH)_pCONR^5R^6$, $-OCONR^5R^7$, y $-NR^5C(O)OR^7$;

R^3 representa un grupo seleccionado de halógeno y CN;

R^4 se selecciona de hidrógeno, alquilo de C_{1-6}, alquenilo de C_{2-6}, alquinilo de C_{2-6}, $-(CH_2)_n$cicloalquilo, $-(CH_2)_n$cicloalquenilo, $-(CH_2)_n$heterociclilo, $-(CH_2)_n$ arilo, y $-(CH_2)_n$heteroarilo;

R^5 y R^6 se seleccionan independientemente de hidrógeno y alquilo de C_{1-4};

R^7 representa un grupo seleccionado de H, alquilo de C_{1-6}, alquenilo de C_{2-6}, alquinilo de C_{2-6}, $-(CH_2)_n$cicloalquilo, $-(CH_2)_n$cicloalquenilo, $-(CH_2)_n$heterociclilo, $-(CH_2)_n$arilo y $-(CH2)_n$heteroarilo;

R^8 representa un grupo seleccionado de alquilo de C_{1-4};

R^9 representa un grupo seleccionado de alquilo de C_{1-6}, alquenilo de C_{2-6}, alquinilo de C_{2-6}, $-(CH_2)_n$cicloalquilo, $-(CH_2)_n$cicloalquenilo, $-(CH_2)_n$heterociclilo, $-(CH_2)_n$arilo, $-(CH_2)_n$heteroarilo y CN;

m representa un entero seleccionado de 1, 2, 3, 4 y 5;

n representa un entero seleccionado de 0, 1 , 2, 3, 4 y 5;

p representa un entero seleccionado de 0 y 1;

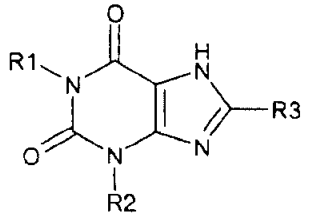
q representa un entero seleccionado de 0, 1 y 2;

t representa un entero seleccionado de 1 y 2; y

w representa un entero seleccionado de 2, 3 y 4.

Los compuestos se usan en el tratamiento de enfermedades en donde la sub-activación del receptor de HM74A contribuye a la enfermedad o en donde la activación del receptor será benéfica. Por ejemplo, en el tratamiento de enfermedades de metabolismo de lípidos incluyendo dislipidemia o hiperlipoproteinemia tal como dislipidemia diabética y dislipidemia mixta, insuficiencia cardiaca, hpercolesteremia, enfermedad cardiovascular incluyendo aterosclerosis, arteriosclerosis e hipertrigliceridemia. Como tales, los compuestos también pueden encontrar utilidad como terapéuticos para enfermedad de arteria coronaria, trombosis, angina, insuficiencia renal crónica, enfermedad vascular periférica y accidente vascular cerebral, así como las indicaciones cardiovasculares asociadas con diabetes mellitus de tipo II, diabetes de tipo I, resistencia a la insulina, hiperlipidemia, anorexia nerviosa, obesidad. Como tales, los compuestos de la presente invención pueden encontrar uso como agonistas o agonistas parciales de HM74A.

De conformidad con otro aspecto de esta invención los inventores de la presente proveen por lo menos una entidad química seleccionada de los compuestos de la fórmula (I)



(I)

y derivados farmacéuticamente aceptables de los mismos, en donde

R^1 representa -(alquileno)$_m$-X-(alquileno)$_n$-Y;

en donde X representa A, A1, A2 o un enlace directo;

A representa un grupo seleccionado de cicloalquileno, cicloalquenileno, arilo, heteroarilo, heterociclilo, y -CH_2-OC(O)-;

A1 representa un grupo seleccionado de

-CH_2-O-$(CH_2)_q$arilo-O-, -CH_2-O-$(CH_2)_w$N(R^5)C(O)O-, -CH_2-N(R^5)C(O)O-, -CH_2-N(R^5)C(O)-, -CH_2-$(O)_p$-$(CH_2)_q$C(O)NR^5-, -CH_2-N(R^5)C(O)N(R^5)-, -CH_2-C(O)N($(CH_2)_w$OH)-, -CH_2-NR^5-S$(O)_2$-, CH_2-S$(O)_2$NR^5-, -CH_2-C(O)O-, -O-, -NH-, y -S-;

A2 representa -CH(OH)-;

Cuando X es A, A1 o A2, Y representa un grupo seleccionado de heteroarilo, heterociclilo, arilo, cicloalquilo, cicloalquenilo, -NH-arilo, -O$(CH_2)_n$-arilo, -O-heteroarilo, -OR^5, -C(O)OR^5, -C(O)O-arilo de C_6, -OC(O)R^5, -CH(arilo)$_2$, -CH(heteroarilo)$_2$, y –halogenoalquilo de C_{1-6};

Cuando X es A1 y Y se selecciona de

-O$(CH_2)_n$-arilo, -O-heteroarilo, -OR^5, -OC(O)R^5, y -NH-arilo,

n es un entero seleccionado de 2, 3, 4 y 5;

Cuando X es A1 y Y es -CF3, o cuando X es A2, n es un entero seleccionado de , 2, 3, 4 y 5;

Cuando X es un enlace directo, (m + n) es un entero seleccionado de 2 a 10;

Cuando X es un enlace directo y (m + n) es un entero

seleccionado de 3 a 10, Y representa un grupo seleccionado de -$C(O)(CH_2)_qOR^5$, -C(O)-arilo, -C(O)-heteroarilo, -C(O)-heterociclilo, heteroarilo, heterociclilo, arilo, sistema fusionado de 3 ó 4 anillos, -$CH(arilo)_2$, -$CH(heteroarilo)_2$, -OR^5, -NR^5R^6, -$NR^5C(O)OR^8$, -$(O)_pC(O)NR^5R^6$, y -$NR^5C(O)R^8$;

Cuando X es un enlace directo y (m + n) es 2, Y representa un grupo seleccionado de:

-OR^5, -NH_2, y -$NR^5C(O)OR^8$;

Cuando Y incorpora un anillo, ese anillo puede ser opcionalmente sustituido por uno o más de alquilo de C_{1-6}, alquenilo de C_{2-6}, alquinilo de C_{2-6}, halógeno, -NH_2, -$(CH_2)_q$-$(O)_p$-$(CH_2)_q$-$N(R^5)C(O)OR^8$, -$(CH_2)_q$-$N(R^5)C(O)R^8$, -$(CH_2)_q$-$(O)_p$-$(CH_2)_q$-$C(O)NR^5R^6$, -$(CH_2)_q$-$N(R^5)C(O)N(R^5)R^6$, -$(CH_2)_q$-$C(O)N((CH_2)_mOH)R^5$, -$(CH_2)_q$-$N(R^5)$-$S(O)_2R^8$, -CH_2-$S(O)_2N(R^5)R^6$, -halogenoalquilo de C_{1-6}, -OCF_3, -$OCH(F)_2$, -OCH_2F, -$C(O)OR^5$, -OR^5, -$(R^8)_pCN$, -SO_2R^9, -$(CH_2)_n$heteroarilo, -$(CH_2)_n$heterociclilo, -$(CH_2)_n$cicloalquilo, -$(CH_2)_n$cicloalquenilo, y -$(CH_2)_n$arilo;

siempre que cuando X es A1, A1 es -O- y Y es un anillo que es sustituido por arilo o heteroarilo, entonces m es un entero seleccionado de 3, 4 y 5;

R^2 se selecciona de: H; o alquilo de C_{1-10}, alquenilo de C_{2-10}, alquinilo de C_{2-10}, cicloalquilo, cicloalquenilo heterociclilo, arilo y heteroarilo, cada uno de los cuales puede ser opcionalmente sustituido por uno o más de: alquilo de C_{1-10}, alquenilo de C_{2-10}, alquinilo de C_{2-10}, cicloalquilo, heterociclilo,

arilo, heteroarilo, halogenoalquilo de C_{1-6}, halógeno, -CN, $-OR^4$, $-(CH_2)_nCOR^4$, $-C(O)OR^4$, $-OCOR^4$, $-(CH_2)_nNR^5R^6$, $-(NH)_pCONR^5R^6$, $-OCONR^5R^7$, y $-NHC(O)OR^7$;

R^3 se selecciona de: halógeno y CN;

R^4 se selecciona de: H, alquilo de C_{1-6}, alquenilo de C_{2-6}, alquinilo de C_{2-6}, $-(CH_2)_n$cicloalquilo, $-(CH_2)_n$cicloalquenilo, $-(CH_2)_n$heterociclilo, $-(CH_2)_n$arilo, y $-(CH_2)_n$heteroarilo;

R^5 y R^6 se seleccionan de: hidrógeno y alquilo de C_{1-4};

R^7 se selecciona de: H, alquilo de C_{1-6}, alquenilo de C_{2-6}, alquinilo de C_{2-6}, $-(CH_2)_n$cicloalquilo, $-(CH_2)_n$cicloalquenilo, $-(CH_2)_n$heterociclilo, $-(CH_2)_n$arilo y $-(CH2)_n$heteroarilo;

R^8 se selecciona de alquilo de C_{1-4};

R^9 se selecciona de, alquilo de C_{1-6}, alquenilo de C_{2-6}, alquinilo de C_{2-6}, $-(CH_2)_n$cicloalquilo, $-(CH_2)_n$cicloalquenilo, $-(CH_2)_n$heterociclilo, $-(CH_2)_n$arilo, y $-(CH_2)_n$heteroarilo, CN;

m representa un entero seleccionado de: 1, 2, 3, 4 y 5;

n representa un entero seleccionado de: 0, 1, 2, 3, 4 y 5;

p representa un entero seleccionado de: 0 and 1;

q representa un entero seleccionado de: 0, 1 y 2;

t representa un entero seleccionado de: 1 y 2;

w representa un entero seleccionado de: 2, 3 y 4.

En una modalidad, X representa A o A1. En una modalidad adicional, A se selecciona de heteroarilo, heterociclilo y A1 se selecciona de

CH_2-O-$(CH_2)_w$N(R^5)C(O)O-, por ejemplo $CH_2O(CH_2)_2NHC(O)O$-, CH_2-N(R^5)C(O)O- por ejemplo CH_2-NHC(O)O, CH_2-N(R_5)C(O)- por ejemplo, CH_2-NHC(O)-, CH_2-$(O)_p$-$(CH_2)_q$C(O)NR^5-, por ejemplo $CH_2C(O)NCH_3$-, CH_2-N(R^5)C(O)N(R^5)-, por ejemplo CH_2-NHC(O)NCH_3-, CH_2-C(O)N(($CH_2)_m$OH)-, por ejemplo CH_2-C(O)N(($CH_2)_2$OH)-, CH_2-NR^5-S$(O)_2$-, por ejemplo CH_2-NH-S$(O)_2$-, CH_2-S$(O)_2$NR^5-, por ejemplo CH_2-S$(O)_2NCH_3$-, y CH_2-C(O)O-. En otra modalidad, X representa A y A representa un heteroarilo. En otra modalidad A representa un heteroarilo que comprende un heteroátomo de nitrógeno, por ejemplo, triazolilo, furazanilo, oxadiazolilo, tetrazolilo, imidazolilo o pirazolilo.

En una modalidad, Y representa un grupo opcionalmente sustituido seleccionado de: arilo, por ejemplo fenilo o naftilo, heteroarilo, por ejemplo piridinilo, tiazolilo, tienilo, benzofuranilo o indolilo, y O-arilo, por ejemplo O-fenilo.

En una modalidad adicional, Y es sustituido por uno o más grupos seleccionados de OR^5, por ejemplo OH o OCH_3, halógeno, por ejemplo F o Cl, arilo, por ejemplo fenilo, halogenoalquilo de C_{1-6}, por ejemplo CF_3 o CH_2CF_3, OCF_3, $(R^8)_p$CN, por ejemplo CN, $(CH_2)_q$-N(R^5)-S$(O)_2R^8$, por ejemplo $NHSO_2CH_3$ y SO_2R^9, por ejemplo SO_2CH_3.

En una modalidad más Y es sustituido por uno o más grupos seleccionados de OR^5, halógeno, halogenoalquilo de C_{1-6}, y -$(CH_2)_q$-N(R^5)C(O)R^8.

En otra modalidad, Y es sustituido por uno o más grupos seleccionados de halógeno, y halogenoalquilo de C_{1-6}.

En una modalidad más, en donde Y es un anillo, ya no es sustituido. 330

En una modalidad de la invención, cuando X representa A o A1, y A representa cicloalquilo, cicloalquenilo, arilo, heteroarilo o heterociclilo, y A1 representa $-CH_2-O-(CH_2)_wN(R^5)C(O)O-$, $-CH_2-N(R^5)C(O)O-$, $-CH_2-N(R^5)C(O)-$, $-CH_2-(O)_p-(CH_2)_qC(O)NR^5-$, $-CH_2-N(R^5)C(O)N(R^5)-$, o $-CH_2-C(O)N((CH_2)_mOH)-$, y Y representa un anillo, por ejemplo, cuando X representa oxadizolilo, tetrazolilo o pirazolilo y Y representa fenilo, piridinilo o tienilo, m es un entero seleccionado de 3 y 4 y n es un entero seleccionado de 0 y 1, por ejemplo m es 4 y n es 0, o m es 3 y n es 1 ;

En una modalidad R^2 representa alquilo de C_{1-10} que puede ser opcionalmente sustituido por uno o más de: cicloalquilo, heterociclilo, arilo, heteroarilo, halogenoalquilo de C_{1-6}, halógeno, -CN, $-OR^4$, $-(CH_2)_nCOR^5$, $-C(O)OR^4$, $-OCOR^4$, $-(CH_2)_nNR^5R^6$, y $-(NH)_pCONR^5R^6$. En una modalidad adicional, R^2 se selecciona de alquilo de C_{1-10} que puede ser opcionalmente sustituido por uno o más de: cicloalquilo, arilo, heteroarilo, halogenoalquilo de C_{1-6}, halógeno, -CN, $-OR_4$, $-(CH_2)_nCOR^5$, $-C(O)OR_4$ y $-OCOR_4$. En una modalidad más, R^2 se selecciona de alquilo de C_{1-6} que puede ser opcionalmente sustituido por uno o más de: cicloalquilo, halogenoalquilo de C_{1-6}, halógeno, -CN o $-OR^4$. en otra modalidad más, R^2 se selecciona de alquilo de C_{3-6}, por ejemplo butilo o pentilo.

En una modalidad, R^3 representa halógeno. En una modalidad adicional, R^3 se selecciona de: cloro y bromo. En otra modalidad, R^3

representa cloro.

Con respecto a estereoisómeros, los compuestos de la fórmula (I) pueden tener uno o más átomos de carbono asimétricos y pueden presentarse como racematos, mezclas racémicas y como enantiómeros o diastereómeros individuales. Todas esas formas isoméricas se incluyen dentro de la presente invención, incluyendo mezclas de los mismos.

En donde un compuesto de la fórmula (I) contiene un grupo alquenilo o alquenileno, también se puede presentar isomerismo cis (E) y trans (Z). La presente invención incluye los estereoisómeros individuales del compuesto de la invención y, en donde es apropiado, las formas tautoméricas individuales de los mismos, junto con mezclas de los mismos.

La separación de diaestereoisómeros o isómeros cis y trans se puede lograr por técnicas convencionales, v.gr., por cristalización fraccionada, cromatografía o CLAR de una mezcla estereoisomérica del agente también se puede preparar a partir de un intermediario óptimamente puro correspondiente o por resolución, tal como CLAR del racemato correspondiente usando un soporte quiral adecuado o por cristalización fraccionada de las sales diastereoisoméricas formadas por reacción del racemato correspondiente con un ácido o base óptimamente activo adecuado, según sea apropiado.

Más aún, algunas de las formas cristalinas de los compuestos de la fórmula (I) pueden existir como polimorfos, que se incluyen en la presente invención. Una forma puede tener una ventaja sobre otra forma, por ejemplo una forma puede tener estabilidad mejorada sobre otra forma.

Cabe entender que la presente invención incluye cualquier combinación de modalidades particulares y cubre todas las combinaciones de sustituyentes particulares descritos anteriormente.

A lo largo de la presente especificación y las reivindicaciones anexas, las palabras "comprende" e "incluye" y variaciones tales como "comprende", "que comprende", "incluye" y "que incluye" se han de interpretar de manera inclusiva. Es decir, se pretende que estas palabras transmitan la posible inclusión de otros elementos o entidades no mencionadas de manera específica, en donde lo permita el contexto.

Como se usa aquí, el término "alquilo" (cuando se usa como un grupo o como parte de un grupo) se refiere a una cadena de hidrocarburo recta o ramificada a menos que se especifique otra cosa, que contiene el número especificado de átomos de carbono. Por ejemplo, alquilo de C_3-C_{10} significa una cadena de hidrocarburo recta o ramificada que contiene por lo menos 3 y cuando mucho 10 átomos de carbono. Ejemplos de alquilo como se usa aquí incluyen, pero no se limitan a metilo (Me), etilo (Et), n-propilo e i-propilo.

El término "alquileno" o como se usa aquí significa grupos enlazadores de hidrocarburo tanto de cadena recta como ramificada o cíclicos saturados. Ejemplos de grupos alquileno incluyen metileno (-CH_2-), etileno (-CH_2CH_2-), etene (-CH=CH-), o ciclopropileno y similares. Por ejemplo, como se usa aquí, -(alk)n-, en donde n es 3 representa -$(CH_2)_3$-, -$C(CH_3)_2$-, -CH_2CH=CH-, o -ciclopropilene- y similares. Por ejemplo, como se usa aquí, -

(alk)m- en donde m es 4 representa $-(CH_2)_4-$, $-CH_2C(CH_3)_2-$, $-CH_2CH=CHCH_2-$, o $-CH_2$ciclopropilene- y similares.

El término "alquenilo" como se usa aquí se refiere a una cadena de hidrocarburo recta o ramificada que contiene el número especificado de átomos de carbono que contiene uno o más dobles enlaces.

El término "alquinilo" como se usa aquí se refiere a una cadena de hidrocarburo recta o ramificada que contiene el número especificado de átomos de carbono que contiene uno o más triples enlaces.

El término "cicloalquilo" como se usa aquí se refiere a un anillo de hidrocarburo monocíclico saturado de 3 a 8 átomos de carbono. Ejemplos de dichos grupos incluyen ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, cicloheptilo o ciclooctilo y similares.

El término "cicloalquileno" como se usa aquí se refiere a un anillo de hidrocarburo monocíclico saturado de 3 a 8 grupos enlazadores de carbono. Ejemplos de dichos grupos incluyen ciclopropileno, ciclobutileno, ciclopentileno, ciclohexileno, cicloheptileno o ciclooctileno y similares.

El término "cicloalquenilo" como se usa aquí se refiere a un anillo de hidrocarburo monocíclico no aromático insaturado de 3 a 8 átomos de carbono que contiene uno o más dobles enlaces carbono-carbono. Ejemplos de dichos grupos incluyen ciclopropenilo, ciclobutenilo, ciclopentenilo, ciclohexenilo, cicloheptenilo o ciclooctenilo y similares.

El término "cicloalquenileno" como se usa aquí se refiere a un anillo de hidrocarburo monocíclico no aromático insaturado de 3 a 8 grupos

enlazadores de carbono que contiene uno o más dobles enlaces carbono-carbono. Ejemplos de dichos grupos incluyen ciclopropenileno, ciclobutenileno, ciclopentenileno, ciclohexenileno, cicloheptenileno o ciclooctenileno y similares.

El término "arilo" como se usa aquí se refiere a un anillo de hidrocarburo monocíclico, bicíclico o tricíclico de C_{6-12} en donde por lo menos un anillo es aromático. Ejemplos de dichos grupos incluyen fenilo, naftilo o tetrahidronaftalenilo y similares.

El término "heteroarilo" como se usa aquí se refiere a un anillo aromático monocíclico de 5-6 miembros o un anillo aromático bicíclico de 8-10 miembro fusionado, que contiene 1 a 4 heteroátomos seleccionados de oxígeno, nitrógeno y azufre. Puede haber uno o más sustituyentes oxo opcionales en los átomos de carbono de anillo. Ejemplos de dichos anillos aromáticos monocíclicos incluyen tienilo, furilo, furazanilo, pirrolilo, triazolilo, tetrazolilo, imidazolilo, oxazolilo, tiazolilo, oxadiazolilo, isotiazolilo, isoxazolilo, tiadiazolilo, piranilo, pirazolilo, pirimidilo, piridazinilo, pirazinilo, piridilo, triazinilo, tetrazinilo y similares. Ejemplos de dichos anillos aromáticos fusionados incluyen quinolinilo, isoquinolinilo, quinazolinilo, quinoxalinilo, pteridinilo, cinolinilo, ftalazinilo, naftyridinilo, indolilo, isoindolilo, azaindolilo, indolizinilo, indazolilo, purinilo, pirrolopiridinilo, furopiridinilo, benzofuranilo, isobenzofuranilo, benzotienilo, benzoimidazolilo, benzoxazolilo, benzoisoxazolilo, benzotiazolilo, benzoisotiazolilo, benzoxadiazolilo, benzotiadiazolilo y similares.

El término "heterociclilo" como se usa aquí se refiere a un anillo monocíclico de 4-7 miembros o un anillo bicíclico de 8-12 miembros fusionado que puede ser saturado o parcialmente insaturado que contiene 1 a 4 heteroátomos seleccionados de oxígeno, nitrógeno o azufre. Puede haber uno o más sustituyentes oxo opcionales en los átomos de carbono de anillo. Ejemplos de dichos anillos monocíclicos incluyen pirrolidinilo, azetidinilo, pirazolidinilo, oxazolidinilo, piperidinilo, piperazinilo, morpholinilo, tiomorfolinilo, tiazolidinilo, hidantoinilo, valerolactamilo, oxiranilo, oxetanilo, dioxolanilo, dioxanilo, oxatiolanilo, oxatianilo, ditianilo, dihidrofuranilo, tetrahidrofuranilo, dihidropiranilo, tetrahidropiranilo, tetrahidropiridinilo, tetrahidropirimidinilo, tetrahidrotiofenilo, tetrahidrotiopiranilo, diazepanilo, azepanilo y similares. Ejemplos de dichos anillos bicíclicos incluyen indolinilo, isoindolinilo, benzopiranilo, quinuclidinilo, 2,3,4,5-tetrahidro-1H-3-benzazepina, tetrahidroisoquinolinilo y similares.

El término "sistema fusionado de 3 ó 4 anillos" como se usa aquí se refiere a un anillo tricíclico o tetracíclico de 12-18 fusionado que contiene 1 a 4 heteroátomos de N y en donde por lo menos un anillo es aromático. Puede haber uno o más sustituyentes oxo opcionales en los átomos de carbono de anillo. Ejemplos de dichos anillos aromáticos fusionados incluyen carbazolilo, acenaftilo, naftotriazolilo y similares.

Los términos "halógeno" o "halo" como se usa aquí se refieren a un átomo de flúor, cloro, bromo o yodo.

El término "halogenoalquilo de C_{1-6}" como se usa aquí se refiere

a un grupo alquilo de C_{1-6} como se define aquí, en donde por lo menos un átomo de hidrógeno es reemplazado con halógeno. Ejemplos de dichos grupos incluyen fluoroetilo, trifluorometilo o trifluoroetilo y similares.

Como se usa aquí, en donde un grupo se refiere como siendo "sustituido" por otro grupo o que tiene "uno o más sustituyentes" a menos que una posición particular para dicha sustitución sea especificada se ha de entender que una sustitución puede estar presente en cualquier posición en el grupo.

El término "derivado farmacéuticamente aceptable" como se usa aquí se refiere a cualquier derivado farmacéuticamente aceptable de un compuesto de la presente invención, por ejemplo, sales, solvatos o ésteres, que al administrarse a un mamífero, tal como un humano, es capaz de proveer (directamente o indirectamente) dicho compuesto o un metabolito activo del mismo. Dichos derivados son claros para los expertos en la técnica, sin experimentación extraordinaria, y con referencia a las enseñanzas de Burger's Medicinal Chemistry And Drug Discovery, 5ª. edición, Vol 1 : Principles And Practice, que se incorpora aquí por referencia.

Como se usa aquí, el término "farmacéuticamente aceptable" usado en relación con un ingrediente (ingrediente activo, diluyente, excipiente o vehículo) que se puede incluir en una formulación farmacéutica para administrarse a un paciente, se refiere a ese ingrediente que es aceptable en el sentido de ser compatible con cualesquiera otros ingredientes presentes en la formulación farmacéutica y sin ser deletérea al receptor de la misma.

Como se usa aquí, el término "solvato" se refiere a un complejo de estequiometría variable formada por un soluto (en esta invención, un compuesto de la fórmula (I) o un derivado farmacéuticamente aceptable del mismo) y un solvente. Dichos solventes para los propósitos de la presente invención puede no interferir con la actividad biológica del soluto. El solvente usado puede ser un solvente farmacéuticamente aceptable. Ejemplos de solventes farmacéuticamente adecuados incluyen agua, etanol y ácido acético. Un ejemplo de un solvente que se puede usar es agua, en cuyo caso el solvato se puede referir como un hidrato del soluto en cuestión.

Se apreciará que, para uso farmacéutico, la "sal o solvato" referred to above will be a farmacéuticamente aceptable salt or solvato. Sin embargo, otras sales o solvatos pueden encontrar uso, por ejemplo, en la preparación de un compuesto de la fórmula (I) o en la preparación de una salt o solvato farmacéuticamente aceptable del mismo.

Las sales farmacéuticamente aceptables incluyen aquellas descritas por Berge, Bighley y Monkhouse, J. Pharm. ScL, 1977, 66, 1-19. Sales farmacéuticamente aceptable adecuadas incluyen sales de metal alcalino formadas a partir de la adición de bases de metal alcalino tales como hidróxidos de metal alcalino. Ejemplos de sales de metal alcalino adecuadas incluyen sales de sodio y sales de potasio. Otras sales farmacéuticamente aceptables adecuadas incluyen sales de metal alcalinotérreo tales como sales de calcio y magnesio, sales de amonio; o sales con bases orgánicas tales como etanolamina, trietanolamina, etilendiamina, trietilamina, colina y

meglumina; o sales con aminoácidos tales como arginina, lisina e histidina.

Los ésteres pueden ser activos por sí mismos y/o pueden ser hidrolizables bajo condiciones *in vivo* en el cuerpo humano. Los grupos éster hidrolizables *in vivo* farmacéuticamente aceptables incluyen aquellos que se descomponen fácilmente en el cuerpo humano para dejar al ácido progenitor o su sal. Un éster se puede formar en un grupo ácido carboxílico (-C(O)OH), por métodos bien conocidos en la técnica que implican reacción con el alcohol correspondiente. Por ejemplo, los ésteres pueden ser ésteres de alquilo de C_{1-6}, v.gr., ésteres metílicos, ésteres etílicos y similares.

Como se usa aquí, el término "compuestos de la invención" significa los compuestos de conformidad con la fórmula I y los derivados farmacéuticamente aceptables de los mismos. El término "un compuesto de la invención" significa cualquiera de los compuestos de la invención como se definió antes.

Como se usa aquí, el término "por lo menos una entidad química" significa por lo menos una sustancia química escogida del grupo de compuestos que consisten de compuestos de la fórmula I y derivados farmacéuticamente aceptables de los mismos.

En un aspecto de la invención se provee una forma 1 de 3-butil-8-cloro-1-{4-[5-(2-piridinil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purino-2,6-diona sustancialmente cristalina. En otro aspecto de la invención se provee una forma 2 de 3-butil-8-cloro-1-{4-[5-(2-piridinil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purino-2,6-diona sustancialmente cristalina.

Se llevó a cabo un análisis térmico sobre muestras de las formas 1 y 2 de 3-butil-8-cloro-1-{4-[5-(2-piridinil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purino-2,6-diona sustancialmente cristalinas. Por lo tanto, se provee 3-butil-8-cloro-1-{4-[5-(2-piridinil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purino-2,6-diona (forma 1 o forma 2) sustancialmente cristalina que tiene un inicio de punto de fusión medido por DSC (± 0.5°C) de: 160°C o mayor y 1470C o mayor, respectivamente.

Muestras de la forma 1 de 3-butil-8-cloro-1-{4-[5-(2-piridinil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purino-2,6-diona, y la forma 2 de 3-butil-8-cloro-1-{4-[5-(2-piridinil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purino-2,6-diona sustancialmente cristalinas, preparadas como se describe más adelante, dieron los patrones de difracción de rayos X de las figuras 1-2. El patrón de difracción de rayos X es único para la forma cristalina. Las formas sustancialmente cristalinas presentan patrones de difracción con un conjunto único de picos de difracción que se pueden expresar en ángulos 2 teta (°).

Angulos de difracción 2 teta representan las posiciones de varios picos en el patrón de difracción de rayos X. Variaciones ligeras en ángulos 2 teta observados se esperan basados en el difractómetro específico utilizado y la técnica de preparación de la muestra del analista.

Las formas sustancialmente cristalinas de 3-butil-8-cloro-1-{4-[5-(2-piridinil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purino-2,6-diona se pueden identificar por la presencia de un pico de ángulo 2 teta característico, o por múltiples ángulos 2 teta que son razonablemente característicos de las

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formas cristalinas particulares. Para identificar 3-butil-8-cloro-1-{4-[5-(2-piridinil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purino-2,6-diona (forma 1) sustancialmente cristalina, estos picos se presentan en las siguientes popsiciones, expresadas em ángulos 2 teta (±0.1 grados): 5.4, 6.7, 9.7, 11.1, 12.9, 14.0, 15.6, 16.3, 16.7, 23.1 grados. Para identificar 3-butil-8-cloro-1-{4-[5-(2-piridinil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purino-2,6-diona (forma 2) sustancialmente cristalina, estos picos se presentan en las siguientes posiciones, expresadas en ánculos 2 teta (±0.1 grados): 5.2, 6.6, 10.4, 11.2, 13.4, 15.6, 18.1, 19.5, 20.9 grados. En una modalidad, por lo menos uno de los ángulos 2 teta anteriores se utilizan para identificar la forma 1 de 3-butil-8-cloro-1-{4-[5-(2-piridinil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purino-2,6-diona sustancialmente cristalina y la forma 2 de 3-butil-8-cloro-1-{4-[5-(2-piridinil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purino-2,6-diona sustancialmente cristalina. En otras modalidades por lo menos 2, 3, 4 ó 5 (en donde es aplicable) de los ángulos 2 teta anteriores se utilizan para identificar la forma 1 de 3-butil-8-cloro-1-{4-[5-(2-piridinil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purino-2,6-diona sustancialmente cristalina, la forma 2 de 3-butil-8-cloro-1-{4-[5-(2-piridinil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purino-2,6-diona sustancialmente cristalina.

Algún margen de error está presente en cada una de las asignaciones de ángulo 2 teta. El margen de error en los ángulos 2 teta anteriores es aproximadamente ±0.1 grados para cada una de las asignaciones de picos anteriores.

Puesto que algún margen de error es posible en la asignación de ángulos 2 teta, el método preferido de comparar patrones de difracción de rayos X en polvo para identificar una forma cristalina particular es traslapar el patrón de difracción de rayos X en polvo de la forma no conocida sobre el patrón de difracción de rayos X en polvo de una forma conocida. Por ejemplo, un experto en la técnica puede traslapar un patrón de difracción de rayos X en polvo de una forma no identificada de 3-butil-8-cloro-1-{4-[5-(2-piridinil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purino-2,6-diona, obtenida usando los métodos described en la misma, véase figura 3 por ejemplo, y determinar fácilmente si el patrón de difracción de rayos X de la forma no identificada es sustancialmente la misma que el patrón de difracción de rayos X en polvo de las formas 1 ó 2 de 3-butil-8-cloro-1-{4-[5-(2-piridinil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purino-2,6-diona sustancialmente cristalina. Si el patrón de difracción de rayos X en polvo es sustancialmente el mismo que el que se muestra en cualquiera de las figuras 1-2, la forma anterior puede ser fácilmente y exactamente identificada.

Como se usa aquí, el término "forma sustancialmente cristalina" significa que es sustancialmente libre de 3-butil-8-cloro-1-{4-[5-(2-piridinil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purino-2,6-diona en forma amorfa. Por "sustancialmente libre" se entiende que contiene menos de 50% de la forma amorfa, en un aspecto menos de 20% de la forma amorfa, en otro aspecto menos de 10% de la forma amorfa, en otro aspecto menos de 5% de la forma amorfa, en otro aspecto menos de 2% de la forma amorfa, en otro aspecto

menos de 1% de la forma amorfa.

La presente invención provee un método para la preparación de la forma 3-butil-8-cloro-1-{4-[5-(2-piridinil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purino-2,6-diona sustancialmente cristalina como se describe aquí.

Los compuestos de la fórmula (I) son de beneficio terapéutico potencial en el tratamiento y alivio de los síntomas de muchas enfermedades de metabolismo de lípidos incluyendo dislipidemia e hiperlipoproteinemia tales como dislipidemia diabética y dislipidemia mixta, insuficiencia cardiaca, hpercolesteremia, enfermedad cardiovascular incluyendo aterosclerosis, arteriosclerosis e hipertrigliceridemia, diabetes mellitus de tipo II, diabetes de tipo I, resistencia a la insulina, hiperlipidemia, anorexia nerviosa, obesidad. Como tales, los compuestos también pueden encontrar utilidad como terapéuticos para enfermedad de arteria coronaria, trombosis, angina, insuficiencia renal crónica, enfermedad vascular periférica y accidente vascular cerebral.

Se ha reportado que los receptores de HM74 y HM74A están implicados en la inflamación (WO02084298). La inflamación representa un grupo de respuestas vasculares, celulares y neurológicas a trauma. La inflamación se puede caracterizar como el movimiento de células inflamatorias tales como monocitos, neutrófilos y granulocitos en los tejidos. Esta está usualmente asociada con función de barrera endotelial reducida y edema en los tejidos. La inflamación con respecto a enfermedad típicamente se refiere como inflamación crónica. Dicha inflamación crónica se puede manifestar a

través de síntomas de enfermedad. La finalidad de terapia anti-inflamatoria es por lo tanto reducir esta inflamación crónica y permitir que el proceso fisiológico de cicatrización y reparación de tejido progrese.

Ejemplos de enfermedades o condiciones inflamatorias para los cuales los compuestos de la presente invención pueden demostrar utilidad incluyen las de las articulaciones, por ejemplo artritis (v.gr., artritis reumatoide, osteoartritis, falla de prótesis de articulaciones), o el tracto gastrointestinal (v.gr., colitis ulcerativa, enfermedad de Crohn, y otras enfermedades intestinales inflamatorias y gastrointestinales, gastritis y mucosal inflamación que resultan de infección, la enteropatía provocada por fármacos anti-inflamatorios no esteroideos), del pulmón (v.gr., síndrome de sufrimiento respiratorio en adultos, asma, fibrosis cística, o enfermedad pulmonar obstructiva crónica), del corazón (v.gr., miocarditis), de tejido nervioso (v.gr., esclerosis múltiple), del páncreas, (v.gr., inflamación asociada con diabetes melitus y complicaciones de la misma, del riñón (v.gr. glomerulonefritis), de la piel (v.gr., dermatitis, psoriasis, eczema, urticaria, lesión por quemadura), de los ojos (v.gr., glaucoma) así como de órganos trasplantados (v.gr., rechazo) y enfermedades de órganos múltiples (v.gr., lupus eritematoso sistémico, sepsis) y secuelas inflamatorias de infecciones virales o bacterianas y condiciones inflamatorias asociadas con aterosclerosis y después de ataques hipóxicos o isquémicos (con o sin reperfusión), por ejemplo en el cerebro o en enfermedad cardiaca isquémica.

En una modalidad, los compuestos de esta invención son útiles

en el tratamiento y prevención de inflamación, diabetes y enfermedades o condiciones cardiovasculares incluyendo aterosclerosis, arteriosclerosis, hipertrigliceridemia, y dislipidemia mixta.

El ácido nicotínico tiene un perfil de efecto colateral significativo, posiblemente debido a que es dosificado a nivel alto (cantidades en gramos diariamente). El efecto colateral más común es un rubor cutáneo intenso. En ciertas modalidades de la presente invención los compuestos pueden presentar efectos colaterales reducidos comparados con el ácido nicotínico. HM74A ha sido identificado como un receptor de alta afinidad para el ácido nicotínico mientras que HM74 es un receptor de afinidad más baja. Los compuestos de la presente invención muestran afinidad más alta para HM74A que para HM74, por lo tanto pueden encontrar uso como agonistas or agonistas parciales de HM74A selectivos.

El potencial para que los compuestos de la fórmula (I) activen HM74A se puede demostrar, por ejemplo, usando las siguientes pruebas de células enteras *in vitro*:

Prueba *in-vitro*

Para transfecciones transitorias, células HEK293T (células HEK293 que expresan establemente el antígeno T grande de SV40) se mantuvieron en DMEM que contenía 10% de suero de ternera fetal y 2 mM de glutamina. La células se sembraron en cajas de cultivo de 90 mm y se hicieron crecer a 60-80% de confluencia (18-24 hr) antes de transfección. HM74A

humana (número de acceso a GenBank™ AY148884) se subclonó a un vector de expresión de mamífero (pcDNA3; Invitrogen) y se transfectó usando reactivo de Lipofectamina. Paratransfección, 9 µg de ADN se mezcló con 30 µl de Lipofectamina en 0.6 ml de Opti-MEM (Life Technologies Inc.) y se incubó a temperatura ambiente durante 30 min antes de la adición de 1.6 ml de Opti-MEM. Las células se expusieron a la mezcla de Lipofectamina/ADN durante 5 hr y 6 ml de 20% (v/v) de suero de ternera fetal en DMEM se añadió después. Las células se cosecharon 48 hr después de la transfección. El tratamiento de toxina de Pertussis se llevó a cabo por complementación en el medio a 50 $ngml^{-1}$ durante 16 hr. Todos los estudios de transfección transitorios implicaron co-transfección de receptor junto con la proteína G, $G_{i/0}$, $G_{01}\alpha$.

Para la generación de líneas de células estables se usó el método anterior para transfectar células CHO-K1 sembradas en seis cajas con pozos cultivadas a 30% de confluencia. Estas células se mantuvieron en un medio DMEM F-12 HAM que contenía 10% de suero de ternera fetal y 2 mM de glutamina. 48 hr después de la transfección el medio se complementó con 400 µg/ml de Geneticin (G418, Gibco) para la selección de células resistentes a antibióticos. Las líneas de células CHO-K1 clonales que expresaban establemente HM74A fueron confirmadas por mediciones de unión a [35S]-GTPγS, después de la adición of ácido nicotínico.

Preparación de membrana de P2 – Membrana plasmática que contenía fracciones de partículas de P2 se prepararon a partir de pastas de células congeladas a -80°C después de la cosecha. Todos los procedimientos

se llevaron a cabo a 4°C. Las pastillas de células se resuspendieron en 1 ml de 10 mM de Tris-HCl y 0.1 mM de EDTA, pH 7.5 (regulador de pH A) y por homogenización durante 20 seg con un Ultra Turrax seguido por el paso (5 veces) a través de una aguja de calibre 25. Los lisados de células se centrifugaron a 1,000 g durante 10 min en una microcentrífuga para formar una pastilla de los núcleos y células no rotas y fracciones de paretículas de P2 se recuperaron por microcentrifugación a 16,000 g durante 30 min. Las fracciones de partículas de P2 se resuspendieron en regulador de pH A y se almacenaron a -80°C hasta que se requirieron.

Unión a [^{35}S]-GTPyS – se realizaron pruebas a temperatura ambiente en formato de 384 pozos basados en métodos descritos anteriormente (Wieland, T. y Jakobs, K.H. (1994) Methods Enzymol. 237, 3-13). En breve, la dilución de compuestos estándares o de prueba se prepararon y se añadieron a una placa de 384 pozos en un volumen de 10 µl. Las membranas (HM74A o HM74) se diluyeron en regulador de pH de prueba (20 mM de HEPES, 100 de mM NaCl, 10 mM de $MgCl_2$, pH7.4) complementado con saponina (60 µg/ml), Esferas de Leadseeker WGA (Amersham; 250 µg/pozo) y 10 µM GDP1 de modo que el volumen de 20 µl añadido a cada pozo contiene 5 µg de membranas. [35S]-GTPyS (1170 Ci/mmol, Amersham) se diluyó (1:1500) en regulador de pH de prueba y 20 µl se añadió a cada pozo. Después de la adición del radioligando, las placas se sellaron, se hicieron girar por pulsos y se incubaron durante 4 horas a temperatura ambiente. Al final del período de incubación las placas se leyeron

en una máquina de Leadseeker (VIEWLUX PLUS; Perkin-Elmer) para determinar los niveles de unión específica.

Estas pruebas se refinaron al reducir el volumen de prueba final a 10 µl. Para esta prueba de 10 µl se usó un protocolo revisado. Esto implicó el uso de 100 nl únicamente de compuesto estándar o prueba por pozo de una placa de 384 pozos y 1.5 µg de membrana y 100 µg de esferas de Leadseeker WGA. Para el protocolo de volumen bajo, membrana, esferas y [^{35}S]-GTPγS se mezclaron juntos y después 10 µl de esta mezcla se suministraron a cada pozo. La incubación y lectura de placas fueron idénticas para las pruebas de 10 µl y 50 µl.

Todos los compuestos ilustrados se probaron en una o ambas de las pruebas de unión a [^{35}S]-GTPγS descritas anteriormente (es decir, las pruebas de 10 µl y 50µl).

Los datos fueron analizados por el ajuste de la curva como se llevó a cabo usando una ecuación logística de cuatro parámetros usando el paquete de software XC50 (máximo 2 puntos suprimidos de cualquier curva). La unión específica se expresa como pEC50 y como % de eficacia comparada con la respuesta máxima de unión a ácido nicotínico.

Prueba *in-vivo*

Agonistas de HM74A se pueden probar en ratas Spague-Dawley machos (200-250 g) que han sido puestas en ayunas por lo menos por 12 horas antes del estudio. Los compuestos son dosificados por vía intravenosa

ya sea a 1 ó 3 mg/kg (5 ml/kg) o por alimentación forzada a dosis que variaban de 1-30 mg/kg (10 ml/kg). Se pueden tomar muestra de sangre de pre-dosis (0.3 ml de sangrado de la vena de la cola) y a tres veces post-dosis (tiempos que variaban de 15 minutos a 6 horas post-dosis). Cada muestra de sangre es transferida a un tubo de heparina (Becton Dickinson Microtainer, PST LH) y centrifugada (10,000 g durante 5 minutos) para producir una muestra de plasma. Las muestras de plasma se prueban para niveles de ácidos grasos no esterificados (NEFA) usando un equipo comercialmente disponible (Randox). La inhibición de niveles de NEFA en el plasma, en relación con los niveles de pre-dosis, se usan como un sustituto para actividad de agonista de HM74A.

A fin de determinar si los compuestos de HM74A presentan la respuesta de rubor asociada con ácido nicotínico, pueden ser dosificados a cobayos conscientes. Cobayos Dunkin Hartley machos (300-600 g; n=10-20 por grupo) se ponen en ayunas por lo menos por 12 horas, pero no en exceso de 24 horas antes de la experimentación. Se toman muestras de sangre de pre-estudio (0.5 ml) de cada animal por punción cardiaca bajo anaestesia de recuperación (Isoflurane 3.5% con additional 02 (1 Umin)). Las mediciones de la temperatura de la oreja se toman colocando la oreja izquierda de cada animal sobre una sonda de temperatura de infrarrojo. Las mediciones se toman a intervalos de un minuto desde 5 minutos pre-dosis hasta 30 minutos post-dosis. Las mediciones de temperatura se toman después a intervalos de 15 minutos hasta 2 horas post-dosis. Los animales reciben compuestos de

prueba por alimentación forzada oral (5 ml/kg). Se toman muestras de sangre (0.5 ml) por punción cardiaca bajo anestesia terminal. Las muestras de sangre se toman de animales individuales para proveer datos a 0.5, 1, 2, 3 y 4 horas post-dosis. Todas las muestras de sangre se colocan en un rollo de sangre durante 5 minutos, después se almacenan sobre hielo hasta el final del estudio. Después de la centrifugación (12000 g durante 5 min) el plasma es transferido a tubos frescos y almacenado a -20°C hasta que se prueba para concentraciones de NEFA.

Los compuestos de conformidad con la fórmula (I) han sido sintetizados (véase ejemplos de síntesis más adelante) y probados en las pruebas de unión a [^{35}S]-GTPyS anteriormente descritos.

Algunos compuestos de conformidad con la fórmula (I) incluyendo:

3-butil-8-cloro-1-[3-(dimetilamino)propil]-3,7-dihidro-1H-purino-2,6-diona;

8-cloro-3-(3,3-dimetilbutil)-1-[2-(etiloxi)etil]-3,7-dihidro-1H-purino-2,6-diona;

3-butil-8-cloro-1-[3-(5-fenil-1,2,4-oxadiazol-3-il)propil]-3,7-dihidro-1H-purino-2,6-diona;

1-[3-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)propil]-1H- afto[2,3-d]triazolo-4,9-diona;

Acetato de 2-({4-[3-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)propil]fenil}oxi)etilo,

Tienen utilidad como intermediarios en la producción de otros compuestos de conformidad con la fórmula (I).

Los compuestos ilustrados (ejemplos 1 - 894) tienen una pEC50 de 4.3 (+/- 0.3 unidad log) o mayor y una eficacia de 30% o mayor (en relación con el ácido nicotínico) en las pruebas de unión a [^{35}S]-GTPγS descritas anteriormente, en las cuales se probaron.

Los siguientes compuestos se probaron y se encontró que tenían actividad más baja que uns pEC50 de 4.3 (+/- 0.3 unidad log) y una eficacia de menos de 30% (en relación con el ácido nicotínico) en las pruebas de unión a [^{35}S]-GTPγS descritas anteriormente, en las cuales se probaron.

8-cloro-1-(3-{3-[(2,4-difluorofenil)metil]-1,2,4-oxadiazol-5-il}propil)-3-[2-(1-piperidinil)etil]-3,7-dihidro-1H-purino-2,6-diona;

8-cloro-1-(3-{3-[(2,4-difluorofenil)metil]-1,2,4-oxadiazol-5-il}propil)-3-[2-(hexahidro-1H-azepin-1-il)etil]-3,7-dihidro-1H-purino-2,6-diona;

8-cloro-1-(3-{3-[(2,4-difluorofenil)metil]-1,2,4-oxadiazol-5-il}propil)-3-[2-(1-pirrolidinil)etil]-3,7-dihidro-1H-purino-2,6-diona;

8-cloro-1-(3-{3-[(2,4-difluorofenil)metil]-1,2,4-oxadiazol-5-il}propil)-3-[2-(dimetilamino)-2-metilpropil]-3,7-dihidro-1H-purino-2,6-diona;

8-cloro-1-(3-{3-[(2,4-difluorofenil)metil]-1,2,4-oxadiazol-5-il}propil)-3-[3-(dimetilamino)propil]-3,7-dihidro-1H-purino-2,6-diona;

8-cloro-1-(3-{3-[(2,4-difluorofenil)metil]-1,2,4-oxadiazol-5-il}propil)-3-[3-(4-metil-1-piperazinil)propil]-3,7-dihidro-1H-purino-2,6-diona;

8-cloro-1-(3-{3-[(2,4-difluorofenil)metil]-1,2,4-oxadiazol-5-

il}propil)-3-[2-(dimetilamino)etil]-3,7-dihidro-1H-purino-2,6-diona.

Métodos de purificación y analíticos generales:

CL/EM: Método

CLAR analítico se condujo sobre una columna de Supelcosil™ ABZ+PLUS (Supelco) (3 µm, 3.3 cm x 4.6 mm de DI) eluyendo con 0.1% de HCO_2H y 0.01 M de acetato de amonio en agua (solvente A), y 95% de MeCN y 5%de agua (que contenía 0.5% de HCO_2H) (solvente B), usando el siguiente gradiente de elución 0-0.7 min 0% de B, 0.7-4.2 min 0→100% de B, 4.2-4.6 minutos 100% de B, 4.6-4.8 min 100→0% de B a una velocidad de flujo de 3 ml/min. La detección de UV por disposición de diodos se llevó a cabo en el intervalo de 215 a 330 nm. Los espectros de masa (EM) se registraron en un espectrómetro de masa Waters ZQ usando los modos de ionización positiva por electroaspersión [(EA+ve para dar iones moleculares de MH+ y $M(NH4)^+$] o ionización negativa por electroaspersión [(EA-ve para dar dar iones moleculares de $(M-H)^-$]. Sólo el ion progenitor de isótopos mayores se anotó.

Los espectros de ^1H RMN se registraron usando un espectrómetro Bruker DPX 400MHz usando tetrametilsilano com el estándar.

Cromatografía de Biotage™ se refiere a purificación llevada a cabo usando ya sea los sistemas de purificación Flash 40i o Flash 150i, vendidos por Biotage AB, usando cartuchos preempacados con KPSil (sílice).

El sistema Companion™ se refiere al sistema de purificación Teledyne Isco Combiflash Companion™. Este es un sistema de purificación

controlado por un gradiente con detección de UV integral, detección de UV de longitud de onda variable con la capacidad para activar la recolección de fracción automatizada por umbral de UV.

La autopreparación dirigida a la masa (MDAP) se refiere a métodos en donde el material se purificó por cromatografía de líquidos de alto rendimiento usando ya sea una columna Supelcosil ABZ+ 5 µm (10 cm x 20 mm de d.i.) o una coluna Supelcosil ABZ+ 10 µm (15 cm x 30 mm de d.i.) con un gradiente adecuado de solvente A: 0.1% de HCO_2H en agua y solvente B: 95% de MeCN, 5% de agua (que contenía 0.5% de HCO_2H). El inyector/recolector Waters 2767 fue activado por un espectrómetro de masa MicroMass ZQ en la detección de la masa de interés (usando software Micromass MassLynx).

CLAR preparativa (CLAR de autopreparación o Autoprep) se refiere a métodos en donde el material fue purificado por cromatografía de líquidos de alto rendimiento en una columna Supelcosil ABZ+ 5 µm (10 cm x 21.2 mm de d.i.) con un gradiente adecuado de 0.1% de HCO_2H en agua y MeCN (con 0.5% de HCO_2H). El colector de fracción Gilson 233 fue activado por detección de UV.

SPE (extracción de fase sólida) se refiere al uso de cartuchos de polietileno que se preempacan con absorbente usado para purificación. El absorbente contenido en estos cartuchos será especificado. Ejemplos usados se detallan más adelante: C18 SPE se refiere al uso de cartuchos preempacados con 40 µM de absorbente de sílice funcionarizado con C18

(vendido por Varian Inc.). El compuesto se cargó, típicamente en 50:50 de DMSO / MeOH, sobre un cartucho previoamente acondicionado con MeCN y equilibrado con 5% de MeCN en agua. El producto se eluyó con un gradiente adecuado de 0.1% de HCO_2H en agua y MeCN (0.5% de HCO_2H).

SPE o columna de aminopropilo se refiere al uso de cartuchos preempacados con 40 µm-120 µm de sílice funcionarizada con aminopropilo (vendido por Varian Inc.). El producto crudo es típicamente cargado en mezclas de DCM / MeOH sobre un cartucho previamente acondicionado con MeOH. Los componentes neutros se eluyeron con MeOH y/o DCM (3 ó 4 volúmenes de columna) y los componentes ácidos usualmente eluidos con un eluyente que contenía una proporción de AcOH (2-20%).

Cartuchos Oasis™ / SPE's Oasis™ se refieren a cartuchos de SPE empacados con un absorbente polimérico fabricado por Waters Corporation. Estos son típicamente acondicionados con 3 volúmenes de columna de MeOH y equilibrados con agua antes de cargar la muestra. Sales y compuestos inorgánicos se eluyen con agua y el producto típicamente se eluye con MeOH o MeCN.

GreenHouse™ se refiere a una plataforma de sintetizador paralelo de reacción 24 disponible de RDT Ltd, R.U. Como se indicó antes, los compuestos de la fórmula (I) pueden encontrar uso en medicina humana o veterinaria, por ejemplo como activadores de HM74A, en el manejo de dislipidemia e hiperlipoproteinemia.

Por lo tanto, se provee como otra modalidad de la presente

invención por lo menos un compuesto de la fórmula (I) o un derivado farmacéuticamente aceptable del mismo, para usarse en medicina humana o veterinaria, por ejemplo en el tratamiento de trastornos del metabolismo de lípidos incluyendo dislipidemia e hiperlipoproteinemia tales como dislipidemia diabética y dislipidemia mixta, insuficiencia cardiaca, hpercolesteremia, enfermedad cardiovascular incluyendo aterosclerosis, arteriosclerosis e hipertrigliceridemia, diabetes mellitus de tipo II, diabetes de tipo I, resistencia a la insulina, hiperlipidemia, anorexia nerviosa y obesidad. Como tales, los compuestos también se proveen para usarse en el tratamiento de enfermedad de arteria coronaria, trombosis, angina, insuficiencia renal crónica, enfermedad vascular periférica y accidente vascular cerebral.

Se provee como una modalidad adicional de la presente invención por lo menos un compuesto de la fórmula (I) o un derivado farmacéuticamente aceptable del mismo, para usarse en la fabricación de un medicamento para el tratamiento de trastornos del metabolismo de lípidos incluyendo dislipidemia e hiperlipoproteinemia tal como dislipidemia diabética y dislipidemia mixta, insuficiencia cardiaca, hpercolesteremia, enfermedad cardiovascular incluyendo aterosclerosis, arteriosclerosis, e hipertrigliceridemia, diabetes mellitus de tipo II, diabetes de tipo I, resistencia a la insulina, hiperlipidemia, anorexia nerviosa, obesidad. Como tales, los compuestos también se proveen para usarse en el tratamiento de enfermedad de arteria coronaria, trombosis, angina, insuficiencia renal crónica, enfermedad vascular periférica y accidente vascular cerebral.

Se apreciará que las referencias aquí al tratamiento se extienden a profilaxis, prevención de recurrencia y supresión de síntomas así como el tratamiento de condiciones establecidas.

En una modalidad de la invención, se provee por lo menos un compuesto de la fórmula (I) o un derivado farmacéuticamente aceptable del mismo para usarse en el tratamiento de trastornos del metabolismo de lípidos incluyendo dislipidemia e hiperlipoproteinemia. Por ejemplo, se provee el uso de por lo menos un compuesto de la fórmula (I) o un derivado farmacéuticamente aceptable del mismo en el tratamiento de dislipidemia diabética, dislipidemia mixta, insuficiencia cardiaca, hpercolesteremia, diabetes mellitus de tipo II, diabetes de tipo I, resistencia a la insulina, hiperlipidemia, anorexia nerviosa, obesidad, enfermedad de arteria coronaria, trombosis, angina, insuficiencia renal crónica, accidente vascular cerebral y enfermedad cardiovascular incluyendo aterosclerosis, arteriosclerosis, e hipertrigliceridemia.

Cabe entender que esta modalidad de la presente invención incluye cualquier combinación de modalidades particulares y cubre todas las combinaciones de sustituyentes particulares descritas aquí antes para compuestos de la fórmula (I).

Además, la presente invención provee el uso de por lo menos un compuesto de la fórmula (I) o un derivado farmacéuticamente aceptable del mismo, en la fabricación de un medicamento para el tratamiento de enfermedades o condiciones inflamatorias de las articulaciones, por ejemplo,

artritis (v.gr., artritis reumatoide, osteoartritis, falla de articulación de prótesis), o del tracto gastrointestinal (v.gr., colitis ulcerativa, enfermedad de Crohn, y otras enfermedades intestinales inflamatorias y gastrointestinal, gastritis e inflamación de la mucosa que resulta de infección, la enteropatía provocada por fármacos antiinflamatorios no esteroideos), de los pulmones (v.gr., síndrome de sufrimiento respiratorio en adultos, asma, fibrosis cística, o enfermedad pulmonar obstructiva crónica), del corazón (v.gr., miocarditis), de tejido nervioso (v.gr., esclerosis múltiple), del páncreas, (v.gr., inflamación asociada con diabetes melitus y complicaciones de la misma, del riñón (v.gr., glomerulonefritis), de la piel (v.gr., dermatitis, psoriasis, eczema, urticaria, lesión por quemafura), de los ojos (v.gr., glaucoma) así como de ´+organos trasplantados (v.gr., rechazo) y enfermedades de órganos múltiples (v.gr., lupus eritematoso sistémico, sepsis) y secuelas inflamatorias de infecciones virales o bacterianas y condiciones inflamatorias asociadas con aterosclerosis y después de ataques hipóxicos o isquémicos (con o sin reperfusión), por ejemplo en el cerebro o en enfermedad cardiaca isquémica.

En modalidades adicionales o alternativas, se provee un método para el tratamiento de un sujeto humano o animal con una condición en donde la sub-activación del receptor de HM74A contribuye a la condición o en donde la activación del receptor será benéfica, dicho método comprende administrar a dicho sujeto humano o animal una cantidad efectiva de por lo menos un compuesto de la fórmula (I) o un derivado farmacéuticamente aceptable del mismo.

Nuevamente, cabe entender que esta modalidad de la presente invención incluye cualquier combinación de modalidades particulares y cubre todas las combinaciones de sustituyentes particulares descritas aquí antes para compuestos de la fórmula (I).

En una modalidad, la presente invención provee un método para el tratamiento de trastornos de metabolismo de lípidos incluyendo dislipidemia e hiperlipoproteinemia tal como dislipidemia diabética y dislipidemia mixta, insuficiencia cardiaca, hpercolesteremia, enfermedad cardiovascular incluyendo aterosclerosis, arteriosclerosis e hipertrigliceridemia, diabetes mellitus de tipo II, diabetes de tipo I, resistencia a la insulina, hiperlipidemia, anorexia nerviosa y obesidad, dicho método comprende administrar a dicho sujeto humano o animal una cantidad efectiva de por lo menos un compuesto de la fórmula (I) o un derivado farmacéuticamente aceptable del mismo. Como tales, estos compuestos también pueden encontrar utilidad en métodos para el tratamiento de enfermedad de arteria coronaria, trombosis, angina, insuficiencia renal crónica, enfermedad vascular periférica y accidente vascular cerebral, dichos métodos comprenden administrar a dicho sujeto humano o animal una cantidad efectiva de por lo menos un compuesto de la fórmula (I) o un derivado farmacéuticamente aceptable del mismo.

La cantidad de un compuesto de la fórmula (I) o un derivado farmacéuticamente aceptable del mismo que se requiere para lograr el efecto biológico deseado, desde luego, dependerá de un número de factores, por ejemplo, el modo de administración y la condición clínica precisa del receptor.

En general, la dosis diaria estará en el intervalo de 0.1 mg - 1 g/kg, típicamente 0.1 – 100 mg/kg. Una dosis intravenosa puede estar, por ejemplo, en el intervalo de 0.01 mg a 0.1 g/kg, típicamente 0.01 mg a 10 mg/kg, que se puede administrar convenientemente como una infusión de 0.1 µg a 1 mg, por minuto. Los fluidos de infusión adecuados para este propósito pueden contener, por ejemplo, de 0.01 µg a 0.1 mg, por mililitro. Las dosis unitarias pueden contener, por ejemplo, de 0.01 µg a 1 g de un compuesto de la invención. Por lo tanto, las ampolletas para inyección pueden contener, por ejemplo, de 0.01 µg a 0.1 g y formulaciones de dosis unitaria administrables por vía oral, tales como tabletas o cápsulas, pueden contener, por ejemplo, de 0.1 mg a 1 g, por ejemplo de 5 mg a 50 mg.

Un compuesto de la fórmula (I) o un derivado farmacéuticamente aceptable del mismo se puede utilizar como el compuesto *per se* en el tratamiento de una enfermedad en donde la sub-activación del receptor de HM74A contribuye a la enfermedad o en donde la activación del receptor será benéfica, un ejemplo de esto es en donde un compuesto de la presente invención se presenta con un vehículo aceptable en forma de una formulación farmacéutica. El vehículo, desde luego, debe ser aceptable en el sentido de ser compatible con los otros ingredientes de la formulación y no deben ser deletéreos para el receptor. El vehículo puede ser un sólido o un líquido, o ambos, y se puede formular con el compuesto de la invención como una formulación de dosis unitaria, por ejemplo, una tableta, que puede contener de 0.05% a 95% en peso del compuesto de la invención.

Las formulaciones incluyen aquellas adecuadas para administración oral, rectal, tópica, bucal (v.gr., sub-lingual) y parenteral (v.gr., subcutánea, intramuscular, intradérmica o intravenosa).

También se provee, de conformidad con la invención, un procedimiento para la preparación de dicha composición farmacéutica que comprende mezclar los ingredientes.

Las formulaciones adecuadas para administración oral se pueden presentar en unidades discretas, tales como cápsulas, cachets, pastillas o tabletas, cada una conteniendo una cantidad predeterminadade un compuesto de la fórmula (I) o un derivado farmacéuticamente aceptable del mismo; como un polvo o gránulos; como una solución o una suspension en un líquido acuoso o no acuoso; o como una emulsión de aceite en agua o agua en aceite. En general, las formulaciones se preparan mezclando uniformemente e íntimamente el compuesto de la fórmula (I) o un derivado farmacéuticamente aceptable del mismo, con un vehículo líquido o sólido finamente dividido, o ambos, y después, si es becesario, configurar el producto. Por ejemplo, una tableta se puede preparar comprimiendo o moldeando un polvo o gránulos del compuesto de la fórmula (I) o un derivado farmacéuticamente aceptable del mismo opcionalmente con uno o más ingredientes accesorios. Las tabletas comprimidas se pueden preparar comprimiendo, en una máquina adecuada, el compuesto en una forma de flujo libre, tal como un polvo o gránulos opcionalmente mezclado con un aglutinante, lubricante, diluyente inerte y/o agente(s) activo de

360

superficie/dispersante. Las tabletas moldeadas se pueden hacer moldeando, en una máquina adecuada, el compuesto en polvo humedecido con un diluyente líquido inerte.

Las tabletas y cápsulas para administración oral pueden contener excipientes convencionales tales como agentes aglutinantes, por ejemplo jarabe, acacia, gelatina, sorbitol, tragacanto, mucílago de almidón o polivinilpirrolidona; llenadores, por ejemplo, lactosa, celulosa microcristalina, azúcar, almidón de maíz, fosfato de calcio o sorbitol; lubricantes, por ejemplo, estearato de magnesio, ácido esteárico, talco, poletilenoglicol o sílice; disintegradores, por ejemplo, almidón de papa, croscarmelosa sódica o glicolato de almidón-sodio; o agentes humectantes tales como laurilsulfato de sodio. Las tabletas pueden ser revestidas de conformidad con métodos bien conocidos en la técnica. Las preparaciones líquidas orales pueden estar en forma de, por ejemplo, suspensiones, soluciones, emulsiones, jarabes o elíxires acuosos u oleosos, o pueden presentarse como un producto seco para constitución con agua u otro vehículo adecuado antes de usarse. Dichas preparaciones líquidas pueden contener aditivos convencionales tales como agentes de suspensión, por ejemplo, jarabe de sorbitol, metilcelulosa, jarabe de glucosa/azúcar, gelatina, hidroximetilcelulosa, hidroxipropilmetilcelulosa, carboximetilcelulosa, gel de estearato de aluminio o grasas comestibles hidrogenadas; agentes emulsionantes, por ejemplo, lecitina, mono-oleato de sorbitán o acacia; vehículos no acuosos (que pueden incluir aceites comestibles), por ejemplo, aceite de almendra, aceite de coco fraccionado,

ésteres oleosos, propilenglicol o alcohol etílico; o conservadores, por ejemplo, p-hidroxibenzoatos de metilo o propilo o ácido sórbico. Las preparaciones también pueden contener sales reguladoras de pH, saborizantes, colorantes y/o agentes edulcorantes (v.gr., manitol) según sea apropiado.

Las formulaciones adeuadas para administración bucal (sub-lingual) incluyen trociscos que comprenden un compuesto de la invención en una base de sabor, usualmente sacarosa y acacia o tragacanto, y pastillas que comprenden el compuesto de la invención en una base inerte tal como gelatina y glicerina o sacarosa y acacia.

Las formulaciones de la presente invención adecuadas para administración parenteral convenientemente comprenden preparaciones acuosas estériles de un compuesto de la fórmula (I) o un derivado farmacéuticamente aceptable del mismo, la formulación puede ser isotónica con la sangre del receptor que lo requiera. Estas preparaciones se podrían administrar por vía intravenosa, aunque la administración también se puede efectuar por medio de inyección subcutánea, intramuscular o intradérmica. Dichas preparaciones se pueden preparar convenientemente mezclando el compuesto de la fórmula (I) o un derivado farmacéuticamente aceptable del mismo con agua haciendo la solución resultante estéril e isotónica con la sangre. Las composiciones inyectables de conformidad con la invención generalmente contendrán de 0.1 a 5% p/p del compuesto de la fórmula (I) o un derivado farmacéuticamente aceptable del mismo.

Por lo tanto, las formulaciones de la presente invención

adecuadas para administración parenteral que comprenden un compuesto de la fórmula (I) o un derivado farmacéuticamente aceptable del mismo se pueden formular para administración parenteral por inyección de bolo o infusión continua y se pueden presentar en una forma de dosis unitaria, por ejemplo como ampolletas, frascos, infusiones de volumen pequeño o jeringas pre-llenadas, o en contenedores de dosis múltiples con un conservador añadido. Las composiciones pueden adoptar formas tales como soluciones, suspensiones o emulsiones en vehículos acuosos o no acuosos, y pueden contener agentes de formulación tales como anti-oxidantes, reguladores de pH, agentes antimicrobianos y/o agentes ajustadores de toxicidad. Ejemplos de las formulaciones adecuadas para administración oral incluyen formulaciones que comprenden un compuesto de la fórmula (I) o un derivado farmacéuticamente aceptable del mismo, en 10% de DMSO y 90% de bicarbonato de sodio en solución salina estéril. Ejemplos de las formulaciones adecuadas para administración intravenosa incluyen formulaciones que comprenden un compuesto de la fórmula (I) o un derivado farmacéuticamente aceptable del mismo, en 5% o 10% de DMSO y 95% ó 90% de bicarbonato de sodio en agua estéril. Alternativamente, el agente terapéuticalmente activo puede estar en forma de polvo para constitución con un vehículo adecuado, v.gr., agua estéril libre de pirógenos, antes de usarse. La presentación sólida seca se puede preparar llenando con un polvo estéril asépticamente contenedores estériles individuales o llenado con solución estéril asépticamente cada contenedor y secado por congelamiento.

Las formulaciones adecuadas para administración rectal se pueden presentar como supositorios de dosis unitaria. Estas se pueden preparar mezclando un compuesto de la fórmula (I) o un derivado farmacéuticamente aceptable del mismo con uno o más vehículos sólidos convencionales, por ejemplo, manteca de cacao o glicéridos y después configurando la mezcla resultante.

Las formulaciones adecuadas para aplicación tópica a la piel pueden adoptar la forma de una pomada, crema, loción, pasta, gel, aspersión, aerosol o aceite. Los vehículos que se pueden usar incluyen vaselina, lanolina, poletilenglicoles, alcoholes y combinaciones de dos o más de los mismos. El compuesto de la fórmula (I) o un derivado farmacéuticamente aceptable del mismo está generalmente presente a una concentración de 0.1 a 15% p/p de la composición, por ejemplo, de 0.5 a 2%.

Por administración tópica, como se usa aquí, los inventores de la presente incluyen administración por insuflación e inhalation. Ejemplos de varios tipos de preparación para administración tópica incluyen pomadas, cremas, lociones, polvos, pesarios, aspersiones, aerosoles, cápsulas o cartuchos para usarse en un inhalador o insuflador o gotas (v.gr., gotas para los ojos o para la nariz).

Las pomadas y cremas se pueden formular, por ejemplo, con una base acuosa u oleosa con la adición de agentes y/o solventes espesante y/o gelificante y/o solventes adecuados. Dichas bases por lo tanto pueden incluir, por ejemplo, agua y/o un aceite tal como parafina líquida o un aceite

vegetal tal como aceite de araquis o aceite de ricino o un solvente tal como un polietilenglicol. Los agentes espesantes que se pueden usar incluyen parafina blanda, estearato de aluminio, alcohol cetoestearílico, polietilenglicoles, cera microcristalina y cera de abeja.

Las lociones se pueden formular con una base acuosa u oleosa y en general también contienen uno o más agentes emulsionantes, agentes estabilizadores, agentes dispersantes, agentes de dispersión o agentes espesantes.

Los polvos para aplicación externa se pueden formar con la ayuda de cualquier nase de polvo adecuada, por ejemplo, talco, lactosa o almidón. Las gotas se pueden formular con una base acuosa o no acuosa también que comprenden uno o más agentes dispersantes, agentes solubilizantes o agentes de suspensión.

Las composiciones de aspersión se pueden formular, por ejemplo, como soluciones o suspensiones acuosas o como aerosoles suministrados desde envases presurizados, con el uso de un propelente adecuado, v.gr., diclorodifluorometano, triclorofluorometano, diclorotetrafluoroetano, 1,1,1,2,3,3,3-heptafluoropropano, 1,1,1,2-tetrafluoretano, dióxido de carbono u otro gas adecuado.

Se pueden formular cápsulas y cartuchos para usarse en un inhalador o insuflador, de por ejemplo gelatina, que contengan una mezcla de polvo de un compuesto de la invención y una base de polvo adecuada tal como lactosa o almidón.

Las composiciones farmacéuticas de conformidad con la invención también se pueden usar en combinación con otros agentes terapéuticos, por ejemplo en combinación con otras clases de fármacos dislipidémicos (v.gr., estatinas, fibratos, resinas de unión de ácido biliar o ácido nicotínico).

Los compuestos de la presente invención se pueden usar en combinación con uno o más de otros agentes terapéuticamente activos, por ejemplo, en combinación con otras clases de fármacos dislipidémicos, v.gr., inhibidores de 3-hidroxi-3-metilglutaril-coenzima A reductasa (estatinas) o fibratos o resinas de unión a ácido biliar, o ácido nicotínico. La invención por lo tanto provee, en una modalidad adicional, el uso de ducha combinación en el tratamiento de enfermedades en donde la sub-activación del receptor de HM74A contribuye a la enfermedad o en donde la activación del receptor será benéfica y el uso de por lo menos un compuesto de la fórmula (I) o un derivado farmacéuticamente aceptable del mismo en la fabricación de un medicamento para la terapia de combinación de trastornos de metabolismo de lípidos incluyendo dislipidemia e hiperlipoproteinemia tal como dislipidemia diabética y dislipidemia mixta, insuficiencia cardiaca, hpercolesteremia, enfermedad cardiovascular incluyendo aterosclerosis, arteriosclerosis, e hipertrigliceridemia, diabetes mellitus de tipo II, diabetes de tipo I, resistencia a la insulina, hiperlipidemia, anorexia nerviosa y obesidad.

Cuando los compuestos de la presente invención se usan en combinación con otros agentes terapéuticamente activos, los compuestos se

pueden administrar ya sea juntos o por separado, secuencialmente o simultáneamente por cualquier vía conveniente.

Las combinaciones referidas anteriormente se pueden presentar convenientemente para usarse en forma de una formulación farmacéutica y por lo tanto formulaciones farmacéuticas que comprenden una combinación como se definió antes opcionalmente junto con un vehículo o excipiente farmacéuticamente aceptable comprenden una modalidad adicional de la invención. Los componentes individuales de dichas combinaciones se pueden administrar ya sea juntos o por separado, secuencialmente o simultáneamente en formulaciones farmacéuticas separadas o combinadas.

Cuando se combinan en la misma formulación, se apreciará que los dos componentes deben ser estables y compatibles unos con otros y los otros componentes de la formulación y se pueden formular para administración. Cuando se formulan por separado, se pueden proveer en cualquier formulación conveniente, convenientemente de la manera como es conocida para dichos compuestos en la técnica.

Cuando en combinación con un segundo agente terapéutico activo contra la misma enfermedad, la dose de cada componente puede diferir de aquella cuando el compuesto se usa solo. Las dosis apropiadas serán fácilmente apreciadas por los expertos en la técnica.

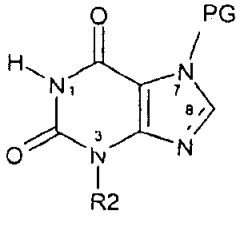
La invención por lo tanto provee, en una modalidad adicional, una combinación que comprende por lo menos un compuesto de la fórmula (I) o un derivado farmacéuticamente aceptable del mismo junto con otro agente

terapéuticamente activo.

La combinación referida anteriormente se puede presentar convenientemente para usarse en forma de una formulación farmacéutica y por lo tanto formulaciones farmacéuticas que comprenden una combinación como se definió antes junto con un vehículo farmacéuticamente aceptable del mismo representa una modalidad adicional de la invención.

Los compuestos de la presente invención y derivados farmacéuticamente aceptables de los mismos se pueden preparar por la métodología descrita más adelante, que constituye una modalidad adicional de esta invención.

En una modalidad, la presente invención provee un método para la preparación de compuesto(s) de la fórmula (I) de un material de partida apropiado, por ejemplo compuesto(s) de la fórmula (II):



(II)

en donde PG = grupo protector, el método comprende:

(i) alquilación en N1 de una xantina N7 protegida;

(ii) alquilación en N3 de una xantina N7 protegida;

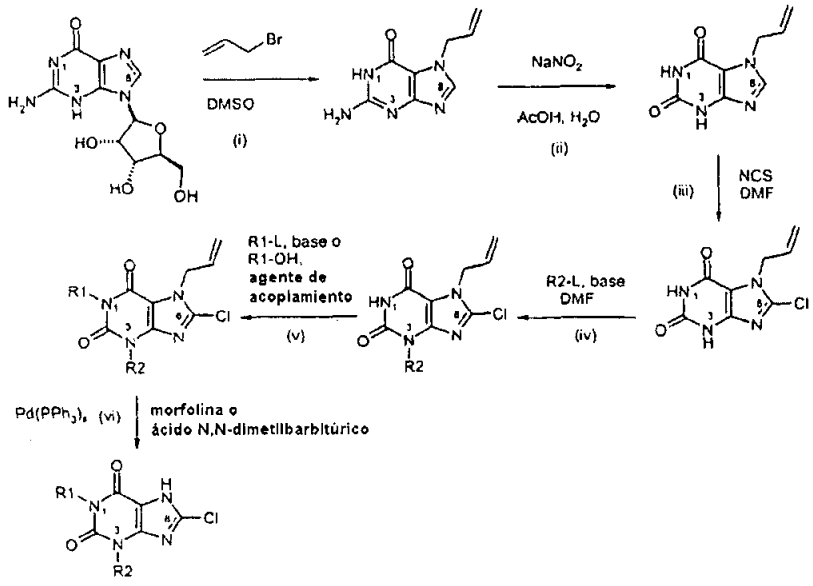
(iii) halogenación en C8; y

(iv) la desprotección de N7; en cualquier orden proveyendo desprotección se lleva a cabo después de la alquilación.

Procedimiento 1

Un procedimiento de conformidad con la invención para preparar un compuesto(s) de la fórmula (I) en el cual

R1 incorpora un cicloalquilo, heterociclilo, cicloalquenilo, heteroarilo o arilo.



i) Alquilación de guanina con bromuro de alilo

ii) Diazotización con nitrito de sodio seguido por hidrólisis para formar la xantina

iii) Cloración

iv) Alquilación en N3

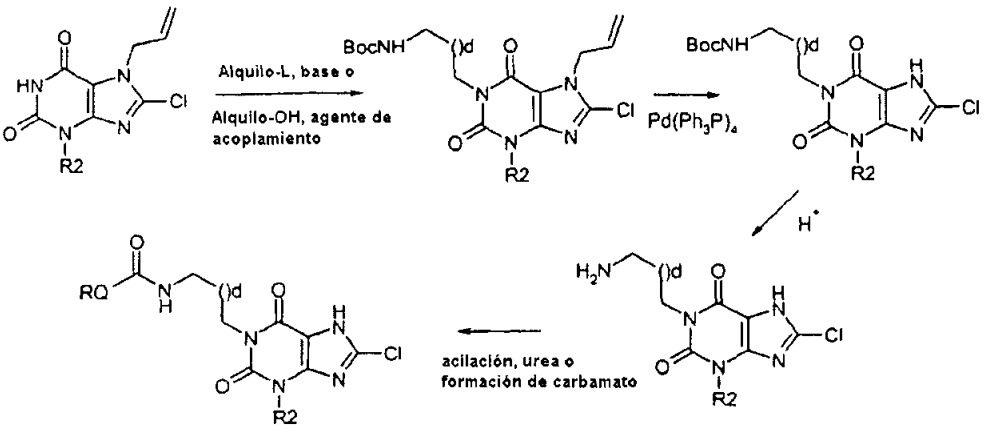
v) Alquilación en N1

vi) Remoción catalizada por paladio del grupo alilo

en donde L representa un grupo reesidual, por ejemplo, halógeno.

Procedimiento 2

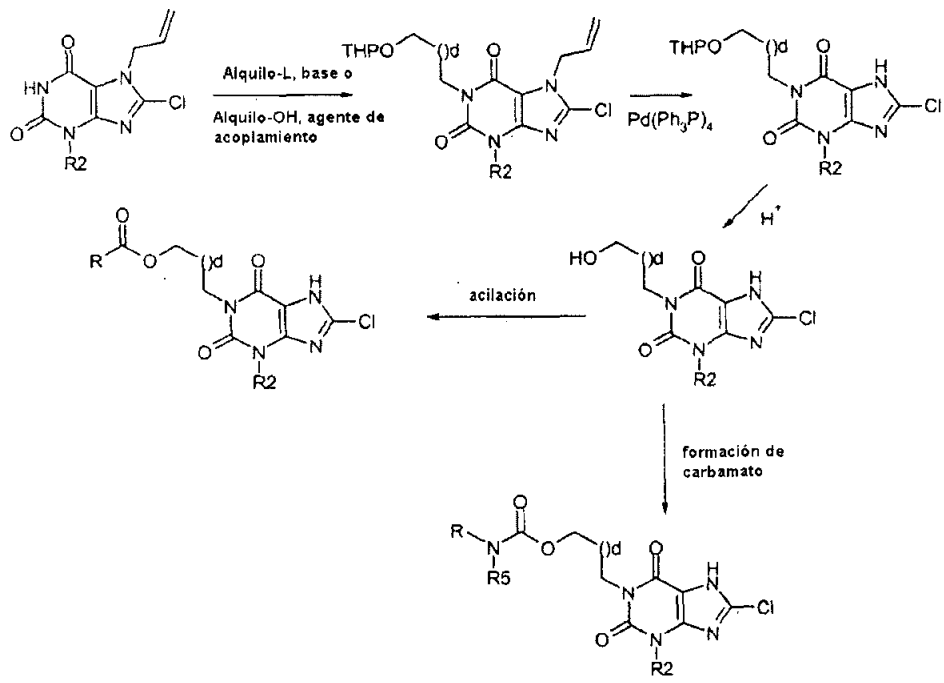
Un procedimiento de conformidad con la invención para preparar un compuesto(s) de la fórmula (I) en el cual R1 incorpora una amida, carbamato o urea



en donde L representa un grupo residual, por ejemplo, halógeno, d representa (m-1) (es decir, d junto con el methileno que le precede = m), R representa -(alquileno)$_n$-Y y Q puede o no estar presente, y si está presente representa ya sea O o NR5.

Procedimiento 3

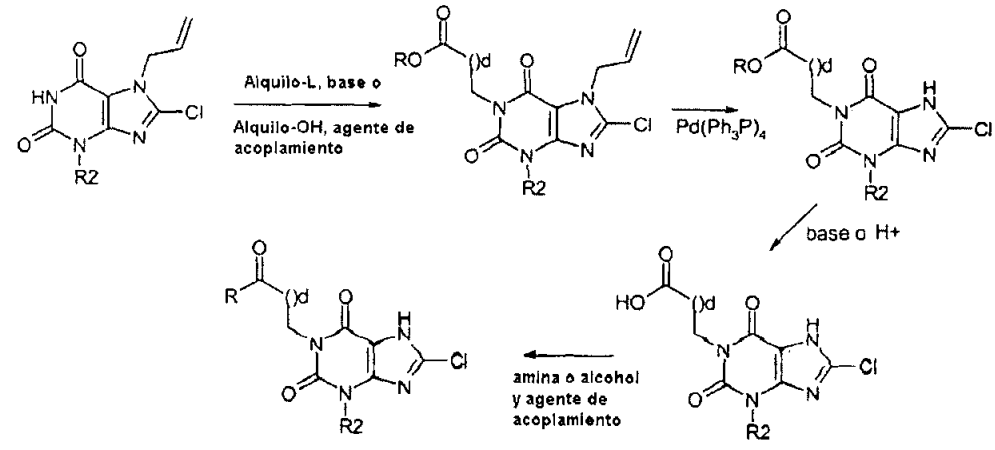
Un procedimiento de conformidad con la invención para preparar un compuesto(s) de la fórmula (I) en el cual R1 incorpora un carbamato o éster de "reversa"



en donde L representa un grupo residual, por ejemplo halógeno, d representa (m-1), y R representa -(alk)n-Y.

Procedimiento 4

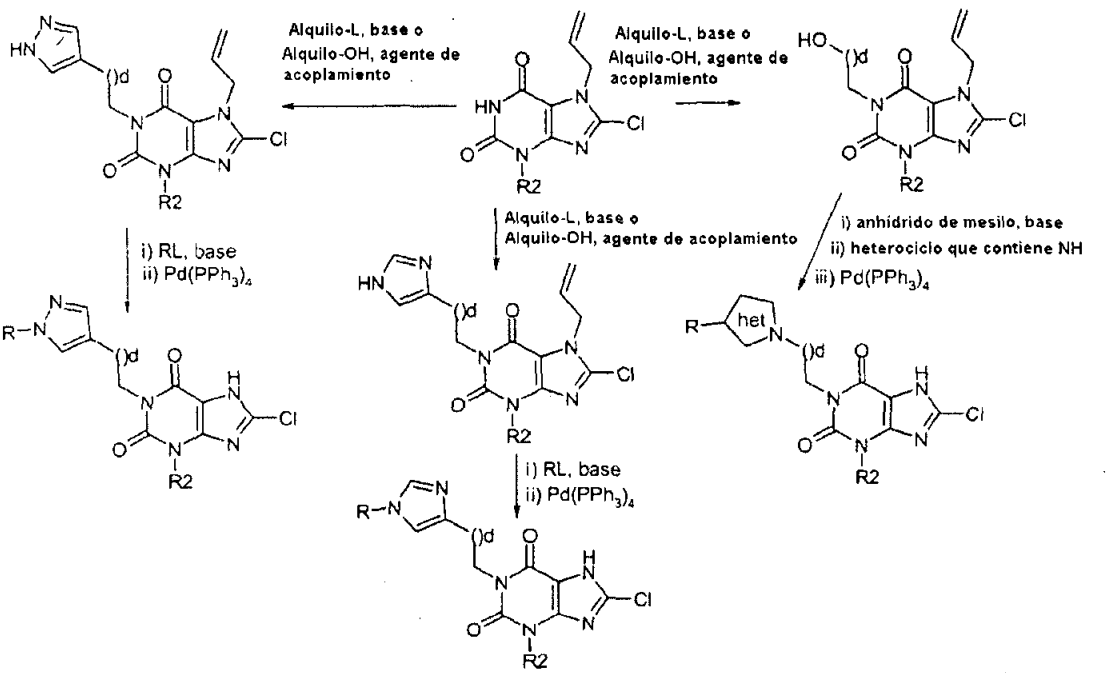
Un procedimiento de conformidad con la invención para preparar un compuesto(s) de la fórmula (I) en el cual R1 incorpora un éster o amida



en donde L representa un grupo residual, por ejemplo halógeno, d representa (m-1), y R representa -NR5R7 o -OR5.

Procedimiento 5

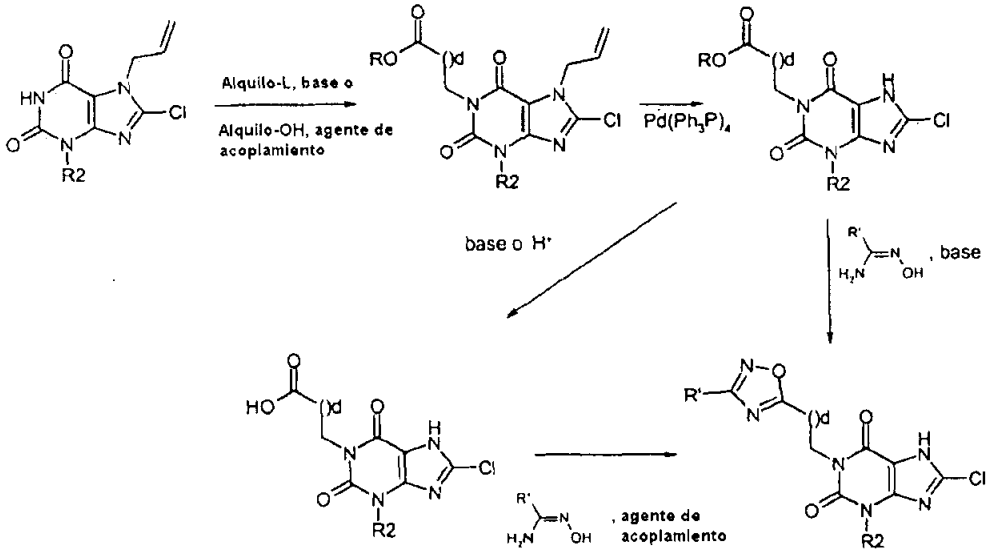
Un procedimiento de conformidad con la invención para preparar un compuesto(s) de la fórmula (I) en el cual R1 incorpora un pirazol, imidazol o tetrazol.



en donde L representa un grupo residual, por ejemplo halógeno, d representa (m-1), y R representa -$(alk)_n$-Y.

Procedimiento 6

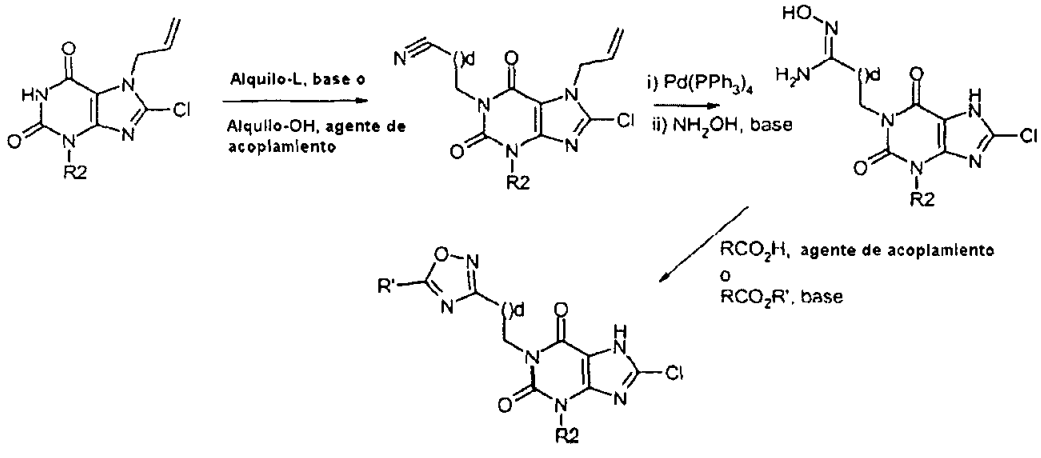
Un procedimiento de conformidad con la invención para preparar un compuesto(s) de la fórmula (I) en el cual R1 incorpora un oxadiazol.



en donde L representa un grupo residual, por ejemplo halógeno, d representa (m-1), R representa an alquilo grupo y R' representa -$(alk)_n$-Y.

Procedimiento 7

Un procedimiento de conformidad con la invención para preparar un compuesto(s) de la fórmula (I) en el cual R1 incorpora un oxadiazol

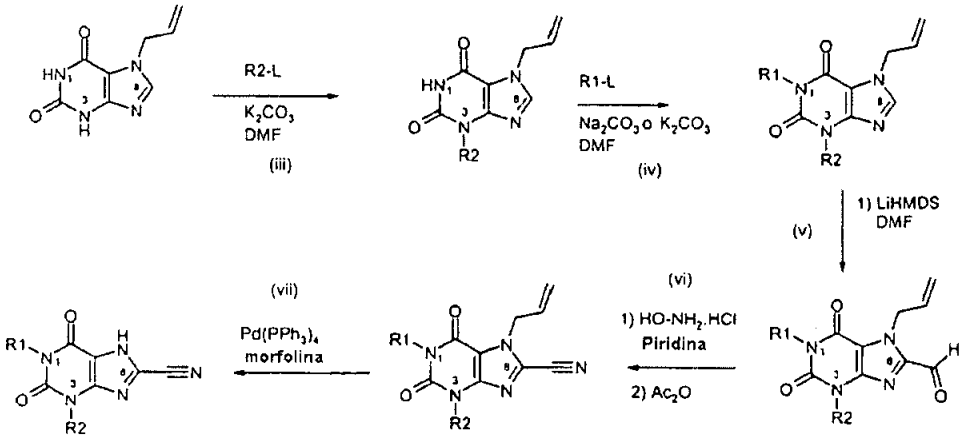


en donde L representa un grupo residual, por ejemplo halógeno,

d representa (m-1), R representa an alquilo grupo y R' representa -$(alk)_n$-Y.

Procedimiento 8

Un procedimiento de conformidad con la invención para preparar un compuesto(s) de la fórmula (I) en el cual R^3 es CN comprende los pasos (i) y (ii) del procedimiento 1 seguido por:



iii) Alquilación en N3

iv) Alquilación en N1

v) Formación de aldehído en C8 por litiación con LiHMDS y extinción con DMF

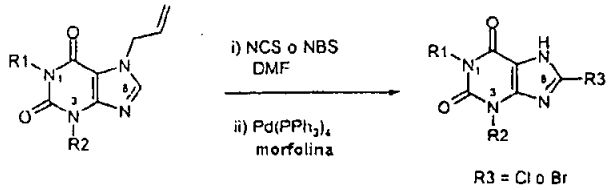
vi) Conversion del aldehído al nitrilo

vii) Remoción catalizada por paladio del grupo alilo

en donde L representa un grupo residual.

Procedimiento 9

Un procedimiento de conformidad con la invención para preparar un compuesto(s) de la fórmula (I) en el cual R^3 es Cl o Br comprende los pasos (i) a (iv) del procedimiento 8 seguido por:

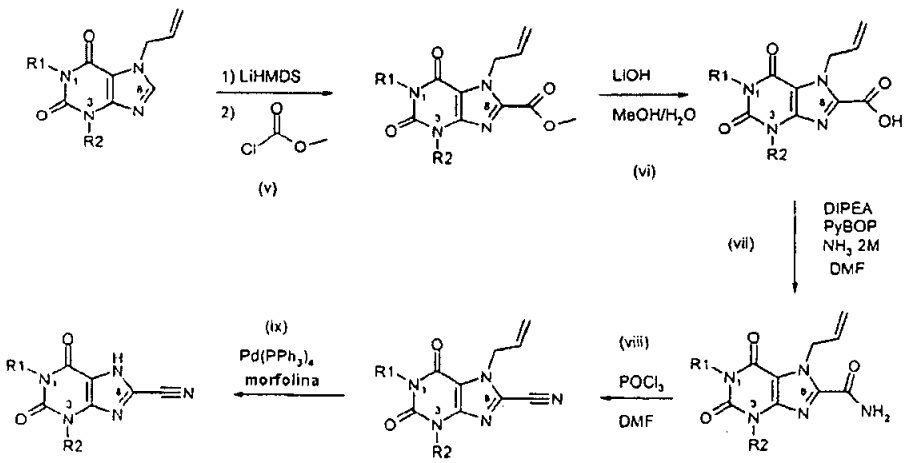


i) Halogenación en C8 usando NCS o NBS

ii) Remoción catalizada por paladio del grupo alilo

Procedimiento 10

Un procedimiento de conformidad con la invención para preparar un compuesto(s) de la fórmula (I) en el cual R^3 es CN comprende los pasos (i) a (iv) del procedimiento 8 seguido por:



v) Formación de éster

vi) Hidrólisis del éster metílico

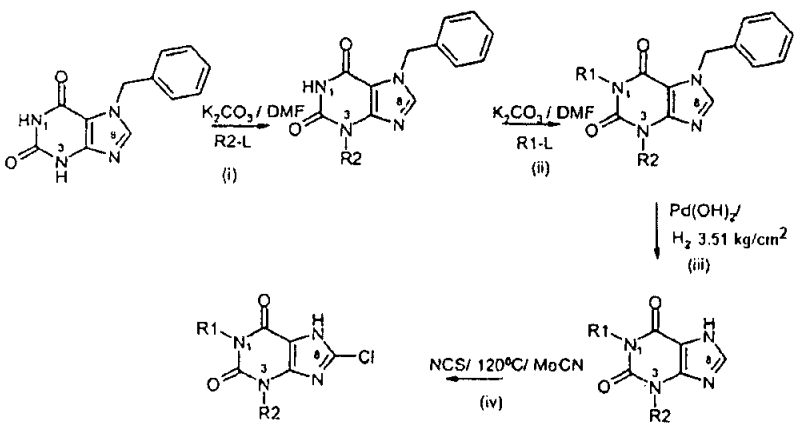
vii) Conversión del ácido a la amida.

viii) Conversión de la amida al nitrito

ix) Remoción catalizada por paladio del grupo alilo

Procedimiento 11

Un procedimiento de conformidad con la invención para preparar un compuesto(s) de la fórmula (I) en el cual R^3 es Cl comprende:



i) Alquilación en N3

ii) Alquilación en N1

iii) Debencilación

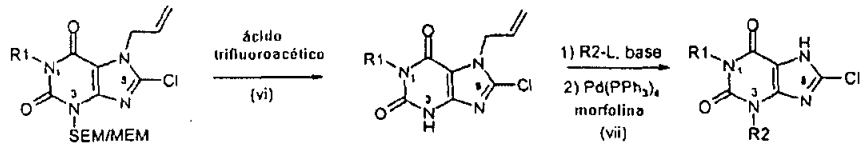
iii) Clorinación en C8

en donde L representa un grupo residual

Procedimiento 12

Un procedimiento de conformidad con la invención para preparar un compuesto(s) de la fórmula (I) en el cual R^1 difiere de R^2 y R^3 es Cl

comprende los pasos (i) a (v) del procedimiento 1 (en donde R2 del procedimiento 1 es específicamente SEM o MEM) seguido por:



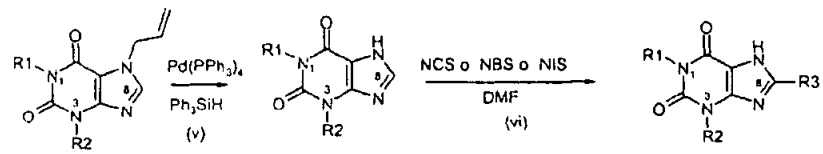
vi) Escisión de grupo protector de MEM o SEM

vii) Alquilación de N3 seguido por remoción catalizada por paladio del grupo alilo

en donde L representa un grupo residual

Procedimiento 13

Un procedimiento de conformidad con la invención para preparar un compuesto(s) de la fórmula (I) en el cual R^3 es Cl, Br o I comprende los pasos (i) a (iv) del procedimiento 8 seguido por:

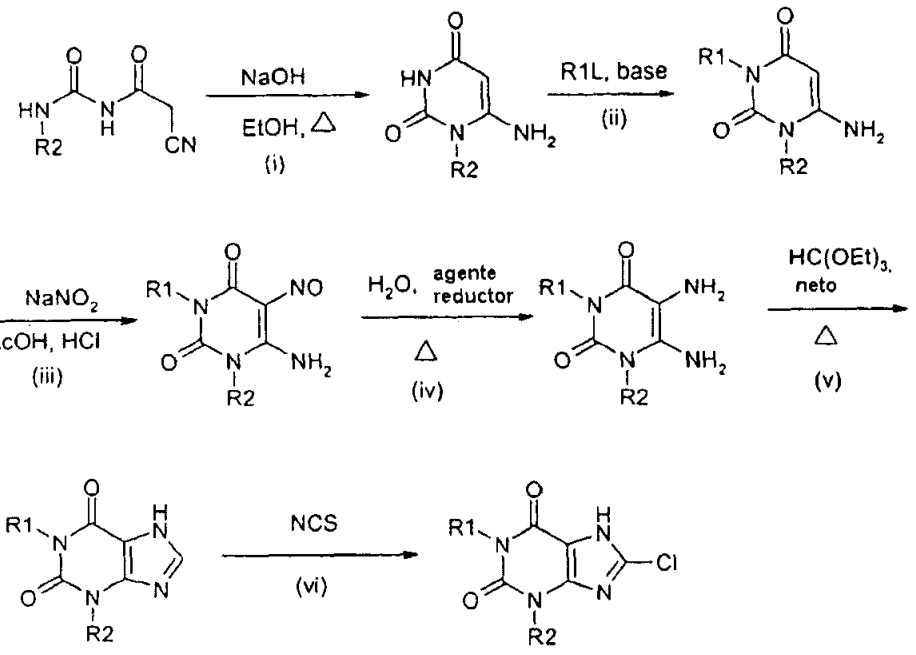


v) Remoción catalizada por paladio de allilo grupo

vi) Halogenación en C8 usando NCS, NBS o NIS

Procedimiento 14

Un procedimiento de conformidad con la invención para preparar compuesto(s) de la fórmula (I) comprende:



i) Formación de pirimidinodiona

ii) Alquilación en N1

iii) Nitrosación

iv) Reducción usando $Na_2S_2O_4$ o un agente reductor similar

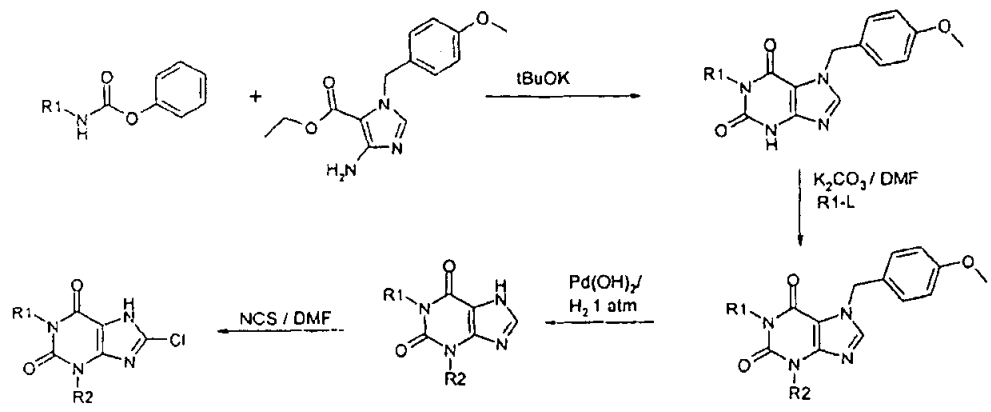
v) Formación de xantina

vi) Halogenación en C8 usando NCS

en donde L representa un grupo residual

Procedimiento 15

Un procedimiento de conformidad con la invención para preparar compuesto(s) de la fórmula (I):



en donde L representa un grupo residual.

Como un paso adicional a los procedimientos generales anteriormente descritos, y en particular para usarse en la preparación de los siguientes ejemplos, hay varias formas de purificación de los compuestos resultantes, uno o más de los cuales puede usarse en la presente invención, por ejemplo el uso de MDAP, por recristalización de uno o más solvents adecuados tales como acetato de etilo, etanol absoluto, acetonitrilo o metanol, o mediante el uso de columna de purificación tal como cartuchos Silica Redisep y elusión subsecuente con un solvente adecuado tal como diclorometano que contiene acetato de etilo.

En donde se desea o es necesario, como una etapa final en cualquiera de los procedimientos de síntesis anteriores, un compuesto resultante de la fórmula (I) puede ser convertido a una forma de sal farmacéuticamente aceptable o viceversa o convirtiendo una forma de sal a otra forma de sal farmacéuticamente aceptable.

Abreviaturas

AcOH	Acido acético
Atm	Atmósfera
br	Banda ancha (RMN)
CDI	Carbonildiimidazol
d	Doblete (RMN)
DBAD	azodicarboxilato de di-t-butilo
DCM	Diclorometano
DIPEA	Diisopropiletilamina
DMSO	Sulfóxido de dimetilo
DMF	N,N-Dimetilformamida
EtOAc	Acetato de etilo
EtOH	Etanol
Hr	Hora(s)
IPA	Alcohol isopropílico
M	Multiplete (RMN)
MDAP	Autopreparación dirigidad a la masa
MeCN	Acetonitrilo
MeOH	Metanol
min	Minuto(s)
NCS	N-Clorosuccinimida
NBS	N-bromosuccinimida
NIS	N-yodosuccinimida

q	cuadriplete (RMN)
t.a.	Temperatura ambiente
TR	Tiempo de retención
S	Singulete (RMN)
SPE	Cartucho de extracción de fase sólida
T	Triplete (RMN)
TFA	Acido trifluoroacético
THF	Tetrahidrofurano
DMEM	Medio de Eagle mdificado por Dulbecco
HEPES	Acido 4-(2-hidroxietil)piperazin-1-etansulpónico
LiHMDS	Hexametildisililamida de litio
Δ	Calor
SEM	2-(trimetilsilil)etoximetilo
MEM	2-metoxietoximetilo
Boc	t-butoxicarbonilo
THP	tetrahidropirano

BREVE DESCRIPCION DE LAS FIGURAS

FigurA 1: Datos de XRPD de la forma 1 de 3-butil-8-cloro-1-{4-[5-(2-piridinil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purino-2,6-diona sustancialmente cristalina.

Figura 2: Datos de XRPD de la forma 2 de 3-butil-8-cloro-1-{4-[5-(2-piridinil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purino-2,6-diona sustancialmente cristalina.

Figura 3: traslape de datos de XRPD para las formas 1 y 2 de 3-butil-8-cloro-1-{4-[5-(2-piridinil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purino-2,6-diona sustancialmente cristalinas

Los siguientes ejemplos no limitantes ilustran la presente invención:

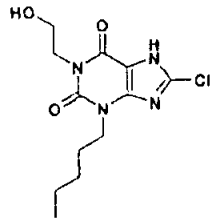
EJEMPLOS DE SINTESIS

Cabe notar que la asignación de la estereoquímica (Z) expuesta en los compuestos ilustrados más adelante no ha sido confirmada por datos experimentales. El experto en la técnica también reconocerá que puede haber interconversión entre isómeros E y Z (Dondoni, Alessandro; Lunazzi, Lodovico; Giorgianni, Patrizia; Macciantelli, Dante. Carbon-nitrogen rotational barrier as a stereochemical probe of benzamidoximes. Journal of Organic Chemistry (1975), 40(20), 2979-80).

EJEMPLO 1

8-Cloro-1-(2-hidroxietil)-3-pentil-3,7-dihidro-1*H*-purino-2,6-diona

a) 8-Cloro-1-(2-hidroxietil)-3-pentil-3,7-dihidro-1*H*-purino-2,6-diona

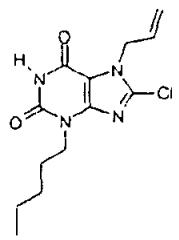


8-Cloro-3-pentil-7-(2-propen-1-il)-3,7-dihidro-1*H*-purino-2,6-diona (1.5 g, 5.1 mmoles), CS_2CO_3 (1.8 g, 5.6 mmoles) y 2-cloroetanol (509 µl, 7.7 mmoles) se hicieron reaccionar juntas en DMF (20 ml) a 60°C durante 18 hr. La reacción se dejó enfriar a t.a. y la mezcla se desgasificó aplicando un vacío y después se introdujo nitrógeno. $Pd(PPh_3)_4$ (428 mg, 0.37 mmoles) se añadió y la mezcla se desgasificó una vez más. Morfolina (2.1 ml, 24.7 mmoles) se añadió y la mezcla se agitó bajo nitrógeno durante 3 hr, y después se dividió entre HCl 2M (ac.) y EtOAc. La capa orgánica se separó, se lavó con salmuera, se secó ($MgSO_4$) y se concentró. El residuo se recogió en MeOH y después se hizo pasar una columna de aminopropilo eluyendo el producto con 3% de AcOH/MeOH. Las fracciones de producto se combinaron y se concentraron, después se purificaron por recristalización a partir de EtOAc. El sólido resultante se recogió por filtración y se lavó con EtOAc para dar el compuesto del título como un sólido blanco (713 mg, 47%).

CL/EM: m/z 301 $[MH]^+$, TR 2.7 min.

1H RMN (DMSO-d_6) δ: 0.86 (t, 3H, J = 7Hz), 1.22-1.36 (m, 4H), 1.63 (m, 2H), 3.50 (br t, 2H, J = 6Hz), 3.90 (t, 2H, J = 7.5Hz), 3.95 (t, 2H, J = 6.5Hz), 4.75 (br s, 1H), 14.5 (br s, 1H).

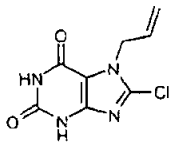
b) 8-Cloro-3-pentil-7-(2-propen-1-il)-3,7-dihidro-1*H*-purino-2,6-diona



A una solución de 8-cloro-7-(2-propen-1-il)-3,7-dihidro-1*H*-purino-2,6-diona (100 mg, 0.44 mmoles) en DMF anhidro (3 ml) se añadió carbonato de sodio (0.051 g, 0.484 mmoles). Después de 10 min agitando a t.a., se añadió yoduro de pentilo (0.063 ml, 0.484 mmoles) y la agitación continuó bajo nitrógeno a t.a. durante 18 hr. La mezcla de reacción se diluyó con agua (25 ml) y se extrajo con EtOAc (2x25 ml). Los extractos orgánicos combinados se secaron ($MgSO_4$) se filtraron y se evaporaron. La purificación por SPE (Si, 5 g) eluyendo con 4:1 de EtOAc/ciclohexano dio el compuesto del título como un sólido blanco (96 mg, 74%).

CL/EM: m/z 297 [MH]+.

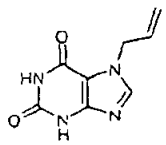
c) 8-Cloro-7-(2-propen-1-il)-3,7-dihidro-1*H*-purino-2,6-diona



A una solución de 7-(2-propen-1-il)-3,7-dihidro-1*H*-purino-2,6-diona) (10.52 g, 54.7 mmoles) en DMF anhidro (60 ml) se añadió NCS (8.04 g, 60.2 mmoles). La mezcla de reacción se dejó agitar bajo nitrógeno a 20°C durante 6 hr. La mezcla de reacción se concentró bajo vacío para dar un aceite color ámbar. Se añadió MeOH y se dejó reposar durante 18 hr. El residuo resultante se filtró y se secó bajo vacío para dar el compuesto del título (7.69 g, 62%).

CL/EM: m/z 227 $[MH]^+$.

d) 7-(2-Propen-1-il)-3,7-dihidro-1*H*-purino-2,6-diona

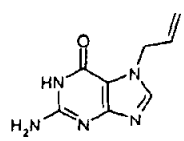


Una mezcla de 2-amino-7-(2-propen-1-il)-1,7-dihidro-6*H*-purin-6-ona (40 g, 0.209 moles) en AcOH (900 ml) y agua (100 ml) se calentó a 55°C. Nitrito de sodio (57.74 g, 0.837 moles) en agua (100 ml) se añadió gota a gota. Cuidado; emanaciones tóxicas. Después de que la adición se completó (aprox. 25 min) la mezcla de reacción se dejó enfriar a temperatura ambiente y después se concentró a aproximadamente. 1/3 de su volumen original. Se

añadió agua (500 ml) y el precipitado resultante se recogió por filtración. El residuo se lavó con agua después se secó a 50°C sobre P_2O_5 y bajo vacío durante 2 hr para dar el compuesto del título (17.20 g). La fracción acuosa se concentró y se añadió agua (100 ml). Nuevamente, el sólido resultante se filtró y se secó. Esto dio más del compuesto del título (2.31 g). Producto combinado (19.52 g, 49%).

CL/EM: m/z 193 $[MH]^+$.

e) 2-Amino-7-(2-propen-1-il)-1,7-dihidro-6*H*-purin-6-ona

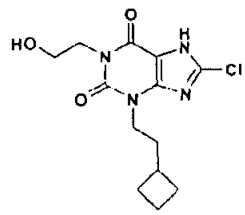


Una mezcla de guanosina (20 g, 0.071 moles), bromuro de alilo (14.7 ml, 0.169 moles) y DMSO anhidro (100 ml) se agitó a t.a., bajo nitrógeno, durante 18 hr. HCl concentrado (50 ml de 37%) se añadió en una porción y la mezcla se agitó durante 45 min, después se vació en MeOH (600 ml). La solución metanólica se neutralizó con solución de NaOH 2M (ac.) y el precipitado blanco resultante se recogió por filtración. El sólido blanco se secó bajo vacío a 50°C durante 18 hr para dar el compuesto del título (16 g) que se usó sin purificación adicional.

CL/EM: m/z 192 $[MH]^+$.

EJEMPLO 2

8-Cloro-3-(2-ciclobutiletil)-1-(2-hidroxietil)-3,7-dihidro-1*H*-purino-2,6-diona



7-(2-Propen-1-il)-3,7-dihidro-1*H*-purino-2,6-diona (575 mg, 2.54 mmoles) se agitó en THF seco (20 ml) con 2-ciclobutiletanol (c.73 % molar, 1-butanol restante) (254 mg). Azodicarboxilato de dibencilo (94%, 1.57 g, 4.95 mmoles) se añadió, la mezcla se enfrió a 0°C y una solución de trifenilfosfina (1.302 g, 4.97 mmoles) en THF seco (10 ml) se añadió gota a gota. La mezcla se agitó durante 30 min. a 0°C, después a t.a. durante 18 hr bajo nitrógeno. El solvente se evaporó y el residuo se purificó sobre un sistema Biotage (100 g) eluyendo con EtOAc-ciclohexano (2:3). El material así obtenido (0.53 g) fue una mezcla del compuesto requerido, el análogo n-butilo correspondiente e hidrazindicarboxilato de dibencilo, y se alquiló sin purificación adicional.

Esta mezcla (256 mg) y Cs_2CO_3 (326 mg, 1 mmol) se agitaron en DMF seco (5 ml). Se añadió 2-cloroetanol (80.5 mg, 1 mmoles) y la mezcla se agitó y se calentó a 55°C durante 65 hr. Después de enfriarse, fue completamente desgasificada, se añadieron tetrakis(trifenilfosfin)paladio(0) (200 mg) y morfolina (0.7 ml), y la mezcla se agitó durante 6 hr. EtOAc y HCl 2M se añadieron y la mezcla se filtró, la fase orgánica se lavó con salmuera, se secó (Na_2SO_4) y se evaporó y el residuo se separó del material no ácido

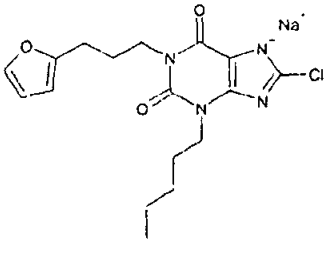
por SPE de aminopropilo (5 g, lavado con MeOH-THF y MeOH, elución con DCM-MeOH con 5% añadido a AcOH). El material obtenido del lavado del ácido (105 mg) además se purificó por MDAP para proveer el compuesto del título (42.7 mg).

CL/EM: m/z 313 $[MH]^+$, TR 2.58 min.

1H RMN (DMSO-d_6) δ: 1.53-1.64 (m, 2H), 1.71-1.84 (m, 4H), 1.94-2.02 (m, 2H), 2.21-2.30 (m, 1H), 3.47-3.53 (m, 2H), 3.84 (t, 2H, J = 7Hz), 3.95 (t, 2H, J = 7Hz), 4.76 (br s, 1H), 14.45 (br s, 1H)

EJEMPLO 3

Sal de sodio de 8-cloro-1-[3-(2-furanil)propil]-3-pentil-3,7-dihidro-1*H*-purino-2,6-diona



Un tubo GreenHouse™ equipado con un agitador se cargó con una alícuota de 0.25 ml de una solución 0.54M de 8-cloro-3-pentil-7-(2-propen-1-il)-3,7-dihidro-1*H*-purino-2,6-diona (0.13 mmoles) en THF. A la mezcla se añadió 3-(2-furanil)-1-propanol (21 mg, 0.16 mmoles, 1.2 eq) en THF (0.25 ml), seguido por una alícuota de 0.25 ml de una solución 0.71 M de (*E*)-1,2-diazendicarboxilato de bis(1,1-dimetiletilo) (0.18 mmoles) en THF y después una alícuota de 0.25 ml de una solución 0.71 M de trifenilfosfina (0.18

mmoles) en THF. La solución se agitó en un GreenHouse™ bajo nitrógeno durante 16 hr. A la mezcla se añadió una alícuota adicional de 0.25 ml de una solución 1.4M de (*E*)-1,2-diazendicarboxilato de bis(1,1-dimetiletilo) (0.36 mmoles) en THF y después una alícuota adicional de 0.25 ml de una solución 1.4M de trifenilfosfina (0.36 mmoles) en THF. La mezcla se agitó durante 16 hr bajo una corriente de nitrógeno.

Tetrakis(trifenilfosfin)paladio(0) (16 mg, 0.014 mmoles) y morfolina (0.12 ml, 1.35 mmoles) se añadieron a la mezcla que se agitó durante 16 hr bajo una corriente de nitrógeno. La mezcla de reacción se concentró bajo nitrógeno y el material crudo se disolvió en solución de NaOH acuosa (0.5 ml, 2M). La solución resultante se purificó usando SPE de aminopropilo (eluyendo con AcOH en DCM y MeOH). Purificación adicional usando SPE de C18 (eluyendo con una mezcla de agua, amoniaco y MeCN) dio el compuesto del título como una goma clara (22 mg, 45%).

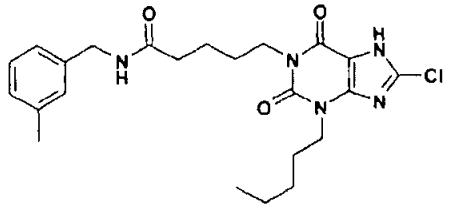
CL/EM: m/z 365 $[MH]^+$, TR 3.48 min.

1H RMN (DMSO-d_6) δ: 0.85 (t, 3H, J = 7Hz), 1.35-1.19 (m, 4H), 1.62 (m, 2H), 1.79 (m, 2H), 2.59 (t, 2H, J = 8Hz), 3.93-3.80 (m, 4H), 6.14 (d, 1H, J = 3Hz), 6.32 (dd, 1H, J = 3 y 2Hz), 7.48 (d, 1H, J = 2Hz).

EJEMPLO 4

5-(8-Cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1*H*-purin-1-il)-*N*-[(3-metilfenil)metil]pentanamida

a) 5-(8-Cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1*H*-purin-1-il)-*N*-[(3-metilfenil)metil]pentanamida

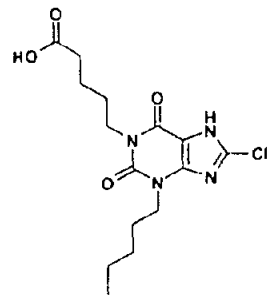


Una mezcla de ácido 5-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1*H*-purin-1-il)pentanoico (50 mg, 0.14 mmoles) en DCM (3 ml) se trató con CDI (27 mg, 0.17 mmoles) y se dejó agitar a t.a. durante 1 hr. Se añadió [(3-metilfenil)metil]amina (25 µl, 0.20 mmoles) y se dejó agitar durante 1 hr adicional. La mezcla se concentró, después se purificó por SPE de aminopropilo. El compuesto del título se eluyó con 2-3% de AcOH/MeOH, después se concentró para dar el compuesto del título como un sólido blanco (56 mg, 87%).

CL/EM: m/z 460 $[MH]^+$, TR 3.3 min.

b) Acido 5-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1*H*-purin-1-il)pentanoico

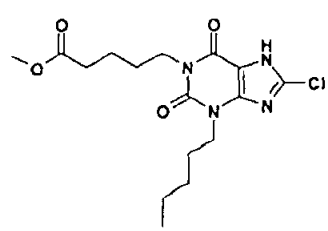
390



Una mezcla de 5-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)pentanoato de metilo (8.40 g, 0.023 moles), LiOH (1.63 g, 0.068 moles), MeOH (150 ml) y agua (10 ml) se dejó agitar a temperatura ambiente durante 64 hr. La mezcla se dividió entre agua y EtOAc y la capa acuosa se acidificó. La capa orgánica se separó y la capa acuosa se extrajo nuevamente con EtOAc. Los extractos combinados se lavaron con salmuera, se secaron ($MgSO_4$) y se concentraron, dando el compuesto del título como un sólido blanquecino (9.09 g).

CL/EM: m/z 357 [MH]+, TR 3.0 min.

c) 5-(8-Cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1*H*-purin-1-il)pentanoato de metilo

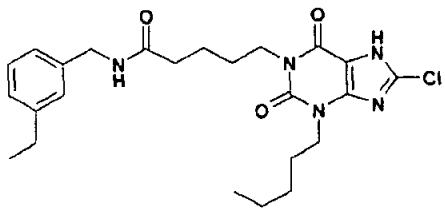


Una solución de 8-cloro-3-pentil-7-(2-propen-1-il)-3,7-dihidro-1*H*-purino-2,6-diona (2.0 g, 6.7 mmoles) en DMF anhidro (40 ml) se trató con Cs_2CO_3 (2.42 g, 7.4 mmoles) y 5-bromovalerato de metilo (1.16 ml, 8.1 mmoles). La mezcla se calentó a 50°C durante 18 hr, después se dejó enfriar a t.a. y se desgasificó bajo un vacío suave, después se introdujo nitrógeno. Esto se repitió dos veces. Se añadió $Pd(PPh_3)_4$ (779 mg, 0.67 mmoles) y la mezcla se desgasificó una vez más. Se añadió morfolina (5.9 ml, 67 mmoles) y se dejó agitar durante 3 hr a t.a. La mezcla se dividió entre HCl 2M (ac.) y EtOAc. La capa orgánica se separó, se lavó con salmuera, se secó ($MgSO_4$) y se concentró, dando un residuo/aceite amarillo (5.16 g). El residuo se recogió en MeOH y se dividió en dos porciones iguales, y después cada una se hizo pasar en SPE de aminopropilo (20 g), eluyendo con MeOH seguido por 5% de AcOH/MeOH, después 10% de AcOH/MeOH y finalmente 15% de AcOH/MeOH. Las fracciones de producto se combinaron y se concentraron dando el compuesto del título como un sólido blanquecino (2.28 g, 91%).

CL/EM: m/z 371 [MH]+, TR 3.1 min.

EJEMPLO 5

5-(8-Cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1*H*-purin-1-il)-*N*-[(3-etilfenil)metil]pentanamida

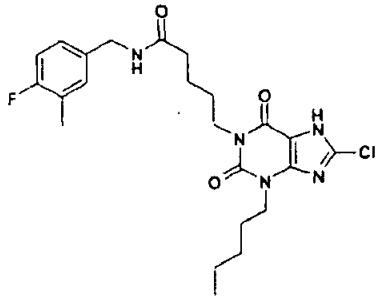


Una mezcla de ácido 5-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1*H*-purin-1-il)pentanoico (50 mg, 0.14 mmoles) en DCM (3 ml) se trató con CDI (27 mg, 0.17 mmoles) y se dejó agitar a t.a. durante 1 hr. Se añadió [(3-etilfenil)metil]amina (25 µl 0.20 mmoles) y se dejó agitar durante 1 hr adicional. La mezcla se concentró, después se purificó sobre un SPE de aminopropilo. El compuesto del título se eluyó con 2-3% de AcOH/MeOH para dar un sólido blanco (61 mg, 92%).

CL/EM: m/z 474 $[MH]^+$, TR 3.5 min.

EJEMPLO 6

5-(8-Cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1*H*-purin-1-il)-N-[(4-fluoro-3-metilfenil)metil]pentanamida

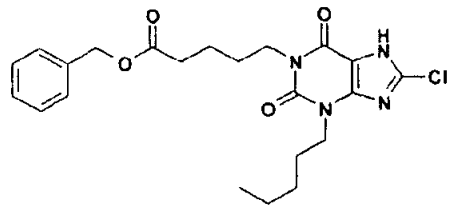


Una mezcla de ácido 5-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1*H*-purin-1-il)pentanoico (50 mg, 0.14 mmoles) y DCM (3 ml) se trató con CDI (27 mg, 0.17 mmoles) y se agitó a t.a. durante 1 hr. Se añadieron 1-(4-fluoro-3-metilfenil)metanamina (27 mg, 0.20 mmoles) y DIPEA (24 µl 0.14 mmoles). Después de 1 hr, la mezcla se concentró y después el residuo se recogió en MeOH y se hizo pasar en una SPE de aminopropilo. El producto se eluyó con 2% de AcOH/MeOH y se purificó adicionalmente por MDAP para dar el compuesto del título como un sólido (15 mg, 22%).

CL/EM: m/z 478 $[MH]^+$, TR 3.4 min.

EJEMPLO 7

5-(8-Cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1*H*-purin-1-il)pentanoato de fenilmetilo



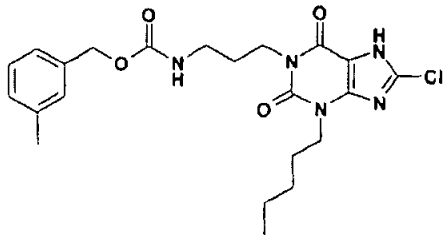
Una mezcla de ácido 5-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1*H*-purin-1-il)pentanoico (50 mg, 0.14 mmoles) en DCM (3 ml) se trató con CDI (27 mg, 0.17 mmoles) y se dejó agitar a t.a. durante 1 hr. Se añadió alcohol bencílico (21 µl, 0.20 mmoles) y se dejó agitar durante 1 hr adicional. La mezcla de reacción se concentró y se añadió DMF (3 ml), después se calentó a 50°C durante 2 hr. La mezcla se concentró, después se purificó por MDAP dando el compuesto del título como un sólido blanco (33 mg, 53%).

CL/EM: m/z 447 $[MH]^+$, TR 3.7 min.

EJEMPLO 8

[3-(8-Cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1*H*-purin-1-il)propil]carbamato de (3-metilfenil)metilo

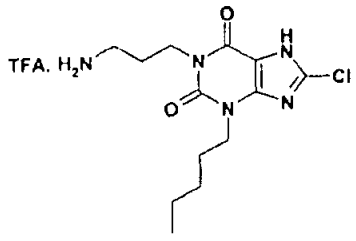
a) [3-(8-Cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1*H*-purin-1-il)propil]carbamato de (3-metilfenil)metilo



Una solución de alcohol 3-metilbencílico (16 µl, 0.13 mmoles) en DCM (3 ml) se trató con CDI (24 mg, 0.15 mmoles) y se dejó agitar a t.a. durante 1 hr. Se añadió trifluoroacetato de 1-(3-aminopropil)-8-cloro-3-pentil-3,7-dihidro-1*H*-purino-2,6-diona (50 mg, 0.16 mmoles) seguido por DIPEA (28 µl, 0.16 mmoles), después se calentó a 50°C durante 56 hr. La mezcla de reacción se concentró, el residuo se recogió en MeOH y se purificó por SPE de aminopropilo. El compuesto del título se eluyó con 2% de AcOH/MeOH y se recogió un sólido blanco (40 mg, 58%).

CL/EM: m/z 462 $[MH]^+$, TR 3.6 min.

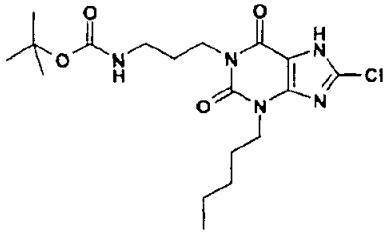
b) Trifluoroacetato de 1-(3-aminopropil)-8-cloro-3-pentil-3,7-dihidro-1*H*-purino-2,6-diona



Una solución de [3-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1*H*-purin-1-il)propil]carbamato de 1,1-dimetiletilo (1.59 g, 4.38 mmoles) en DCM (16 ml) se trató con TFA (16 ml) y se agitó a t.a. durante 2 hr, después se concentró bajo vacío. TFA residual se removió por azeotropismo con DCM, después el residuo se trituró con Et_2O para dar el compuesto del título como un sólido (1.48 g, cuant.).

CL/EM: m/z 314 $[MH]^+$, TR 2.1 min.

c) [3-(8-Cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1*H*-purin-1-il)propil]carbamato de 1,1-dimetiletilo



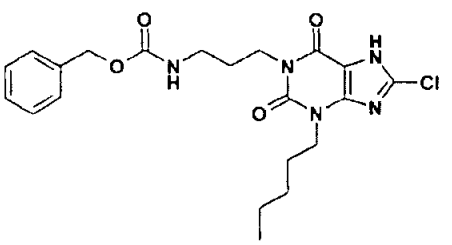
Una solución de (3-hidroxipropil)carbamato de 1,1-dimetiletilo (1.0 ml, 6.1 mmoles) en THF (40 ml) se trató con 8-cloro-3-pentil-1-[3-(tetrahidro-2*H*-piran-2-iloxi)propil]-3,7-dihidro-1*H*-purino-2,6-diona (1.5 g, 5.1

mmoles) y PPh_3 (1.73 g, 6.6 mmoles) a t.a. bajo nitrógeno. Se añadió DBAD (1.52 g, 6.6 mmoles) en una porción y se agitó durante 18 hr. La mezcla se desgasificó aplicando un vacío y después se introdujo nitrógeno. $Pd(PPh_3)_4$ (586 mg, 0.51 mmoles) se añadió y la mezcla se desgasificó una vez más. Se añadió morfolina (4.4 ml, 50.7 mmoles) y la mezcla se agitó bajo nitrógeno durante 3 hr, después se dividió entre HCl 2M (ac.) y EtOAc. La capa orgánica se separó, se lavó con salmuera, se secó ($MgSO_4$) y se concentró, dando un aceite amarillo. Se añadió MeOH y después se hizo pasar un SPE de aminopropilo eluyendo el producto con 2-3% de AcOH/MeOH. Las fracciones de producto se combinaron y se concentraron, dando el compuesto del título como un sólido gomoso claro (1.59 g, 75%).

CL/EM: m/z 414 $[MH]^+$, TR 3.4 min.

EJEMPLO 9

[3-(8-Cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1*H*-purin-1-il)propil]carbamato de fenilmetilo



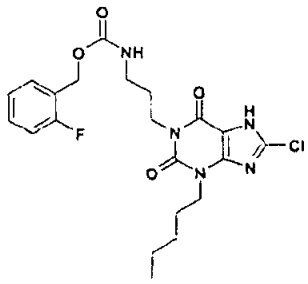
Trifluoroacetato de 1-(3-aminopropil)-8-cloro-3-pentil-3,7-dihidro-1*H*-purino-2,6-diona (50 mg, 0.12 mmoles) en DCM (3 ml) se trató con DIPEA (51 µl, 0.29 mmoles) y cloroformiato de bencilo (20 µl, 0.14 mmoles). Después

de 1 hr, la mezcla de reacción se concentró y se purificó sobre una SPE de aminopropilo. El compuesto del título se eluyó con 2% de AcOH/MeOH y se recogió un sólido blanco (35 mg, 67%).

CL/EM: m/z 448 $[MH]^+$, TR 3.4 min.

EJEMPLO 10

[3-(8-Cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1*H*-purin-1-il)propil]carbamato de (2-fluorofenil)metilo

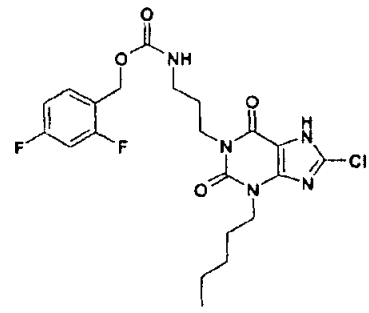


(2-Fluorofenil)metanol (11 µl, 0.10 mmoles) en DCM (3 ml) se hizo reaccionar con CDI (17 mg, 0.11 mmoles) bajo nitrógeno durante 1 hr. Trifluoroacetato de 1-(3-aminopropil)-8-cloro-3-pentil-3,7-dihidro-1*H*-purino-2,6-diona (50 mg, 0.16 mmoles) se añadió seguido por DIPEA (20 µl, 0.12 mmoles), después se calentó a reflujo durante 18 hr. Se añadió THF (3 ml) y se calentó a 75°C durante 5 hr. Después de enfriarse, la mezcla se concentró bajo vacío y se purificó por MDAP para dar el compuesto del título como un sólido (21 mg, 39%).

CL/EM: m/z 466 $[MH]^+$, TR 3.4 min.

EJEMPLO 11

[3-(8-Cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1*H*-purin-1-il)propil]carbamato de (2,4-difluorofenil)metilo



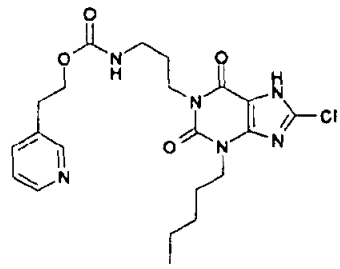
(2,4-Difluorofenil)metanol (11 µl, 0.10 mmoles) en DCM (3 ml) se hizo reaccionar con CDI (17 mg, 0.11 mmoles) bajo nitrógeno durante 1 hr. Se añadió trifluoroacetato de 1-(3-aminopropil)-8-cloro-3-pentil-3,7-dihidro-1*H*-purino-2,6-diona (50 mg, 0.16 mmoles) seguido por DIPEA (20 µl, 0.12 mmoles), después se calentó a reflujo durante 18 hr. Se añadió THF (3 ml) y se calentó a 75°C durante 5 hr. Después de enfriarse, la mezcla se concentró bajo vacío y se purificó por MDAP para dar el compuesto del título como un sólido (29 mg, 21%).

CL/EM: m/z 484 $[MH]^+$, TR 3.4 min.

EJEMPLO 12

[3-(8-Cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1*H*-purin-1-il)propil]carbamato de 2-(3-piridinil)etilo

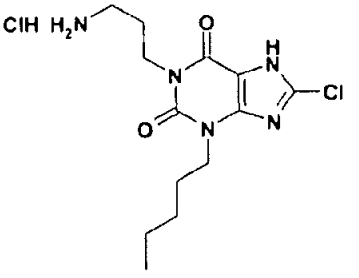
a) [3-(8-Cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1*H*-purin-1-il)propil]carbamato de 2-(3-piridinil)etilo



Una solución de CDI (21 mg, 0.13 mmoles) en THF (2 ml) se trató con 2-(3-piridinil)etanol (16 mg, 0.13 mmoles) y se calentó a reflujo durante 1 hr, antes de la adición de clorhidrato de 1-(3-aminopropil)-8-cloro-3-pentil-3,7-dihidro-1*H*-purino-2,6-diona (50 mg, 0.14 mmoles) y DIPEA (25 µl, 0.14 mmoles). La reacción se dejó a reflujo durante 18 hr, después se concentró y se purificó por MDAP para proveer el compuesto del título como un sólido (30 mg, 24%).

CL/EM: m/z 463 $[MH]^+$, TR 2.6 min.

b) Clorhidrato de 1-(3-aminopropil)-8-cloro-3-pentil-3,7-dihidro-1*H*-purino-2,6-diona

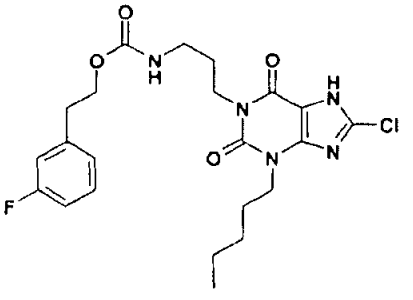


Una mezcla de [3-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1*H*-purin-1-il)propil]carbamato de 1,1-dimetiletilo (5.19 g, 12.5 mmoles) y HCl 4M en 1,4-dioxano (80 ml) se agitó a t.a. durante 3 hr. La mezcla se concentró bajo vacio y se secó bajo vacío para proveer el producto del título como un sólido blanco (4.49 g, cuant.).

CL/EM: m/z 314 $[MH]^+$, TR 2.2 min.

EJEMPLO 13

[3-(8-Cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)propil]carbamato de 2-(3-fluorofenil)etilo



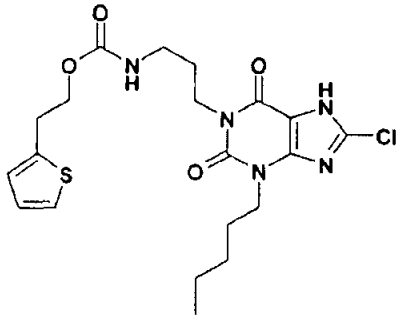
Una solución de CDI (21 mg, 0.13 mmoles) en THF (2 ml) se

trató con 2-(3-fluorofenil)etanol (16 µl, 0.13 mmoles) y se calentó a reflujo durante 1 hr antes de la adición de clorhidrato de 1-(3-aminopropil)-8-cloro-3-pentil-3,7-dihidro-1*H*-purino-2,6-diona (50 mg, 0.14 mmoles) y DIPEA (25 µl, 0.14 mmoles). La reacción se dejó a reflujo durante 18 hr, después se concentró y se purificó por MDAP para proveer el compuesto del título como un sólido (27 mg, 39%).

CL/EM: m/z 480 $[MH]^+$, TR 3.5 min.

EJEMPLO 14

[3-(8-Cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1*H*-purin-1-il)propil]carbamato de 2-(2-tienil)etilo



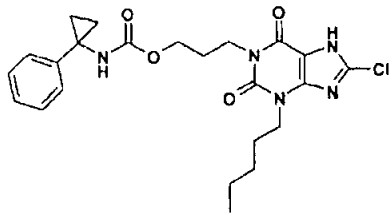
Una solución de CDI (21 mg, 0.13 mmoles) en THF (2 ml) se trató con 2-(2-tienil)etanol (15 µl, 0.13 mmoles) y se calentó a reflujo durante 1 hr antes de la adición de clorhidrato de 1-(3-aminopropil)-8-cloro-3-pentil-3,7-dihidro-1*H*-purino-2,6-diona (50 mg, 0.14 mmoles) y DIPEA (25 µl, 0.14 mmoles). La reacción se dejó a reflujo durante 18 hr, después se concentró y se purificó por MDAP para proveer el compuesto del título como un sólido (34 mg, 51%).

CL/EM: m/z 468 $[MH]^+$, TR 3.4 min.

EJEMPLO 15

(1-Fenilciclopropil)carbamato de 3-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1*H*-purin-1-il)propilo

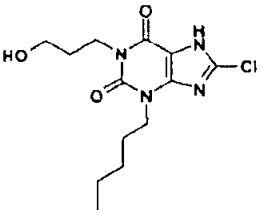
a) (1-Fenilciclopropil)carbamato de 3-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1*H*-purin-1-il)propilo



Una solución de 8-cloro-1-(3-hidroxipropil)-3-pentil-3,7-dihidro-1*H*-purino-2,6-diona (50 mg, 0.16 mmoles) se trató con CDI (28 mg, 0.18 mmoles) y se dejó agitar a t.a. durante 1 hr. Se añadió 1-fenilciclopropanamina (30 mg, 0.20 mmoles) y la mezcla se calentó a reflujo bajo nitrógeno durante 18 hr. Se añadió otra alícuota de 1-fenilciclopropanamina (30 mg, 0.20 mmoles) seguido por THF (3 ml). La reacción se calentó a 75°C durante 18 hr, después se concentró y se purificó por MDAP. Esto dio el compuesto del título como un sólido blanco (13 mg, 18%).

CL/EM: m/z 474 [MH]+, TR 3.5 min.

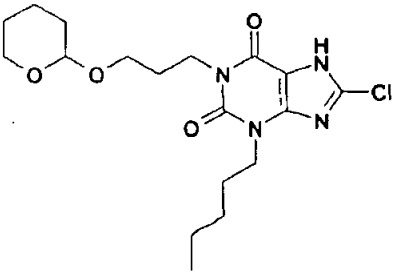
b) 8-Cloro-1-(3-hidroxipropil)-3-pentil-3,7-dihidro-1*H*-purino-2,6-diona



Una solución de 8-cloro-3-pentil-1-[3-(tetrahidro-2*H*-piran-2-iloxi)propil]-3,7-dihidro-1*H*-purino-2,6-diona (5.87 g, 14.8 mmoles) en EtOH (100 ml) se trató con pTsOH (2.8 g, 14.8 mmoles) y se agitó a t.a. durante 18.5 hr. La mezcla se dividió entre HCl 1M (ac.) y EtOAc. La capa orgánica se separó y la capa acuosa se extrajo una vez más. Los extractos combinados se lavaron con agua (x5), salmuera, después se secaron ($MgSO_4$) y se concentraron, dando un sólido amarillo pálido. El sólido se lavó con Et_2O y se recogió por filtración dando un sólido blanco (2.42 g, 52%).

CL/EM: m/z 315 $[MH]^+$, TR 2.7 min.

c) 8-Cloro-3-pentil-1-[3-(tetrahidro-2*H*-piran-2-iloxi)propil]-3,7-dihidro-1H-purino-2,6-diona

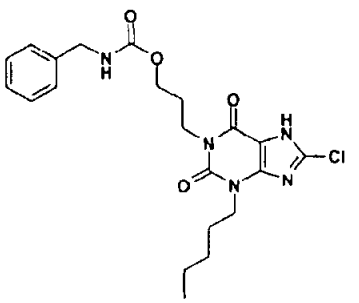


8-Cloro-3-pentil-7-(2-propen-1-il)-3,7-dihidro-1*H*-purino-2,6-diona (5.0 g, 16.8 mmoles), Cs_2CO_3 (6.0 g, 18.5 mmoles) y 2-(3-bromopropoxi)tetrahidro-2*H*-piran (3.4 ml, 20 mmoles) se hicieron reaccionar juntos en DMF (100 ml) a 50°C bajo nitrógeno durante 24 hr. La reacción se dejó enfriar a t.a. y la mezcla se desgasificó aplicando un vacío y después se introdujo nitrógeno. Se añadió $Pd(PPh_3)_4$ (1.4 g, 1.2 mmoles) y la mezcla se desgasificó una vez más. Se añadió morfolina (14.7 ml, 170 mmoles) y la mezcla se agitó bajo nitrógeno durante 3 hr, después se dividió entre HCl 2M (ac.) y EtOAc. La capa orgánica se separó, se lavó con salmuera, se secó ($MgSO_4$) y se concentró, dando un residuo amarillo (5.16 g). MeOH se añadió y después se hizo pasar un SPE de aminopropilo eluyendo el producto con 5% de AcOH/MeOH. Las fracciones de producto se combinaron y se concentraron, dando el compuesto del título como un sólido amarillo pálido (5.97 g, 89%).

CL/EM: m/z 399 $[MH]^+$, TR 3.3 min.

EJEMPLO 16

(Fenilmetil)carbamato de 3-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)propilo

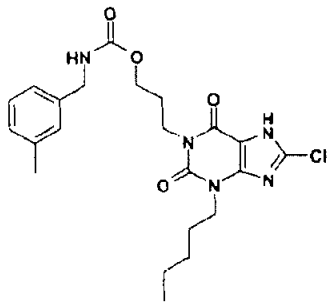


Una solución de 8-cloro-1-(3-hidroxipropil)-3-pentil-3,7-dihidro-1H-purino-2,6-diona (50 mg, 0.16 mmoles) en THF (3 ml) se trató con trifosgeno (47 mg, 0.16 mmoles) y piridina (13 µl, 0.16 mmoles). Después de 30 min, se añadió bencilamina (217 µl, 2.0 mmoles) y se dejó agitar durante 30 min adicionales. La mezcla se dividió entre HCl 2M (ac.) y EtOAc. La capa orgánica se separó, se lavó con salmuera, se secó ($MgSO_4$) y se concentró. El residuo se recogió en MeOH y se purificó haciendo pasar un SPE de aminopropilo, el producto se eluyó con 2-5% de AcOH/MeOH. El compuesto del título se obtuvo como un sólido blanquecino (67 mg, 94%).

CL/EM: m/z 448 $[MH]^+$, TR 3.2 min.

EJEMPLO 17

[(3-Metilfenil)metil]carbamato de 3-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1*H*-purin-1-il)propil



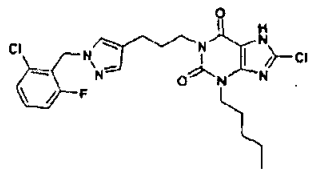
Una solución de 8-cloro-1-(3-hidroxipropil)-3-pentil-3,7-dihidro-1*H*-purino-2,6-diona (50 mg, 0.16 mmoles) en DCM (3 ml) se trató con CDI (31 mg, 0.19 mmoles) y se agitó a t.a. durante 1 hr. Se añadió 3-metilbencilamina (26 µl, 0.21 mmoles) y se calentó a reflujo durante 18 hr. Otra alícuota de metilbencilamina (4 µl, 0.03 mmoles) se añadió y la mezcla se dejó durante 4 hr a reflujo. La mezcla se concentró, después se recogió en MeOH y se hizo pasar un SPE de aminopropilo. El producto se eluyó con 2% de AcOH/MeOH y después se purificó adicionalmente por MDAP. Esto dio el compuesto del título como un sólido blanco (42 mg, 57%).

CL/EM: m/z 462 $[MH]^+$, TR 3.5 min.

EJEMPLO 18

8-Cloro-1-(3-[1-[(2-cloro-6-fluorofenil)metil]-1*H*-pirazol-4-il}propil)-3-pentil-3,7-dihidro-1*H*-purino-2,6-diona

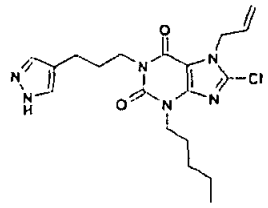
a) 8-Cloro-1-(3-{1-[(2-cloro-6-fluorofenil)metil]-1*H*-pirazol-4-il}propil)-3-pentil-diona



8-Cloro-3-pentil-7-(2-propen-1-il)-1-[3-(1*H*-pirazol-4-il)propil]-3,7-dihidro-1*H*-purino-2,6-diona (61 mg, 0.15 mmoles) en DMF seco (2 ml) se agitó con carbonato de sodio (64 mg, 0.6 mmoles) y bromuro de 2-cloro-6-fluorobencilo (134 mg, 0.6 mmoles) y se calentó a 45°C durante 18 hr bajo nitrógeno. Después de enfriarse a t.a. la mezcla se desgasificó evacuando y readmitiendo nitrógeno, y se agitó con tetrakis(trifenilfosfin)paladio(0) (35 mg, 0.303 mmoles) y morfolina (0.13 ml) durante 5.5 hr. La mezcla se dividió entre EtOAc y HCl 2M, la fase orgánica se separó y se evaporó y el residuo se purificó por SPE de aminopropilo (5 g, lavado con THF-MeOH (1:1), después MeOH neto y finalmente eluyendo con DCM-MeOH (1:1) que contenía 5% de AcOH) para dar el compuesto del título (57 mg) como un sólido.

CL/EM: m/z 507 $[MH]^+$, TR 3.64 min.

b) 8-Cloro-3-pentil-7-(2-propen-1-il)-1-[3-(1*H*-pirazol-4-il)propil]-3,7-dihidro-1H-purino-2,6-diona

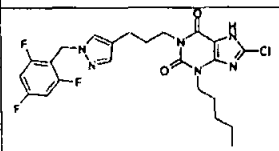
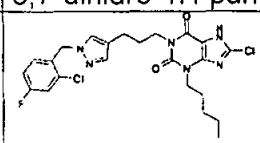
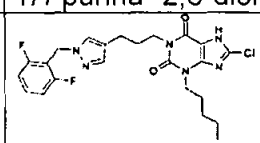
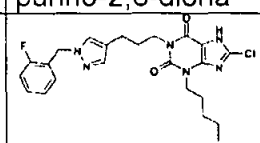


3-Pentil-8-cloro-7-(2-propen-1-il)-3,7-dihidro-1*H*-purino-2,6-diona (5 g, 16.86 mmoles) y 3-(1H-pirazol-4-il)propan-1-ol (2.12 g, 16.8 mmoles) se agitaron en THF seco (150 ml) a 3°C. Se añadió azodicarboxilato de dibencilo (10.05 g, 33.7 mmoles) seguido por la adición gota a gota de trifenilfosfina (8.83 g, 33.7 mmoles) en THF seco (70 ml). La mezcla se dejó calentar a t.a. y se agitó durante 18 hr. Se añadió agua (1 ml) y los solventes se evaporaron. El residuo se recogió en Et_2O (200 ml) a partir del cual un sólido blanco, mayormente óxido de trifenilfosfina, se cristalizó y se filtró. El filtrado se concentró y subproductos adicionales se cristalizaron a partir de éter-ciclohexano. El filtrado restante se concentró (19.2 g) y se purificó en un sistema Biotage™ (400 g) eluyendo con EtOAc-ciclohexano (2:1) para dar el compuesto del título como un sólido blanco (2.89 g).

CL/EM: m/z 405 $[MH]^+$, TR 3.19 min.

Los siguientes compuestos (cuadro 1) se prepararon usando un método análogo al del ejemplo 18, a partir de los halogenuros de bencilo correspondientes.

CUADRO 1

Ejemplo	Estructura	Rendimiento (mg)	CL/EM:
19	 8-cloro-3-pentil-1-(3-{1-[(2,4,6-trifluorofenil)metil]-1H-pirazol-4-il}propil)-3,7-dihidro-1H-purino-2,6-diona	68	m/z 509 $[MH]^+$ TR 3.58 min
20	 8-cloro-1-(3-{1-[(2-cloro-4-fluorofenil)metil]-1*H*-pirazol-4-il)propil)-3-pentil-3,7-dihidro-1*H*-purina- 2,6-diona	56	m/z 507 $[MH]^+$ TR 3.73 min
21	 8-cloro-1-(3-{1-[(2,6-difluorofenil)metil]-1*H*-pirazol-4-il)propil)-3-pentil-3,7-dihidro-1*H*-purino-2,6-diona	29	m/z 491 $[MH]^+$ TR 3.53 min
22	 8-cloro-1-(3-{1-[(2-fluorofenil)metil]-1*H*-pirazol-4-il}propil)-3-pentil-3,7-dihidro-1*H*-purino-2,6-diona	32*	m/z 473 $[MH]^+$ TR 3.55 min

* después de purificación adicional por MDAP.

Detalles de RMN para ejemplos seleccionados del cuadro 1

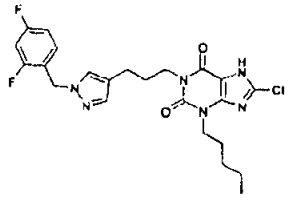
EJEMPLO 19

8-Cloro-3-pentil-1-(3-{1-[(2 ,4,6-trifluorofenil)metil]-1*H*-pirazol-4-il}propil)-3,7-dihidro-1*H*-purino-2,6-diona

^{1}H RMN (DMSO-d_6) δ: 0.85 (t, 3H, J = 7 Hz), 1.20-1.40 (m, 4H), 1.60-1.70 (m, 2H), 1.70-1.82 (m, 2H), 2.39 (t, 2H, J = 8 Hz), 3.83-3.94 (m, 4H), 5.24 (s, 2H), 7.18-7.30 (m, 3H), 7.57 (s, 1H).

EJEMPLO 23

8-Cloro-1-(3-{1-[(2,4-difluorofenil)metil)-1*H*-pirazol-4-il}propil)-3-pentil-3,7-dihidro-1*H*-purino-2,6-diona



8-Cloro-3-pentil-7-(2-propen-1-il)-1-[3-(1*H*-pirazol-4-il)propil]-3,7-dihidro-1*H*-purino-2,6-diona (81 mg, 0.2 mmoles) y carbonato de sodio (85 mg, 0.8 mmoles) se agitaron en DMF seco (2 ml) con bromuro de 2,4-difluorobencilo (166 mg, 0.8 mmoles) a 45°C durante 18 hr. La mezcla se desgasificó y se agitó con tetrakis(trifenilfosfin)paladio(0) (46 mg, 0.04 mmoles) y morfolina (176 mg, 2 mmoles) a t.a. durante 6 hr. La reacción se

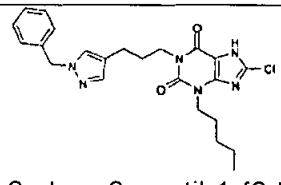
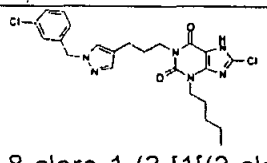
trató y se purificó por SPE de aminopropilo (5 g, lavado con THF-MeOH (1:1), después MeOH neto, eluyendo con DCM-MeOH (1:1) con 5% de AcOH añadido) para dar el compuesto del título (37.7 mg) como un sólido.

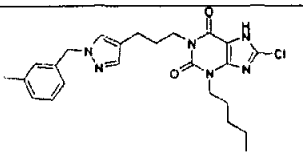
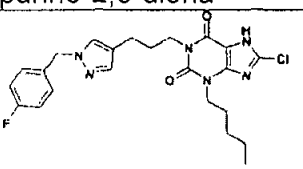
CL/EM: m/z 491 $[MH]^+$, TR 3.42 min.

^1H RMN (d^6 DMSO) 0.85 (3H, t, J = 7Hz), 1.21-1.34 (4H, m), 1.58-1.68 (2H, m), 1.71-1.80 (2H, m), 2.41 (2H, t, J = 8Hz), 3.84-3.93 (4H, m), 5.26 (2H, s), 7.02-7.09 (1H, m), 7.15-7.29 (2H, m), 7.31 (1H, s), 7.61 (1H, s).

Los siguientes compuestos (cuadro 2) se prepararon usando un método análogo al del ejemplo 23, a partir de los halogenuros de bencilo correspondientes.

CUADRO 2

Ejemplo	Estructura	Rendimiento (mg)	CL/EM:
24	 8-cloro-3-pentil-1-{3-[1-(fenilmetil)-1*H*-pirazol-4-il]propil}-3,7-dihidro-1*H*-purino-2,6-diona	17*	m/z 455 $[MH]^+$ TR 3.52 min
25	 8-cloro-1-(3-[1[(3-clorofenil)metil]1*H*-pirazol-4-il}propil)-3-pentil-3,7-dihidro-1*H*-purino-2,6-diona	11.6*	m/z 489 $[MH]^+$ TR 3.52 min

26	 8-cloro-1-(3-{1-[(3-metilpentil)metil]-1H-pirazol-4-il}propil)-3-pentil-3,7-dihidro-1H-purino-2,6-diona	33	m/z 469 [MH]$^+$ TR 3.54 min
27	 8-cloro-1-(3-{1-[(4-fluorofenil)metil]-1*H*-pirazol-4-il}propil)-3,7-dihidro-1*H*-purino-2,6-diona	42	m/z 473 [MH]$^+$ TR 3.44 min

*después de purificación adicional por MDAP.

Detalles de RMN para ejemplos seleccionados del cuadro 2

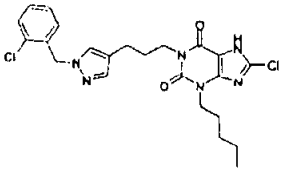
EJEMPLO 24

8-Cloro-3-pentil-1-{3-[1-(fenilmetil)-1*H*-pirazol-4-il]propil}-3,7-dihidro-1*H*-purino-2,6-diona

^{1}H RMN (DMSO-d_6) δ: 0.87 (t, 3H, J = 7 Hz), 1.20-1.36 (m, 4H), 1.60-1.70 (m, 2H), 1.72-1.85 (m, 2H), 2.42 (t, 2H, J = 8 Hz), 3.83-3.95 (m, 4H), 5.24 (s, 2H), 7.13-7.38 (m, 6H), 7.61 (s, 1H).

EJEMPLO 28

8-Cloro-1-(3-{1-[(2-clorofenil)metil]-1*H*-pirazol-4-il}propil)-3-pentil-3,7-dihidro-1*H*-purino-2,6-diona



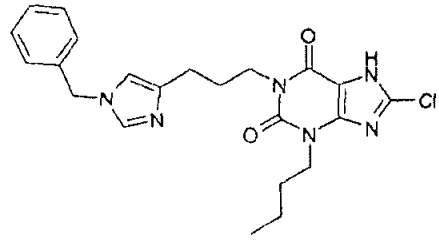
Se preparó mediante el método para 8-cloro-1-(3-{1-[(2,4-difluorofenil)metil]-1*H*-pirazol-4-il}propil)-3-pentil-3,7-dihidro-1*H*-purino-2,6-diona pero a partir de bromuro de 2-clorobencilo (164 mg, 0.8 mmoles). Sin embargo, a fin de completar el paso de desprotección adicional se añadieron tetrakis(trifenilfosfin)paladio(0) (40 mg) y morfolina (0.15 ml) y la agitación continuó durante 5.5 hr adicionales. La purificación por SPE de aminopropilo como antes dio el compuesto del título como un sólido (42 mg).

CL/EM: m/z 489 $[MH]^+$, TR 3.67 min.

EJEMPLO 29

3-Butil-8-cloro-1-{3-[1-(fenilmetil)-1*H*-imidazol-4-il]propil}-3,7-dihidro-1*H*-purino-2,6-diona

a) 3-Butil-8-cloro-1-{3-[1-(fenilmetil)-1*H*-imidazol-4-il]propil}-3,7-dihidro-1*H*-purino-2,6-diona



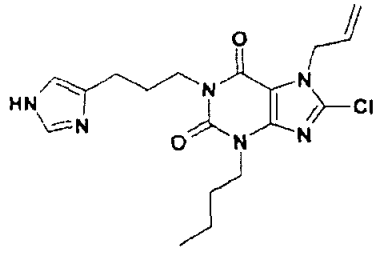
Una solución de 3-butil-8-cloro-1-[4-(1*H*-imidazol-4-il)butil]-7-(2-propen-1-il)-3,7-dihidro-1*H*-purino-2,6-diona (300 mg, 0.77 mmoles) en THF anhidro (5 ml) se trató con bromuro de bencilo (144 mg, 0.84 mmoles) y DIPEA (147 µl, 0.84 mmoles). La mezcla se dejó agitar a t.a. bajo nitrógeno durante 4 días. La mezcla se dividió entre EtOAc y HCl 2M (ac.). La capa orgánica se separó, se lavó con salmuera, se secó ($MgSO_4$) y se concentró. El material crudo se purificó mediante una columna de SPE de sílice usando un gradiente de 0.5-5% de MeOH/DCM. Las fracciones de producto se combinaron y se concentraron bajo alto vacío. El producto se disolvió en THF (5 ml), después se añadieron $Pd(PPh_3)_4$ (88 mg, 0.077 mmoles) y morfolina (670 µl, 7.67 mmoles) y la mezcla se dejó agitar a t.a. bajo nitrógeno durante 3 hr. Se añadieron 88 mg de $Pd(PPh_3)_4$ (0.077 mmoles) y la mezcla se dejó agitar a t.a. bajo nitrógeno durante 16 hr. La mezcla se dividió entre EtOAc y

H_2O. La capa orgánica se separó y la capa acuosa se extrajo con EtOAc (x2). Las capas orgánicas se combinaron, se lavaron con salmuera, se secaron ($MgSO_4$) y se concentraron. El producto crudo se purificó por MDAP para dar el compuesto del título como un sólido blanco (9 mg, 2%).

CL/EM: m/z 441 $[MH]^+$, TR 2.50 min.

^{1}H RMN (DMSO-d_6) δ: 0.89 (t, 3H, J = 7.5 Hz), 1.28 (m, 2H), 1.60 (m, 2H), 1.79 (m, 2H), 2.48 (traslape de t con DMSO, 2H, J =7.5 Hz), 3.89 (m, 4H), 5.17 (s, 2H), 7.08 (s, 1H), 7.31, (m, 6H), 8.03 (s, 1H).

b) 3-Butil-8-cloro-1-[3-(1*H*-imidazol-4-il)propil]-7-(2-propen-1-il)-3,7-dihidro-1*H*-purino-2,6-diona

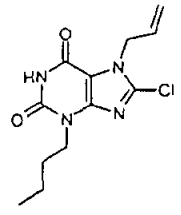


Una solución de 3-butil-8-cloro-7-(2-propen-1-il)-3,7-dihidro-1*H*-purino-2,6-diona (2.8 g, 9.9 mmoles) en THF anhidro (60 ml) se trató con 3-(1*H*-imidazol-4-il)-1-propanol (1.5 g, 12 mmoles) en THF anhidro (10 ml) y PPh_3 (3.4 g, 13 mmoles). DBAD (2.9 g, 13 mmoles) se añadió en una porción y la mezcla se dejó agitar a t.a., bajo nitrógeno durante 18 hr. La mezcla se dividió entre EtOAc y H_2O. La capa acuosa se extrajo y se lavó con EtOAc. Las capas orgánicas se combinaron, se lavaron con salmuera, se secaron ($MgSO_4$) y se concentraron. El producto crudo se purificó por un cartucho de

SPE de sílice usando un gradiente de MeOH/EtOAc (0.5%-7% de MeOH). Las fracciones de producto se combinaron y se concentraron para dar el compuesto del título como un sólido blanco (2.16 g, 55%).

CL/EM: m/z 391 $[MH]^+$, TR 2.40 min.

c) 3-Butil-8-cloro-7-(2-propen-1-il)-3,7-dihidro-1*H*-purino-2,6-diona

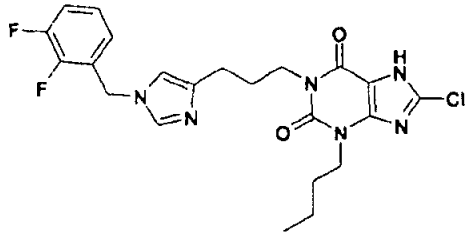


A una solución de 3-butil-7-(2-propen-1-il)-3,7-dihidro-1*H*-purino-2,6-diona (3.34 g, 13.4 mmoles) en DMF anhidro (19 ml) se añadió NCS (1.97 g, 14.8 mmoles) y se dejó agitar a t.a. bajo nitrógeno durante 22 hr. La mezcla se concentró bajo vacío para dar un sólido amarillo que se filtró y se lavó con MeOH para proveer una primera cosecha. El filtrado se concentró a un sólido y se lavó con MeOH para proveer una segunda cosecha y se repitió dos ocasiones más para proveer el compuesto del título. En el lavado final, el filtrado además se purificó por cartucho de SPE (Si, 20 g) eluyendo con EtOAc:ciclohexano (1:1). Los sólidos combiandos se secaron bajo vacío para dar el compuesto del título (2.42 g, 64%).

CL/EM: m/z 283 $[MH]^+$.

EJEMPLO 30

3-Butil-8-cloro-1-(3-{1-[(2,3-difluorofenil)metil]-1*H*-imidazol-4-il)propil)-3,7-dihidro-1*H*-purino-2,6-diona



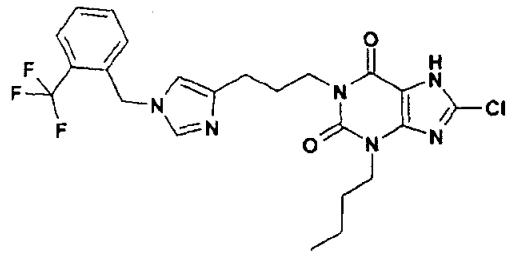
Una solución de 3-butil-8-cloro-1-[4-(1*H*-imidazol-4-il)butil]-7-(2-propen-1-il)-3,7-dihidro-1*H*-purino-2,6-diona (150 mg, 0.38 mmoles) en DMF anhidro (3 ml) se trató con 1-(bromometil)-2,4-difluorobenceno (54 µl, 0.42 mmoles) y DIPEA (73 µl, 0.42 mmoles). La mezcla se dejó agitar a t.a. bajo nitrógeno durante 3 días. La mezcla se dividió entre EtOAc y HCl 2M (ac.). La capa orgánica se separó, se lavó con salmuera, se secó ($MgSO_4$) y se concentró. El producto crudo se purificó sobre una columna de SPE de sílice usando DCM para cargar el material en la columna y para lavar las impurezas, después un gradiente de 0-5% de MeOH/DCM para eluir el compuesto. Las fracciones de producto se combinaron y se concentraron y los residuos se disolvieron en DMF anhidro (3 ml). La solución se desgasificó, después se añadió $Pd(PPh_3)_4$ (39 mg, 0.034 mmoles) y morfolina (200 µl, 2.3 mmoles) y la mezcla se dejó agitar a t.a. bajo nitrógeno durante 3 hr. El producto crudo se purificó por un SPE de aminopropilo usando MeOH para cargar el compuesto en la columna y para lavar las impurezas, después un gradiente de 0-5% de AcOH/MeOH para eluir el producto. Las fracciones de producto se combinaron

y se concentraron por alto vacío para dejar el compuesto del título como un sólido blanco (14 mg, 7%).

CL/EM: m/z 477 $[MH]^+$, TR 2.54 min.

EJEMPLO 31

3-Butil-8-cloro-1-[3-(1-{[2-(trifluorometil)fenil]metil}-1*H*-imidazol-4-il)propil]-3,7-dihidro-1*H*-purino-2,6-diona



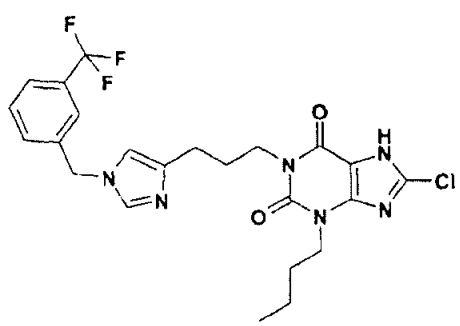
Una solución de 3-butil-8-cloro-1-[4-(1*H*-imidazol-4-il)butil]-7-(2-propen-1-il)-3,7-dihidro-1*H*-purino-2,6-diona (150 mg, 0.38 mmoles) en DMF anhidro (3 ml) se trató con 1-(clorometil)-2-(trifluorometil)benceno (61 µl, 0.42 mmoles) y DIPEA (73 µl, 0.42 mmoles). La mezcla se dejó agitar a t.a. bajo nitrógeno durante 3 días. La mezcla se dividió entre EtOAc y HCl 2M (ac.). La capa orgánica se separó, se lavó con salmuera, se secó ($MgSO_4$) y se concentró. El producto crudo se purificó sobre una columna de SPE de sílice usando DCM para cargar el material en la columna y para lavar de las impurezas, después un gradiente de 0-5% MeOH/DCM para eluir el compuesto. Las fracciones de producto se combinaron y se concentraron y los residuos se disolvieron en DMF anhidro (3 ml). La solución se desgasificó, después se añadió $Pd(PPh_3)_4$ (35 mg, 0.030 mmoles) y morfolina (174 µl, 2.0

mmoles) y la mezcla se dejó agitar a t.a. bajo nitrógeno durante 3 hr. El producto crudo se purificó por un SPE de aminopropilo usando MeOH para cargar el compuesto en la columna y para lavar de las impurezas, después un gradiente de 0-5% de AcOH/MeOH para eluir el producto. Las fracciones de producto se combinaron y se concentraron por alto vacío para dejar el compuesto del título como un sólido blanco (50 mg, 26%).

CL/EM: m/z 509 $[MH]^+$, TR 2.64 min.

EJEMPLO 32

3-Butil-8-cloro-1-[3-(1-([3-(trifluorometil)fenil]metil)-1*H*-imidazol-4-il)propil]-3,7-dihidro-1*H*-purino-2,6-diona



Una solución de 3-butil-8-cloro-1-[4-(1*H*-imidazol-4-il)butil]-7-(2-propen-1-il)-3,7-dihidro-1H-purino-2,6-diona (150 mg, 0.38 mmoles) en DMF anhidro (3 ml) se trató con 1-(clorometil)-3-(trifluorometil)benceno (65 µl, 0.42 mmoles) y DIPEA (73 µl, 0.42 mmoles). La mezcla se dejó agitar a t.a. bajo nitrógeno durante 3 días. La mezcla se dividió entre EtOAc y HCl 2M (ac.). La capa orgánica se separó, se lavó con salmuera, se secó ($MgSO_4$) y se concentró. El producto crudo se purificó sobre una columna de SPE de sílice

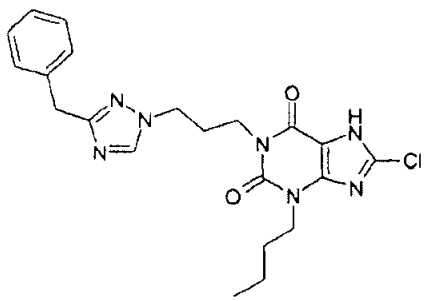
usando DCM para cargar el material en la columna y para lavar las impurezas, después un gradiente de 0-5% MeOH/DCM para eluir el compuesto. Las fracciones de producto se combinaron y se concentraron y los residuos se disolvieron en DMF anhidro (3 ml). La solución se desgasificó, después se añadió $Pd(PPh_3)_4$ (30 mg, 0.027 mmoles) y morfolina (156 µl, 1.8 mmoles) y la mezcla se dejó agitar a t.a. bajo nitrógeno durante 3 hr. El producto crudo se purificó por un SPE de aminopropilo usando MeOH para cargar el compuesto en la columna y para lavar las impurezas, después un gradiente de 0-5% de AcOH/MeOH para eluir el producto. Las fracciones de producto se combinaron y se concentraron por alto vacío para dejar el compuesto del título como un sólido blanco (18 mg, 9%).

CL/EM: m/z 509 $[MH]^+$, TR 2.78 min.

EJEMPLO 33

3-Butil-8-cloro-1-{3-[3-(fenilmetil)-1*H*-1,2,4-triazol-1-il]propil}-3,7-dihidro-1*H*-purino-2,6-diona

a) 3-Butil-8-cloro-1-{3-[3-(fenilmetil)-1*H*-1,2,4-triazol-1-il]propil}-3,7-dihidro-1*H*-purino-2,6-diona



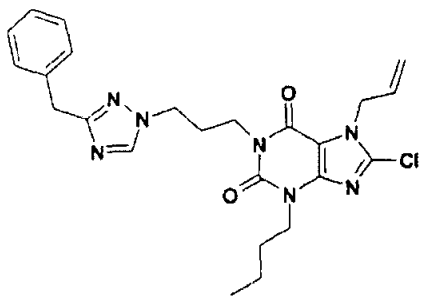
Una solución de 3-butil-8-cloro-1-{3-[3-(fenilmetil)-1*H*-1,2,4-triazol-1-il]propil}-7-(2-propen-1-il)-3,7-dihidro-1*H*-purino-2,6-diona (669 mg, 1.39 mmoles) en THF (7 ml) se desgasificó aplicando un vacío y después se introdujo nitrógeno. Se añadió $Pd(PPh_3)_4$ (160 mg, 0.14 mmoles) y la mezcla se desgasificó una vez más. Se añadió morfolina (1.2 ml, 13.9 mmoles) y la mezcla se agitó bajo nitrógeno durante 18 hr, después se dividió entre HCl 2M (ac.) y EtOAc. La capa orgánica se separó y la capa acuosa se extrajo nuevamente con EtOAc. Los extractos combinados se lavaron con salmuera, se secaron ($MgSO_4$) y se concentraron, dando un residuo amarillo. MeOH se añadió y después se hizo pasar un SPE de aminopropilo con eluyendo el producto con 2-3% de AcOH/MeOH. Las fracciones de producto se combinaron y se concentraron dando un sólido amarillo pálido (380 mg).

Aproximadamente una cuarta parte del material se purificó por CLAR autoprep. y el resto se cristalizó a partir de MeOH:DMSO (1:1) dando el compuesto del título como un sólido blanco (125 mg, 31%).

CL/EM: m/z 442 $[MH]^+$, TR 3.0 min.

^{1}H RMN (DMSO-d_6) δ: 0.89 (t, 3H, J = 7Hz), 1.30 (m, 2H), 1.62 (m, 2H), 2.07 (m, 2H), 3.90 (m, 6H), 4.13 (t, 2H, J = 7Hz), 7.24 (m, 5H), 8.36 (1H, s), 14.5 (br s, 1H).

b) 3-Butil-8-cloro-1-{3-[3-(fenilmetil)-1*H*-1,2,4-triazol-1-il]propil}-7-(2-propen-1-il)-3,7-dihidro-1*H*-purino-2,6-diona



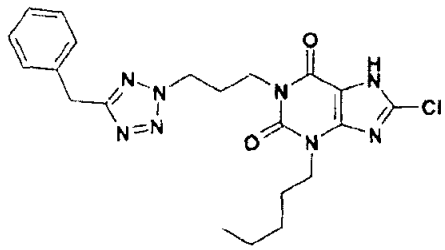
Una solución de 3-(fenilmetil)-1*H*-1,2,4-triazol (2.1 g, 13.2 mmoles) en MeOH (40 ml) se trató con NaOMe 0.5M en MeOH (29 ml) seguido por 1,3-dibromopropano (1.7 ml). Después de agitar durante 5 hr a 50°C, la mezcla se dividió entre HCl 2M (ac.) y EtOAc. La capa orgánica se separó, se lavó con salmuera, se secó ($MgSO_4$) y se concentró, dando un residuo oleoso (1.0 g). A esto, se añadió butil-8-cloro-7-(2-propen-1-il)-3,7-dihidro-1*H*-purino-2,6-diona (917 mg, 3.2 mmoles) y Cs_2CO_3 (1.2 g, 3.6 mmoles). Se añadió DMF (15 ml) y la mezcla se agitó a 50°C durante 20 hr,

después se dividió entre HCl 2M (ac.) y EtOAc. La capa orgánica se separó, se lavó con salmuera, se secó ($MgSO_4$) y se concentró. El aceite resultante (1.52 g) se hizo pasar en una columna de SPE de sílice (50 g) eluyendo con mezclas de EtOAc/ciclohexano. Se obtuvieron dos productos isoméricos del triazol como una mezcla de 2:1, a favor del compuesto del título, como una pasta amarilla (697 mg, 67% con base en la relación de isómeros presentes).

CL/EM: m/z 482 $[MH]^+$, TR 3.3 min.

EJEMPLO 34

8-Cloro-3-pentil-1-(3-[5-(fenilmetil)-2*H*-tetrazol-2-il]propil)-3,7-dihidro-1*H*-purino-2,6-diona



Una solución de 5-bencil-1*H*-tetrazol (1.0 g, 6.24 mmoles) en MeOH (5 ml) se trató con 1-cloro-3-yodopropano (1.0 ml, 9.36 mmoles) y una solución de NaOMe 0.5M en MeOH (4.7 ml, 9.36 mmoles). La reacción se calentó a reflujo durante 18 hr, después se dividió entre HCl 2M (ac.) y EtOAc. La capa orgánica se separó y la capa acuosa se extrajo una vez más con EtOAc. Los extractos combinados se lavaron con salmuera, se secaron ($MgSO_4$) y se concentraron, dando un sólido amarillo. (796 mg). 700 mg de este material se hizo reaccionar con 8-cloro-3-pentil-7-(2-propen-1-il)-3,7-

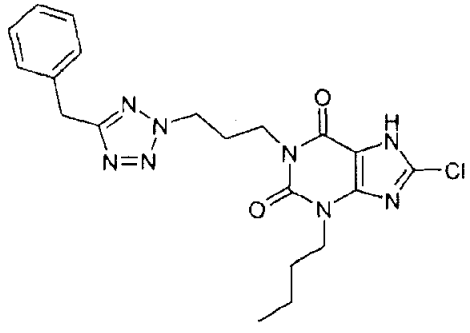
dihidro-1*H*-purino-2,6-diona (732 mg, 2.47 mmoles) y Cs_2CO_3 (967 mg, 3.0 mmoles) en DMF (20 ml) a 75°C durante 24 hr. La reacción se dejó enfriar a t.a. y la mezcla se desgasificó aplicando un vacío y después se introdujo nitrógeno. Se añadió $Pd(PPh_3)_4$ (428 mg, 0.37 mmoles) y la mezcla se desgasificó una vez más. Se añadió morfolina (2.1 ml, 24.7 mmoles) y la mezcla se agitó bajo nitrógeno durante 3 hr, después se dividió entre HCl 2M (ac.) y EtOAc. La capa orgánica se separó y la capa acuosa se extrajo una vez más. Los extractos combinados se concentraron, dando un residuo amarillo. Se añadió MeOH y después se hizo pasar un SPE de aminopropilo, eluyendo el producto con 2-3% de AcOH/MeOH. Las fracciones de producto se combinaron y se concentraron, después se purificaron por MDAP para dar el compuesto del título como un sólido blanco (35 mg, 3%).

CL/EM: m/z 457 $[MH]^+$, TR 3.5 min.

^1H RMN; (DMSO-d_6) δ: 0.85 (t, 3H, J = 7Hz), 1.21-1.34 (m, 4H), 1.62 (m, 2H), 2.22 (m, 2H), 3.88 (t, 2H, J = 7Hz), 3.97 (t, 2H, J = 7Hz), 4.17 (s, 2H), 4.67 (t, 2H, J = 7Hz), 7.20-7.32 (m, 5H), 14.5 (br s, 1H).

EJEMPLO 35

3-Butil-8-cloro-1-{3-[5-(fenilmetil)-2*H*-tetrazol-2-il]propil}-3,7-dihidro-1*H*-purino-2,6-diona



Una solución de 5-bencil-1H-tetrazol (1.8 g, 11.2 mmoles) en MeOH (30 ml) se trató con 1,3-dibromopropano (5.7 ml, 56.2 mmoles) y NaOMe 0.5M en MeOH (31.5 ml), después se agitó a 40°C bajo nitrógeno durante 60 hr. La mezcla se dividió entre HCl 2M (ac.) y EtOAc. La capa orgánica se separó, se lavó con salmuera, se secó ($MgSO_4$) y se concentró. La purificación parcial por SPE (20 g de sílice, mezclas de ciclohexano/EtOAc) y por el sistema Companion™ (SPE de sílice, mezclas de ciclohexano/EtOAc) dio un aceite (1.98 g, 62% de una mezcla de isómeros, 2:1 a favor de 2-(3-bromopropil)-5-(fenilmetil)-2*H*-tetrazol) que se recogió en crudo en el siguiente paso. Una mezcla de 3-butil-8-cloro-7-(2-propen-1-il)-3,7-dihidro-1*H*-purino-2,6-diona (1.74 g, 6.1 mmoles), 2-(3-bromopropil)-5-(fenilmetil)-2*H*-tetrazol) crudo (1.9 g, 6.8 mmoles), Cs_2CO_3 (2.2 g, 6.8 mmoles) y DMF (60 ml) se agitó a 45°C bajo nitrógeno durante 24 hr. La mezcla se desgasificó aplicando un vacío y después se introdujo nitrógeno. Se añadió $Pd(PPh_3)_4$ (705 mg, 0.61 mmoles) y la mezcla se desgasificó una vez más. Se añadió morfolina (5.4 ml,

61.4 mmoles) y la mezcla se agitó bajo nitrógeno durante 4 hr, y después se dividió entre HCl 2M (ac.) y EtOAc. La capa orgánica se separó, se lavó con salmuera, se secó ($MgSO_4$) y se concentró, dando un residuo amarillo. Se añadió MeOH y después se hizo pasar una columna de aminopropilo eluyendo el producto con 2% de AcOH/MeOH. El producto además se purificó por el sistema Companion™ usando mezclas de EtOAc/ciclohexano. El sólido resultante se agitó con Et_2O en ebullición y se filtró después de enfriarse a t.a.. El compuesto del título se recogió como un sólido blanco (1.01 g, 37%) y se secó a 50°C bajo vacío.

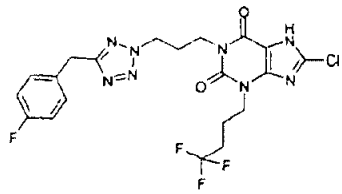
CL/EM: m/z 443 $[MH]^+$, TR 3.3 min.

^1H RMN (DMSO-d_6) δ: 0.89 (t, 3H, J = 7Hz), 1.29 (m, 2H), 1.61 (m, 2H), 2.22 (m, 2H), 3.89 (t, 2H, J = 7Hz), 3.97 (t, 2H, J = 7Hz), 4.17 (s, 2H), 4.67 (t, 2H, J = 7Hz), 7.20-7.32 (m, 5H), 14.5 (br s, 1H).

EJEMPLO 36

8-Cloro-1-(3-{5-[(4-fluorofenil)metil]-2*H*-tetrazol-2-il}propil)-3-(4,4,4-trifluorobutil)-3,7-dihidro-1*H*-purino-2,6-diona

a) 8-Cloro-1-(3-{5-[(4-fluorofenil)metil]-2*H*-tetrazol-2-il}propil)-3-(4,4,4-trifluorobutil)-3,7-dihidro-1*H*-purino-2,6-diona



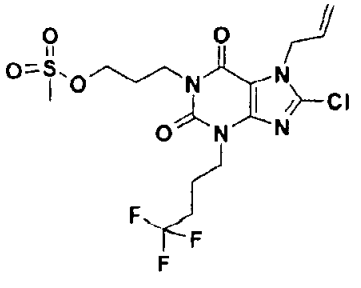
5-[(4-Fluorofenil)metil]-1H-tetrazol (75 mg, 0.4 mmoles) se trató con carbonato de potasio (100 mg, 0.7 mmoles) y DMF (3 ml). La mezcla se trató con una solución metansulfonato de 3-[8-cloro-2,6-dioxo-7-(2-propen-1-il)-3-(4,4)4-trifluorobutil)-2,3,6,7-tetrahidro-1H-purin-1-il]propilo (100 mg, 0.2 mmoles) en DMF (0.5 ml). La mezcla se agitó y se calentó a 60°C 3 horas, después se enfrió y se evaporó. El residuo se dividió entre cloroformo (4 ml) y agua (2 cm^3). 1 cm^3 de bicarbonato de sodio acuoso saturado (3 ml) se añadió a cada uno. La mezcla se separó y la fase orgánica se evaporó. El residuo se disolvió en THF anhidro (3 ml) y la mezcla se desgasificó mediante la cuidadosa aplicación sucesiva de vacío y presión de nitrógeno a la mezcla. La mezcla se trató con tetrakis(trifenilfosfin)paladio(0) (10 mg, 0.008 mmoles) y morfolina (0.2 ml, 2.3 mmoles) y después se agitó en una atmósfera de nitrógeno durante 2 hr. La mezcla se evaporó y se dividió entre cloroformo (4 ml) y cloruro de amonio acuoso saturado (3 ml). La mezcla se separó, y la

fase acuosa se volvió a extraer con cloroformo. La fase orgánica se evaporó y el residuo se disolvió en MeOH (3 ml). La solución se añadió a la parte superior de un SPE de aminopropilo de 2 g y se lavó con MeOH (15 ml). El producto deseado se eluyó del cartucho con una solución al 3% v/v de AcOH en MeOH (20 ml). Las fracciones que contenían producto se combinaron y se evaporaron y el residuo se sometió a purificación por cromatografía en columna instantánea (gradiente de elución de 10:1 de ciclohexano/EtOAc a EtOAc). El producto, que contenía fracciones se combinó y se evaporó para dar el producto como un aceite incoloro. La trituración en un mínimo de éter dietílico hizo que el producto se solidificara y éste se secó completamente para dar el compuesto del título como un sólido blanco (18.7 mg, 18%).

CL/EM: m/z 515 $[MH]^+$, TR 3.31 min.

^{1}H RMN ($CDCl_3$) δ: 2.06 (m, 2H), 2.21 (m, 2H), 2.45 (m, 2H), 4.17 (m, 4H), 4.24 (t, 2H, J = 7.0Hz), 4.70 (t, 2H, J = 7.2Hz), 6.96 (m, 2H), 7.25 (m, 2H).

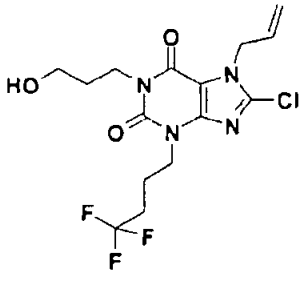
b) Metansulfonato de 3-[8-cloro-2,6-dioxo-7-(2-propen-1-il)-3-(4,4,4-trifluorobutil)-2,3,6,7-tetrahidro-1*H*-purin-1-il]propilo



Una solución de 8-cloro-1-(3-hidroxipropil)-7-(2-propen-1-il)-3-(4,4,4-trifluorobutil)-3,7-dihidro-1*H*-purino-2,6-diona (0.82 g, 2.1 mmoles) en DCM (20 ml) se trató con trietilamina (0.42 ml, 3.1 mmoles) y anhídrido metansulfónico (0.40 g, 2.3 mmoles). Después de 1 hr, la mezcla se trató con bicarbonato de sodio acuoso saturado (20 ml). La mezcla se separó y la fase orgánica se secó ($MgSO_4$), se filtró y se evaporó para dar el compuesto del título (0.91 g), que se usó sin purificación adicional.

CL/EM: m/z 473 $[MH]^+$, TR 3.17 min.

c) 8-Cloro-1-(3-hidroxipropil)-7-(2-propen-1-il)-3-(4,4,4-trifluorobutil)-3,7-dihidro-1*H*-purino-2,6-diona

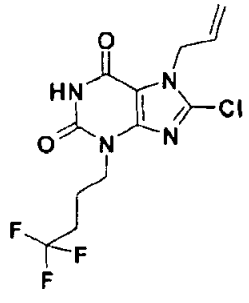


Una solución de 8-cloro-7-(2-propen-1-il)-3-(4,4,4-trifluorobutil)-3,7-dihidro-1*H*-purino-2,6-diona (1.0 g, 3.0 mmoles) en DMF (15 ml) se trató con carbonato de cesio (1.16 g, 3.6 mmoles) y 3-bromo-1-propanol (0.3 ml, 3.3 mmoles). La mezcla se calentó a 60°C durante 4 hr y después se enfrió y se evaporó. El residuo se dividió entre EtOAc (50 ml) y agua (50 ml). La fase orgánica se secó ($MgSO_4$), se filtró y se evaporó. El producto se purificó por cromatografía instantánea usando un gradiente de elución de ciclohexano a

EtOAc. Las fracciones que contenían producto se combinaron y se evaporaron para dar el compuesto del título como un aceite incoloro (0.82 g, 75%).

CL/EM: m/z 395 $[MH]^+$, TR 2.90 min.

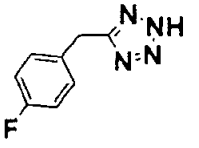
d) 8-Cloro-7-(2-propen-1-il)-3-(4,4,4-trifluorobutil)-3,7-dihidro-1*H*-purino-2,6-diona



Una solución de 8-cloro-7-(2-propen-1-il)-3,7-dihidro-1*H*-purino-2,6-diona (2.0 g, 8.8 mmoles) en DMF (20 ml) se trató con carbonato de sodio (1.15 g, 10.8 mmoles) y 4-bromo-1,1,1-trifluorobutano (1.86 g, 9.7 mmoles). La mezcla se agitó a 50°C durante 18 hr, después se enfrió y se evaporó. El residuo se dividió entre EtOAc (100 ml) y bicarbonato de sodio acuoso saturado (50 ml). La fase orgánica se secó ($MgSO_4$), se filtró y se evaporó. El residuo se trituró en una mezcla de éter dietílico y ciclohexano, después el producto se filtró y se secó para dar el compuesto del título como un sólido blanco (1.18 g, 40%).

CL/EM: m/z 337 $[MH]^+$, TR 2.83 min.

e) 5-[(4-Fluorofenil)metil]-1*H*-tetrazol



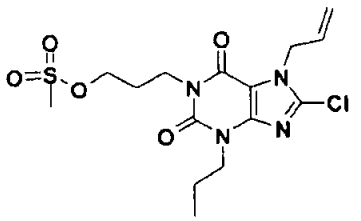
Una mezcla de cloruro de trietilamonio (4.14 g, 30 mmoles) y azida de sodio (1.95 g, 30 mmoles) se trató con una solución de (4-fluorofenil)acetonitrilo (1.35 g, 10 mmoles) en tolueno (14 ml) y la mezcla se agitó y se calentó a 100°C durante 5 hr. La mezcla enfriada se trató con agua (10 ml) y la mezcla se separó. La fase acuosa se agitó y se trató gota a gota con ácido clorhídrico concentrado hasta que el producto se precipitpo de la solución. El producto precipitado se filtró, se lavó con agua y se secó para dar el compuesto del título como un sólido blanco (1.27 g, 72%).

CL/EM: m/z 179 $[MH]^+$, TR 2.24 min.

Los compuestos en el cuadro 3 se prepararon usando un método análogo al del ejemplo 36: 8-cloro-1-(3-{5-[(4-fluorofenil)metil]-2*H*-tetrazol-2-il}propil)-3-(4,4,4-trifluorobutil)-3,7-dihidro-1H-purino-2,6-diona, con el metansulfonato y tetrazol apropiados. MDAP se usó para purificar adicionalmente esos compuestos insuficientemente puros siguiendo la cromatografía de fase normal.

Los intermediarios de metansulfonatos y sus alcoholes precursores se prepararon de conformidad con los siguientes procedimientos:

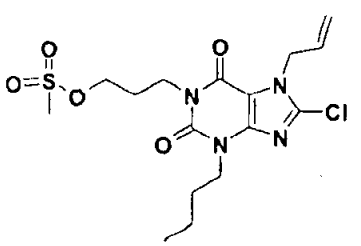
Metansulfonato de 3-[8-cloro-2,6-dioxo-7-(2-propen-1-il)-3-propil-2,3,6,7-tetrahidro-1*H*-purin-1-il]propilo



Una solución de 8-cloro-1-(3-hidroxipropil)-7-(2-propen-1-il)-3-propil-3,7-dihidro-1*H*-purino-2,6-diona (1.99 g, 6.1 mmoles) en DCM (50 ml) se trató con trietilamina (1.2 ml, 8.6 mmoles) y anhídrido metansulfónico (1.2 g, 6.9 mmoles). Después de 1.5 hr, la mezcla se trató con agua (50 ml). La mezcla se separó y la fase acuosa se extrajo con DCM (25 ml), las fases orgánicas combinadas se secaron ($MgSO_4$), se filtraron y se evaporaron para dar el compuesto del título como un aceite amarillo pálido (2.38 g), que se usó sin purificación adicional.

CL/EM: m/z 405 $[MH]^+$, TR 2.93 min.

Metansulfonato de 3-[3-butil-8-cloro-2,6-dioxo-7-(2-propen-1-il)-2,3,6,7-tetrahidro-1*H*-purin-1-il]propilo

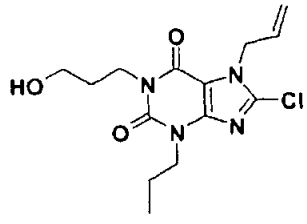


Se preparó de conformidad con el método usado para

metansulfonato de 3-[8-cloro-2,6-dioxo-7-(2-propen-1-il)-3-propil-2,3,6,7-tetrahidro-1*H*-purin-1-il]propilo para dar el compuesto del título como un aceite amarillo pálido (2.44 g).

CL/EM: m/z 419 $[MH]^+$, TR 3.14 min.

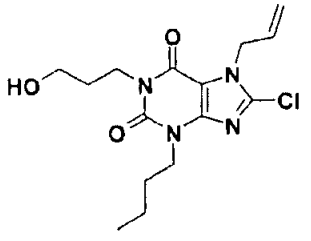
8-Cloro-1-(3-hidroxipropil)-7-(2-propen-1-il)-3-propil-3,7-dihidro-1*H*-purino-2,6-diona



Una solución de 8-cloro-7-(2-propen-1-il)-3-propil-3,7-dihidro-1*H*-purino-2,6-diona (3.0 g, 11.1 mmoles) en DMF (20 ml) se trató con carbonato de cesio (3.7 g, 11.4 mmoles) y 3-bromo-1-propanol (1.6 g, 11.5 mmoles). La mezcla se calentó a 60°C durante 4 hr y después se enfrió y se evaporó. El residuo se dividió entre EtOAc (60 ml) y bicarbonato de sodio acuoso saturado (50 ml). La fase acuosa se extrajo con EtOAc (60 ml), las fases orgánicas combinadas se secaron ($MgSO_4$), se filtraron y se evaporaron. El producto se purificó usando el sistema Companion™ y un gradiente de elución de ciclohexano a EtOAc. Las fracciones que contenían producto se combinaron y se evaporaron para dar el compuesto del título como un aceite incoloro (2.6 g).

CL/EM: m/z 327 $[MH]^+$, TR 2.62 min.

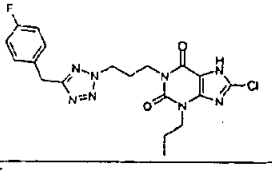
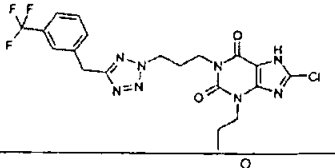
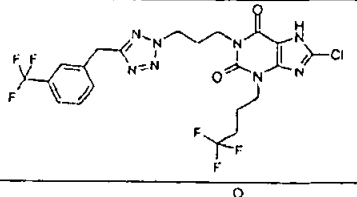
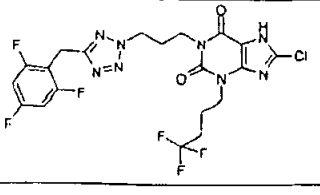
3-Butil-8-cloro-1-(3-hidroxipropil)-7-(2-propen-1-il)-3,7-dihidro-1*H*-purino-2,6-diona

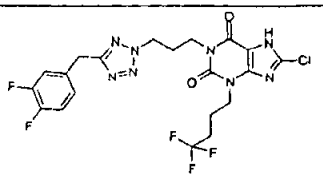
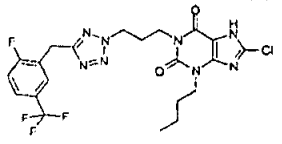
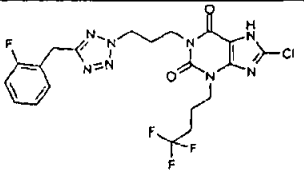
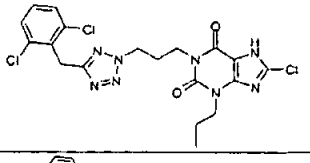
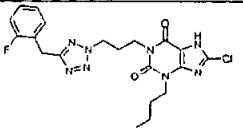
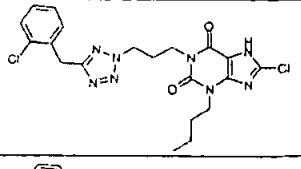
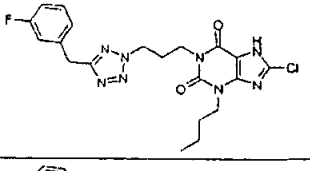
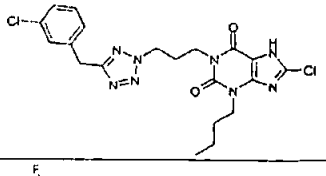
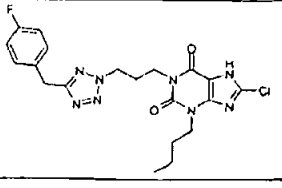


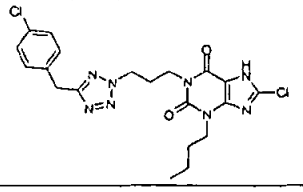
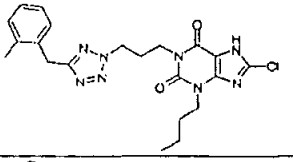
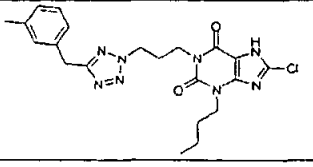
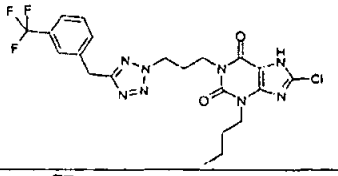
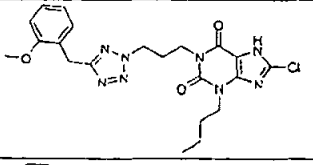
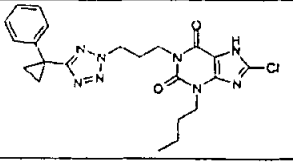
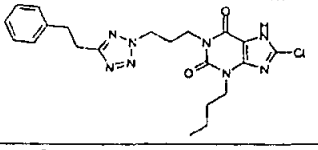
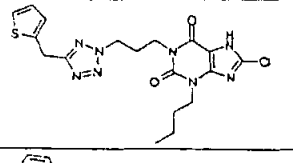
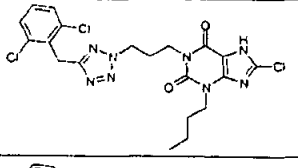
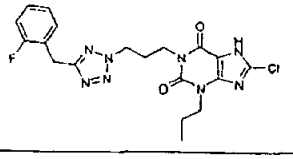
Se preparó de conformidad con el método usado para 8-cloro-1-(3-hidroxipropil)-7-(2-propen-1-il)-3-propil-3,7-dihidro-1*H*-purino-2,6-diona para dar el compuesto del título como un aceite incoloro (2.3 g).

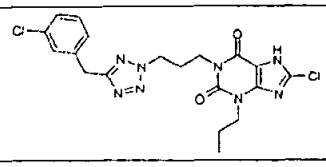
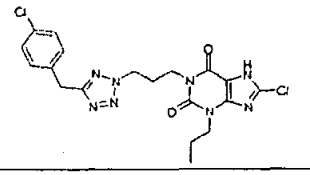
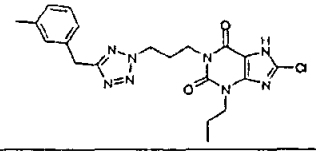
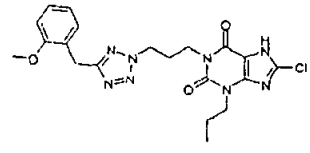
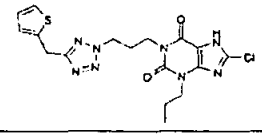
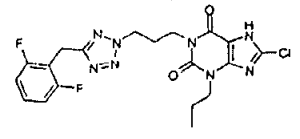
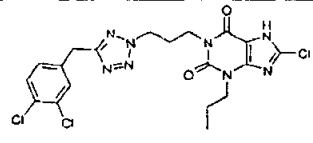
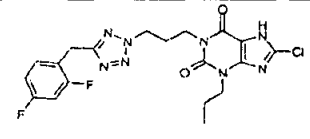
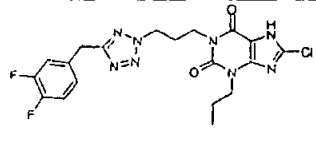
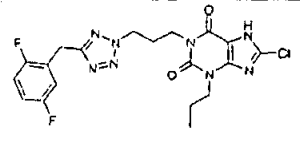
CL/EM: m/z 341 $[MH]^+$, TR 2.85 min.

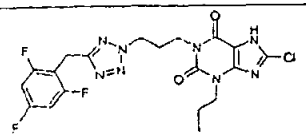
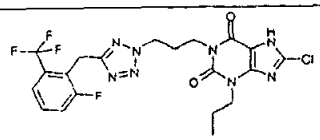
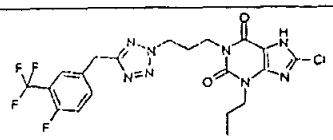
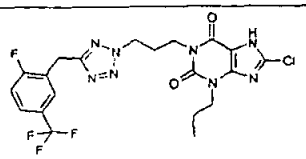
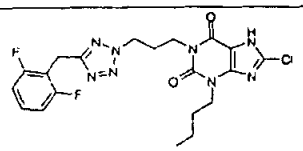
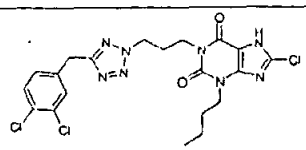
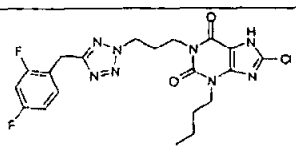
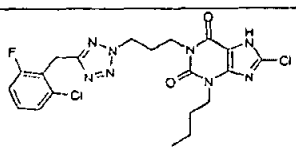
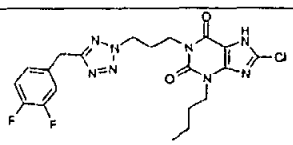
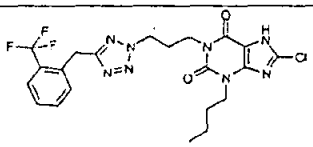
CUADRO 3

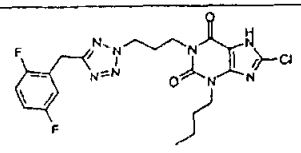
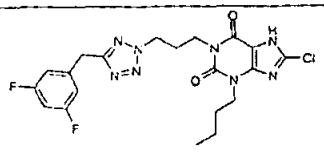
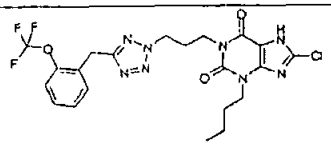
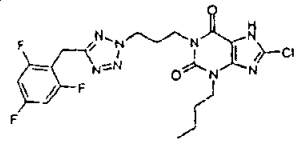
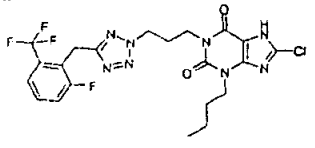
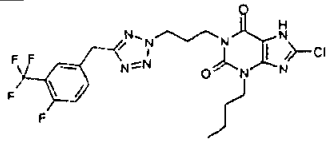
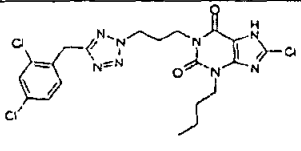
No.	Estructura	Nombre	Rend.	CL/EM:
37		8-cloro-1-(3-{5-[(4-fluorofenil)metil]-2H-tetrazol-2-il)propil)-3-propil-3,7-dihidro-1H-purino-2,6-diona	12.4 mg (14%)	m/z 447 $[MH]^+$ TR 3.14 min
38		8-cloro-3-propil-1-[3-(5-([3-(trifluorometil) fenil]metil)-2H-tetrazol-2-il)propil}-3,7-dihidro-1H-purino-2,6-diona	8.0 mg (8%)	m/z 497 $[MH]^+$ TR 3.36 min
39		8-cloro-3-(4,4,4-trifluorobutil)-1 -[3-(5-([3-(trifluorometil)-fenil]metil}-2H-tetrazol-2-il)propil]-3,7-dihidro-1H-purino-2,6-diona	21.0 mg (19%)	m/z 565 $[MH]^+$ TR 3.34 min
40		8-cloro-3-(4,4,4-trifluorobutil)-1-(3-{5-[(2,4,6-trifluorofenil)-metil]-2H-tetrazol-2-il}propil)-3,7-dihidro-1H-purino-2,6-diona	17.0 mg (15%)	m/z 551 $[MH]^+$ TR 3.27 min

41		8-cloro-1-(3-(5-[(3,4-difluorofonil)metil]2H-tetrazol-2-il}propil)-3-(4,4,4-trifluorobutil)-3,7-dihidro-1H-purino-2,6-diona	19.1 mg (18%)	m/z 533 $[MH]^+$ TR 3.36 min
42		3-butil-8-cloro-1-[3-(5-{[2-fluoro-5-(trifluorometil)fenil]metil}-2H-tetrazol-2-il)propil]-3,7-dihidro-1H-purino-2,6-diona	23.9 mg (23%)	m/z 529 $[MH]^+$ TR 3.50 min
43		8-cloro-1-(3-{5-[(2-fluorofenil)metil]-2H-tetrazol-2-il}propil)-3-(4,4,4-trifluorobutil)-3,7-dihidro-1H-purino-2,6-diona	19.8 mg (19%)	m/z 515 $[MH]^+$ TR 3.31 min
44		8-cloro-1-(3-{5-[(2,6-diclorofenil)metil]-2H-tetrazol-2-il}propil)-3-propil-3,7-dihidro-1H-purino-2,6-diona	50.7 mg (51%)	m/z 497 $[MH]^+$ TR 3.33 min
45		3-butil-8-cloro-1-(3-{5[(2-fluorofenil)metil]-2H-tetrazol-2-il}propil)-3,7-dihidro-1H-purino-2,6-diona	46.4 mg (48%)	m/z 461 $[MH]^+$ TR 3.27 min
46		3-butil-8-cloro-1-(3-{5-[(2-clorofenil)metil]-2H-tetrazol-2-il}propil)-3,7-dihidro-1H-purino-2,6-diona	25.4 mg (27%)	m/z 477 $[MH]^+$ TR 3.40 min
47		3-butil-8-cloro-1-(3-{5-[(3-fluorofenil)metil]-2H-tetrazol-2-il}propil)-3,7-dihidro-1H-purino-2,6-diona	36.8 mg (40%)	m/z 461 $[MH]^+$ TR 3.31 min
48		3-butil-8-cloro-1-(3-{5-[(3-clorofenil)metil]-2H-tetrazol-2-il}propil)-3,7-dihidro-1H-purino-2,6-diona	38.5 mg (40%)	m/z 477 $[MH]^+$ TR 3.45 min
49		3-butil-8-cloro-1-(3-{5-[(4fluorofenil)metil]-2H-tetrazol-2-il}propil)-3,7-dihidro-1H-purino-2,6-diona	31.6 mg (34%)	m/z 461 $[MH]^+$ TR 3.31 min

50		3-butil-8-cloro-1-(3-(5-[(4-clorofenil)metil]-2H-tetrazol-2-metilfenil)metil]2H-tetrazol-2-il}propil)-3,7-dihidro-1H-purino-2,6-diona	33.1 mg (35%)	m/z 477 $[MH]^+$ TR 3.46 min
51		3-butil-8-cloro-1-(3-{5-[(2-metilfenil)metil]-2H-tetrazol-2-il}propil)-3,7-dihidro-1H-purino-2,6-diona	39.5 mg (43%)	m/z 457 $[MH]^+$ TR 3.37 min
52		3-butil-8-cloro-1-(3-{5-[(3-metilfenil)metil]-2H-tetrazol-2-il}propil)-3,7-dihidro-1H-purino-2,6-diona	36.5 mg (40%)	m/z 457 $[MH]^+$ TR 3.40 min
53		3-butil-8-cloro-1-[3-(5-{[3-(trifluorometil)fenil]metil}-2H-tetrazol-2-il)propil]-3,7-dihidro-1H-purino-2,6-diona	43.7 mg (43%)	m/z 511 $[MH]^+$ TR 3.50 min
54		3-butil-8-cloro-1-[3-(5-{[2-(metiloxi)fenil]metil}-2H-tetrazol-2-il)propil]-3,7-dihidro-1H-purino-2,6-diona	28.6 mg (30%)	m/z 473 $[MH]^+$ TR 3.29 min
55		3-butil-8-cloro-1-{3-[5-(1-fenilciclopropil)-2H-tetrazol-2-il]propil}-3,7-dihidro-1H-purino-2,6-diona	44.2 mg (47%)	m/z 469 $[MH]^+$ TR 3.41 min
56		3-butil-8-cloro-1-{3-[5-(2-feniletil)-2H-tetrazol-2-il]propil}-3,7-dihidro-1H-purino-2,6-diona	39.2 mg (43%)	m/z 457 $[MH]^+$ TR 3.36 min
57		3-butil-8-cloro-1{3[5-(2-tienilmetil)-2H-tetrazol-2-il]propil}-3,7-diihidro-1H-purino-2,6-diona	33.4 mg (37%)	m/z 449 $[MH]^+$ TR 3.20 min
58		3-butil-8-cloro-1-(3-[5-[(2,6-diclorofenil)metil]-2H-tetrazol-2-il}propil)-3,7-dihidro-1H-purino-2,6-diona	36.4 mg (36%)	m/z 511 $[MH]^+$ TR 3.49 min
59		8-cloro-1-(3-{5-[(2-fluorofenil)metil]-2H-tetrazol-2-il}propil)-3-propil-3,7-dihidro-1H-purino-2,6-diona	5.6 mg (6%)	m/z 447 $[MH]^+$ TR 3.10 min

60		8-cloro-1-(3-{5-[(3-clclorofenil)metil]-2H-tetrazol-2-il}propil)-3-propil-3,7-dihidro-1H-purino-2,6-diona	5.9 mg (6%)	m/z 463 $[MH]^+$ TR 3.29 min
61		8-cloro-1-(3-{5-[(4-clorofenil)metil]-2H-tetrazol-2-il}propil)-3-propil-3,7-dihidro-1H-purino-2,6-diona	14.9 mg (16%)	m/z 463 $[MH]^+$ TR 3.30 min
62		8-cloro-1-(3-{5-[(3-metilfenil)metil]-2H-tetrazol-2-il}propil)-3-propil-3,7-dihidro-1H-purino-2,6-diona	17.5 mg (20%)	m/z 443 $[MH]^+$ TR 3.23 min
63		8-cloro-1-[3-(5-{[2-(metiloxi)fenil]metil}-2H-tetrazol-2-il)propil]-3-propil-3,7-dihidro-1H-purino-2,6-diona	14.5 mg (16%)	m/z 459 $[MH]^+$ TR 3.12 min
64		8-cloro-3-propil-1-{3-[5-(2-tienilmetil)-2H-tetrazol-2-il]propil}-3,7-dihidro-1H-purino-2,6-diona	17.0 mg (20%)	m/z 435 $[MH]^+$ TR 3.02 min
65		8-cloro-1-(3-{5-[(2,6-difluorofenil)metil]-2H-tetrazol-2-il}propil)-3-propil-3,7-dihidro-1H-purino-2,6-diona	18.4 mg (20%)	m/z 465 $[MH]^+$ TR 3.11 min
66		8-cloro-1-(3-{5-[(3,4-diclorofenil)metil]-2H-tetrazol-2-il}propil)-3-propil-3,7-dihidro-1H-purino-2,6-diona	19.4 mg (20%)	m/z 497 $[MH]^+$ TR 3.44 min
67		8-cloro-1-(3-{5-[(2,4-difluorofenil)metil]-2H-tetrazol-2-il}propil)-3-propil-3,7-dihidro-1H-purino-2,6-diona	19.1 mg (21%)	m/z 465 $[MH]^+$ TR 3.16 min
68		8-cloro-1-(3-{5-[(3,4-difluorofenil)metil]-2H-tetrazol-2-il}propil)-3-propil-3,7-dihidro-1H-purina-2.6-diona	21.5 mg (23%)	m/z 465 $[MH]^+$ TR 3.19 min
69		8-cloro-1-(3-{5-[(2,5-difluorofenil)metil]-2H-tetrazol-2-il}propil)-3-propil-3,7-dihidro-1H-purino-2,6-diona	8.5 mg (9%)	m/z 465 $[MH]^+$ TR 3.14 min

70		8-cloro-3-propil-1-(3-{5-[(2,4,6-trifluorofenil)metil]-2H-tetrazol-2-il}propil)-3,7-dihidro-1H-purino-2,6-diona	17.4 mg (18%)	m/z 483 $[MH]^+$ TR 3.09 min
71		8-cloro-1-[3-(5-{[2-fluoro-6-(trifluorometil)fenil]metil}-2H-tetrazol-2-il)propil]-3-propil-3,7-dihidro-1H-purino-2,6-diona	22.3 mg (22%)	m/z 515 $[MH]^+$ TR 3.28 min
72		8-cloro-1-[3-(5-{[4-fluoro-3-(trifluorometil)fenil]metil}-2H-tetrazol-2-il)propil]-3-propil-3,7-dihidro-1H-purino-2,6-diona	17.2 mg (17%)	m/z 515 $[MH]^+$ TR 3.30 min
73		8-cloro-1-[3-(5-{[2-fluoro-5-(trifluorometil)fenil]metil}-2H-tetrazol-2-il)propil]-3-propil-3,7-dihidro-1H-purino-2,6-diona	18.2 mg (18%)	m/z 515 $[MH]^+$ TR 3.34 min
74		3-butil-8-cloro-1-(3-{5-[(2,6-difluorofenil)metil]-2H-tetrazol-2-il}propil)-3,7-dihidro-1H-purino-2,6-diona	18.2 mg (19%)	m/z 479 $[MH]^+$ TR 3.29 min
75		3-butil-8-cloro-1-(3-{5-[(3,4-diclorofenil)metil]-2H-tetrazol-2-il}propil)-3,7-dihidro-1H-purino-2,6-diona	20.1 mg (20%)	m/z 511 $[MH]^+$ TR 3.58 min
76		3-butil-8-cloro-1-(3-{5-[(2,4-difluorofenil)metil)-2H-tetrazol-2-il}propil)-3,7-dihidro-1H-purino-2,6-diona	19.3 mg (20%)	m/z 479 $[MH]^+$ TR 3.33 min
77		3-butil-8-cloro-1-(3-{5-[(2-cloro-6-fluorofenil)metil]-2H-tetrazol-2-il}propil)-3,7-dihidro-1H-purino-2,6-diona	18.9 mg (19%)	m/z 495 $[MH]^+$ TR 3.33 min
78		3-butil-8-cloro-1-(3-{5-[(3,4-difluorofenil)metil]-2H-tetrazol-2-il}propil)-3,7-dihidro-1H-purino-2,6-diona	21.7 mg (23%)	m/z 479 $[MH]^+$ TR 3.33 min
79		3-butil-8-cloro-1-[3-(5-{[2-(trifluorometil)fenil]metil}-2H-tetrazol-2-il)propil]-3,7-dihidro-1H-purino-2,6-diona	18.1 mg (18%)	m/z 511 $[MH]^+$ TR 3.32 min

80		3-butil-8-cloro-1-(3-{5-[(2,5-difluorofenil)metil]-2H-tetrazol-2-il}propil)-3,7-dihidro-1H-purino-2,6-diona	24.0 mg (25%)	m/z 479 $[MH]^+$ TR 3.31 min
81		3-butil-8-cloro-1-(3-{5-[(3,5-difluorofenil)metil]-2H-tetrazol-2-il}propil)-3,7-dihidro-1H-purino-2,6-diona	15.9 mg (17%)	m/z 479 $[MH]^+$ TR 3.38 min
82		3-butil-8-cloro-1-{3-[5-({2-[(trifluorometil)oxi]fenil}metil)-2H-tetrazol-2-il]propil}-3,7-dihidro-1H-purino-2,6-diona	32.8 mg (31%)	m/z 527 $[MH]^+$ TR 3.51 min
83		3-butil-8-cloro-1-(3-{5-[(2,4,6-trifluorofenil)metil]-2H-tetrazol-2-il}propil)-3,7-dihidro-1H-purino-2,6-diona	20.7 mg (21%)	m/z 497 $[MH]^+$ TR 3.35 min
84		3-butil-8-cloro-1-[3-(5-{[2-fluoro-6-(trifluorometil)fenil]metil}-2H-tetrazol-2-il)propil]-3,7-dihidro-1H-purino-2,6-diona	23.9 mg (23%)	m/z 529 $[MH]^+$ TR 3.44 min
85		3-butil-8-cloro-1-[3-(5-{[4-fluoro-3-(trifluorometil)fenil]metil}-2H-tetrazol-2-il)propil]-3,7-dihidro-1H-purino-2,6-diona	13.9 mg (13%)	m/z 529 $[MH]^+$ TR 3.53 min
86		3-butil-8-cloro-1-(3-{5-[[2,4-diclorofenil)metil]-2H-tetrazol-2-il}propil)-3,7-dihidro-1H-purino-2,6-diona	17.5 mg (17%)	m/z 511 $[MH]^+$ TR 3.63 min

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Detalles de RMN para ejemplos seleccionados del cuadro 3

EJEMPLO 37

8-Cloro-1-(3-{5-[(4-fluorofenil)metil]-2*H*-tetrazol-2-il}propil)-3-propil-3,7-dihidro-1*H*-purino-2,6-diona

^{1}H RMN ($CDCl_3$) δ: 0.99 (t, 3H, J = 7.5 Hz), 1.80 (m, 2H), 2.46 (m, 2H), 4.06 (m, 2H), 4.18 (s, 2H), 4.25 (t, 2H, J = 7Hz), 4.70 (t, 2H, J = 7.5Hz), 6.96 (m, 2H), 7.26 (m, 2H), 13.15 (br s, 1H).

EJEMPLO 40

8-Cloro-3-(4,4,4-trifluorobutil)-1-(3-{5-[(2,4,6-trifluorofenil)metil]-2*H*-tetrazol-2-il}propil)-3,7-dihidro-1*H*-purino-2,6-diona

^{1}H RMN ($CDCl_3$) δ: 2.07 (m, 2H), 2.21 (m, 2H), 2,44 (m, 2H), 4.18 (t, 2H, J = 7.1Hz), 4.20 (s, 2H), 4.24, (t, 2H, J = 6.8Hz), 4.68 (t, 2H, J = 7.3Hz), 6.67 (t, 2H, J = 8.1Hz), 13.04 (br s, 1H).

EJEMPLO 41

^{1}H RMN ($CDCl_3$): 2.03-2.10 (m, 2H), 2.16-2.28 (m, 2H), 2.43-2.50 (m, 2H), 4.16-4.19 (m, 2H), 4.17 (s, 2H), 4.24 (t, 2H, J=7.1Hz), 4.71 (t, 2H, J=7.1Hz), 7.00-7.13 (m, 3H), 13.06 (bs, 1H).

EJEMPLO 44

^{1}H RMN ($CDCl_3$): 0.99 (t, 3H, J=7.5Hz), 1.76-1.86 (m, 2H), 2.40-2.47 (m, 2H), 4.05-4.09 (m, 2H), 4.23-4.26 (m, 2H), 4.54 (s, 2H), 4.65-4.69 (m, 2H), 7.14-7.18 (m, 1H), 7.31-7.33, (m, 2H), 13.18 (bs, 1H).

EJEMPLO 45

^{1}H RMN ($CDCl_3$): 0.97 (t, 3H, J=7.5Hz), 1.36-1.46 (m, 2H), 1.71-1.79 (m, 2H), 2.42-2.49 (m, 2H), 4.08-4.11 (m, 2H), 4.25 (s, 2H), 4.24-4.27 (m, 2H), 4.68-4.71 (m, 2H), 7.02-7.09 (m, 2H), 7.20-7.26, (m, 2H), 13.14 (bs, 1H).

EJEMPLO 46

^{1}H RMN ($CDCl_3$): 0.97 (t, 3H, J=7.5Hz), 1.36-1.45 (m, 2H), 1.71-1.79 (m, 2H), 2.42-2.49 (m, 2H), 4.09 (t, 2H, J=7.5Hz), 4.26 (t, 2H, J=7.5Hz), 4.34 (s, 2H), 4.70 (t, 2H, J=7.3Hz), 7.18-7.21 (m, 2H), 7.25-7.27, (m, 1H), 7.35-7.37, (m, 1H), 13.34 (bs, 1H).

EJEMPLO 47

3-Butil-8-cloro-1-(3-{5-[(3-fluorofenil)metil]-2*H*-tetrazol-2-il}propil)-3,7-dihidro-1*H*-purino-2,6-diona

^{1}H RMN ($CDCl_3$) δ: 0.97 (t, 3H, J = 7Hz), 1.40 (m, 2H), 1.75 (m, 2H), 2.46 (m, 2H), 4.10 (t, 2H, J = 7.5Hz), 4.21 (s, 2H), 4.26 (t, 2H 1 J = 6.5Hz), 4.70 (t, 2H, J = 7.5Hz), 6.90 (m, 1H)1 6.99 (m, 1H), 7.07 (m, 1H), 7.25 (m, 1H), 13.25 (br s, 1H).

EJEMPLO 48

^{1}H RMN ($CDCl_3$): 0.99 (t, 3H, J=7.5Hz), 1.38-1.48 (m, 2H), 1.73-1.81 (m, 2H), 2.44-2.51 (m, 2H), 4.12 (t, 2H, J=7.5Hz), 4.20 (s, 2H), 4.27 (t, 2H, J=7.5Hz), 4.70 (t, 2H, J=7.3Hz), 6.95-7.00 (m, 2H), 7.26-7.30, (m, 2H), 13.35 (bs, 1H).

EJEMPLO 49

3-Butil-8-cloro-1-(3-{5-[(4-fluorofenil)metil]-2*H*-tetrazol-2-il}propil)-3,7-dihidro-1*H*-purino-2,6-diona

^{1}H RMN ($CDCl_3$) δ: 0.99 (t, 3H, J = 7Hz), 1.43 (m, 2H), 1.77 (m, 2H), 2.48 (m, 2H), 4.12 (t, 2H, J = 7.5Hz), 4.20 (s, 2H), 4.27 (t, 2H 1 J = 7Hz), 4.72 (t, 2H, J = 7.5Hz), 6.98 (m, 2H), 7.27 (m, 2H), 13.35 (br s, 1H).

EJEMPLO 50

3-Butil-8-cloro-1-(3-{5-[(4-clorofenil)metil]-2*H*-tetrazol-2-il}propil)-3,7-dihidro-1*H*-purino-2,6-diona

^{1}H RMN ($CDCl_3$) δ: 1.02 (t, 3H, J = 7.5Hz), 1.45 (m, 2H), 1.79 (m, 2H), 2.50 (m, 2H), 4.14 (t, 2H, J = 7.5Hz), 4.22 (s, 2H), 4.29 (t, 2H 1 J = 7Hz), 4.75 (t, 2H, J = 7.5Hz), 7.27 (S, 4H), 13.35 (br s, 1H).

EJEMPLO 55

3-Butil-8-cloro-1-{3-[5-(1-fenilciclopropil)-2*H*-tetrazol-2-il]propil}-3,7-dihidro-1*H*-purino-2,6-diona

^{1}H RMN ($CDCl_3$) δ: 0.93 (t, 3H, J = 7.3Hz), 1.36 (m, 4H), 1.55 (m, 2H), 1.71 (m, 2H), 2.38 (m, 2H), 4.06 (t, 2H1 J = 7.5Hz), 4.20 (t, 2H, J =6.7Hz), 4.59 (t, 2H, J = 7.5Hz), 7.25 (m, 3H), 7.36 (m, 2H), 13.30 (br s, 1H).

EJEMPLO 67

8-Cloro-1-(3-{5-[(2,4-difluorofenil)metil]-2*H*-tetrazol-2-il}propil)-3-propil-3,7-dihidro-1*H*-purino-2,6-diona

^{1}H RMN ($CDCl_3$) δ: 0.99 (t, 3H, J = 7.5 Hz), 1.80 (m, 2H), 2.45 (m, 2H), 4.06 (m, 2H), 4.20 (s, 2H), 4.25 (t, 2H, J = 7Hz), 4.70 (t, 2H, J = 7.5Hz), 6.80 (m, 2H), 7.23 (m, 1H).

EJEMPLO 70

8-Cloro-3-propil-1-(3-{5-[(2,4,6-trifluorofenil)metil]-2*H*-tetrazol-2-il}propil)-3,7-dihidro-1*H*-purino-2,6-diona

^{1}H RMN ($CDCl_3$) δ: 0.99 (t, 3H, J = 7.3 Hz), 1.80 (m, 2H), 1.98 (m, 2H), 2.01 (m, 2H), 4.20 (s, 2H), 4.25 (t, 2H, J = 6.5Hz), 4.67 (t, 2H, J = 7.3Hz), 6.68 (t, 2H, J = 8.1Hz).

EJEMPLO 71

^{1}H RMN ($CDCl_3$): 0.99 (t, 3H, J=7.3Hz), 1.76-1.85 (m, 2H), 2.39-2.46 (m, 2H), 4.05-4.08 (m, 2H), 4.24 (t, 2H, J=7.1Hz), 4.39 (s, 2H), 4.64 (t, 2H, J=7.1Hz), 7.29-7.32 (m, 1H), 7.38-7.44, (m, 1H), 7.49-7.51, (m, 1H), 13.17 (bs, 1H).

EJEMPLO 78

^{1}H RMN ($CDCl_3$): 0.99 (t, 3H, J=7.6Hz), 1.36-1.45 (m, 2H), 1.71-1.79 (m, 2H), 2.42-2.49 (m, 2H), 4.09 (t, 2H, J=7.5Hz), 4.17 (s, 2H), 4.24 (t, 2H, J=7.5Hz), 4.71 (t, 2H, J=7.3Hz), 7.00-7.14 (m, 3H), 13.07 (bs, 1H).

EJEMPLO 80

^{1}H RMN ($CDCl_3$): 0.96 (t, 3H, J=7.2Hz), 1.32-1.47 (m, 2H), 1.68-

1.80 (m, 2H), 2.40-2.51 (m, 2H), 4.06-4.12 (m, 2H), 4.22 (s, 2H), 4.22-4.27 (m, 2H), 4.67-4.73 (m, 2H), 6.84-7.04 (m, 3H), 13.05 (bs, 1H).

EJEMPLO 83

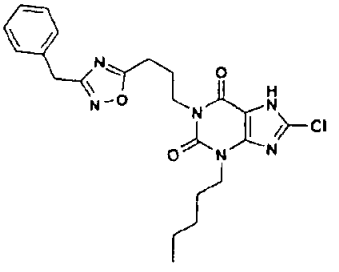
3-Butil-8-cloro-1-(3-{5-[(2,4,6-trifluorofenil)metil]-2*H*-tetrazol-2-il}propil)-3,7-dihidro-1*H*-purino-2,6-diona

1H RMN ($CDCl_3$) δ: 0.97 (t, 3H, J = 7.3Hz), 1.41 (m, 2H), 1.75 (m, 2H), 2.44 (m, 2H), 4.10 (t, 2H, J = 7.5Hz), 4.20 (s, 2H), 4.25 (t, 2H, J = 6.5Hz), 4.67 (t, 2H, J = 7.4Hz), 6.67 (t, 2H, J = 8.0Hz), 13.25 (br s, 1H).

EJEMPLO 87

8-Cloro-3-pentil-1-{3-[3-(fenilmetil)-1,2,4-oxadiazol-5-il]propil}-3,7-dihidro-1*H*-purino-2,6-diona

a) 8-Cloro-3-pentil-1-{3-[3-(fenilmetil)-1,2,4-oxadiazol-5-il]propil}-3,7-dihidro-1*H*-purino-2,6-diona



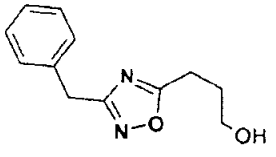
Una solución de 3-[3-(fenilmetil)-1,2,4-oxadiazol-5-il]-1-propanol

(88 mg, 0.4 mmoles) en THF (4 ml) se trató con 8-cloro-3-pentil-7-(2-propen-1-il)-3,7-dihidro-1*H*-purino-2,6-diona (100 mg, 0.34 mmoles) y PPh_3 (115 mg, 0.44 mmoles) bajo nitrógeno. Se añadió DBAD (101 mg, 0.44 mmoles) en una porción y la reacción se dejó reaccionar durante 5 hr. La mezcla se desgasificó aplicando un vacío y después se introdujo nitrógeno. Se añadió $Pd(PPh_3)_4$ (39 mg, 0.034 mmoles) y la mezcla se desgasificó una vez más. Se añadió morfolina (294 µl, 3.4 mmoles) y la mezcla se agitó bajo nitrógeno durante 3 hr. La mezcla se dividió entre HCl 2M (ac.) y EtOAc. La capa orgánica se separó, se lavó con salmuera, se secó ($MgSO_4$) y se concentró. El compuesto del título se obtuvo como un sólido blanco después de purificación por MDAP (64 mg, 42%).

CL/EM: m/z 457 $[MH]^+$, TR 3.4 min.

^{1}H RMN (DMSO-d_6) δ: 0.85 (t, 3H, J = 7Hz), 1.22-1.34 (m, 4H), 1.62 (m, 2H), 2.02 (m, 2H), 2.91 (t, 2H, J = 7Hz), 3.88 (t, 2H, J = 7Hz), 3.95-4.00 (m, 4H), 7.22-7.33 (m, 5H), 14.5 (br s, 1H).

b) 3-[3-(Fenilmetil)-1,2,4-oxadiazol-5-il]-1-propanol



Una mezcla de γ-butirolactona (223 µl, 2.9 mmoles), benzamidin oxima (480 mg, 3.2 mmoles), solución al 21% de NaOEt en EtOH (1.3 ml) y EtOH (3 ml) se calentó en el microondas a 140°C durante 10 min. La mezcla

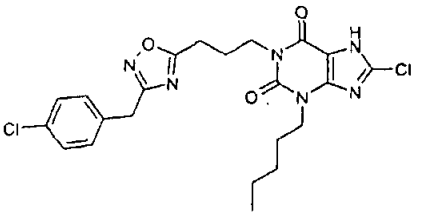
se dividió entre HCl 2M (ac.) y EtOAc. La capa orgánica se separó, se lavó con salmuera, se secó ($MgSO_4$) y se concentró. El producto del título se purificó sobre sílice usando el sistema Companion™ para dar un aceite amarillo pálido (143 mg, 23%).

CL/EM: m/z 219 $[MH]^+$, TR 2.4 min.

EJEMPLO 88

8-Cloro-1-(3-{3-[(4-clorofenil)metil]-1,2,4-oxadiazol-5-il)propil)-3-pentil-3,7-dihidro-1*H*-purino-2,6-diona

a) 8-Cloro-1-(3-{3-[(4-clorofenil)metil]-1,2,4-oxadiazol-5-il}propil)-3-pentil-3,7-dihidro-1*H*-purino-2,6-diona

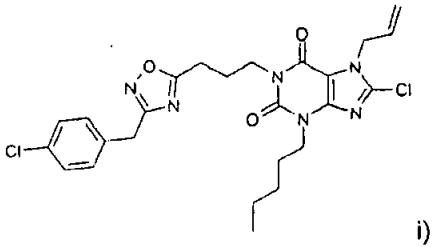


Una solución de 8-cloro-1-(3-{3-[(4-clorofenil)metil]-1,2,4-oxadiazol-5-il}propil)-3-pentil-7-(2-propen-1-il)-3,7-dihidro-1*H*-purino-2,6-diona (0.18 g, 0.34 mmoles) en DMF (5 ml) se desgasificó por evacuación secuencial del matraz y admisión de nitrógeno (x3) y morfolina (0.5 ml, 5.8 mmoles), y se añadió $Pd(PPh_3)_4$ (80 mg, 0.068 mmoles). La solución se agitó durante 72 hr, después se concentró y los residuos se cargaron en un SPE de aminopropilo (10 g) con MeOH. La elución con MeOH seguida por 5% de

AcOH/MeOH dio el compuesto del título como un sólido amarillo pálido, que se lavó con éter para dar un sólido blanco (0.053 g, 32%).

CL/EM: m/z 491 $[MH]^+$, TR 3.69 min.

b) 8-Cloro-1-(3-{3-[(4-clorofenil)metil]-1,2,4-oxadiazol-5-il}propil)-3-pentil-7-(2-propen-1-il)-3,7-dihidro-1*H*-purino-2,6-diona



i)

i) Una mezcla de γ-butirolactona (8 ml, 104 mmoles), 4-clorobenzamidin oxima (3.0 g, 16.25 mmoles), solución al 30% de NaOMe en MeOH (5 ml) y MeOH (80 ml) se puso a reflujo durante 30 hr, se enfrió y se concentró. Los residuos se purificaron por cromatografía instantánea sobre sílice eluyendo con DCM/EtOH/0.88 de amoniaco acuoso (200:8:1) para proveer un aceite amarillo (13 g). Este material se disolvió en DCM (150 ml) y se lavó con hidróxido de sodio 2M (100 ml) y los compuestos orgánicos se separaron, se secaron y se concentraron para dar 3-{3-[(4-clorofenil)metil]-1,2,4-oxadiazol-5-il}-1-propanol como un aceite viscoso (3.95 g, 96%) que se usó en el siguiente paso.

ii) A una solución de 8-cloro-3-pentil-7-(2-propen-1-il)-3,7-dihidro-1*H*-purino-2,6-diona (0.10 g, 0.34 mmoles), 3-{3-[(4-clorofenil)metil]-1,2,4-oxadiazol-5-il}-1-propanol (0.086 g, 0.34 mmoles) y trifenilfosfina (0.186 g,

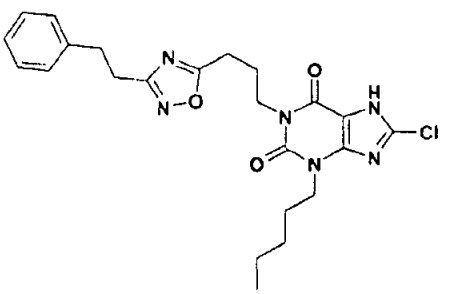
0.69 mmoles) en THF (5 ml) se añadió dicarboxilato de dibencilo (0.204 g, 0.68 mmoles) y la solución se agitó durante 18 hr. La solución después se concentró y los residuos se sometieron a cromatografía sobre sílice (20 g, SPE) eluyendo inicialmente con DCM, después con mezclas de DCM/Et_2O para dar el compuesto del título contaminado con subproductos de dicarboxilato de dibencilo (0.18 g). El material se usó crudo en el paso de desprotección.

CL/EM: m/z 531 $[MH]^+$, TR 3.83 min.

EJEMPLO 89

8-Cloro-3-pentil-1-{3-[3-(2-feniletil)-1,2,4-oxadiazol-5-il]propil}-3,7-dihidro-1*H*-purino-2,6-diona

a) 8-Cloro-3-pentil-1-{3-[3-(2-feniletil)-1,2,4-oxadiazol-5-il]propil}-3,7-dihidro-1*H*-purino-2,6-diona



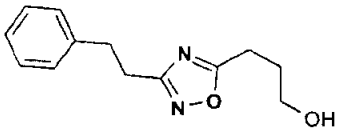
Una solución de 3-[3-(2-feniletil)-1,2,4-oxadiazol-5-il]-1-propanol (150 mg, 0.65 mmoles) en THF (6 ml) se trató con 8-cloro-3-pentil-7-(2-propen-1-il)-3,7-dihidro-1*H*-purino-2,6-diona (160 mg, 0.54 mmoles) y PPh_3

(183 mg, 0.70 mmoles) bajo nitrógeno. Se añadió DBAD (161 mg, 0.70 mmoles) en una porción y la reacción se dejó reaccionar durante 18 hr. La mezcla se desgasificó aplicando un vacío y después se introdujo nitrógeno. Se añadió $Pd(PPh_3)_4$ (39 mg, 0.034 mmoles) y la mezcla se desgasificó una vez más. Se añadió morfolina (294 µl, 3.4 mmoles) y la mezcla se agitó bajo nitrógeno durante 3 hr. La mezcla se dividió entre HCl 2M (ac.) y EtOAc. La capa orgánica se separó, se lavó con salmuera, se secó ($MgSO_4$) y se concentró. El residuo se recogió en MeOH y se purificó haciendo pasar un SPE de aminopropilo, el producto se eluyó con 2-5% de AcOH/MeOH. El compuesto del título se obtuvo como un sólido blanquecino (185 mg, 73%).

CL/EM: m/z 471 $[MH]^+$, TR 3.6 min.

^1H RMN; (DMSO-d_6) δ: 0.85 (t, 3H, J = 7Hz), 1.23-1.34 (m, 4H), 1.63 (m, 2H), 2.06 (m, 2H), 2.87 (m, 4H), 2.93 (t, 2H, J = 7Hz), 3.89 (t, 2H, J = 7Hz), 4.00 (t, 2H, J = 6.5Hz), 7.16-7.29 (m, 5H), 14.5 (br s, 1H).

b) 3-[3-(2-Feniletil)-1,2,4-oxadiazol-5-il]-1-propanol



Una mezcla de γ-butirolactona (426 µl, 5.5 mmoles), fenetilamidin oxima (1.0 g, 6.1 mmoles), solución al 21% de NaOEt en EtOH (2 ml) y EtOH (3 ml) se calentó en el microondas a 140°C durante 10 min. La mezcla se dividió entre HCl 2M (ac.) y EtOAc. La capa orgánica se separó, se lavó con

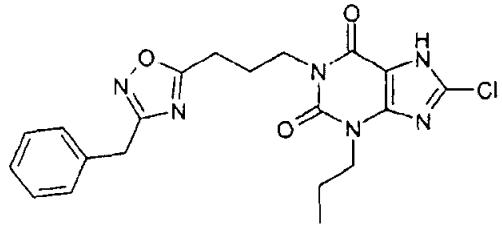
salmuera, se secó ($MgSO_4$) y se concentró. El producto del título se purificó por Si-SPE eluyendo con mezclas de EtOAc/ciclohexano para dar el compuesto del título como un aceite amarillo pálido (390 mg, 31%).

CL/EM: m/z 233 $[MH]^+$, TR 2.5 min.

EJEMPLO 90

8-Cloro-1-{3-[3-(fenilmetil)-1,2,4-oxadiazol-5-il]propil)-3-propil-3,7-dihidro-1*H*-purino-2,6-diona

a) 8-Cloro-1-{3-[3-(fenilmetil)-1,2,4-oxadiazol-5-il]propil}-3-propil-3,7-dihidro-1*H*-purino-2,6-diona



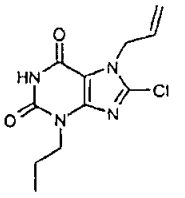
Una solución de 8-cloro-7-(2-propen-1-il)-3-propil-3,7-dihidro-1*H*-purino-2,6-diona (200 mg, 0.74 mmoles) en THF (4 ml) se trató con 3-[3-(fenilmetil)-1,2,4-oxadiazol-5-il]-1-propanol (195 mg, 0.89 mmoles) y PPh_3 (254 mg, 0.96 mmoles). Se añadió DBAD (223 mg, 0.96 mmoles) en una porción y la mezcla se dejó agitar a t.a. bajo nitrógeno durante 18 hr. La mezcla se dividió entre EtOAc y HCl 2M (ac.). La capa orgánica se separó, se lavó con salmuera, se secó ($MgSO_4$) y se concentró. El producto crudo se purificó mediante una columna de SPE de sílice usando un gradiente de 0-70% de ciclohexano/EtOAc. Las fracciones de producto se combinaron, se

concentraron y se purificaron adicionalmente mediante una columna de SPE de sílice usando un gradiente de 0-60% de ciclohexano/EtOAc. Las fracciones de producto se combinaron y se concentraron, después se disolvió en THF anhidro (4 ml). La solución se desgasificó por alto vacío, después se añadieron $Pd(PPh_3)_4$ (86 mg, 0.074 mmoles) y morfolina (644 µl, 7.4 mmoles) y la mezcla se dejó agitar a t.a. bajo nitrógeno durante 1 día. La mezcla se dividió entre EtOAc y HCl (ac.). La capa orgánica se separó, se lavó con salmuera, se secó ($MgSO_4$) y se concentró por alto vacío. El producto crudo se purificó mediante un SPE de aminopropilo usando MeOH para cargar el compuesto en la columna y para lavar las impurezas, después un gradiente de 2-4% de AcOH/MeOH para eluir el producto. Las fracciones de producto se combinaron y se concentraron por alto vacío para dejar el compuesto del título como un sólido blanco (74 mg, 23%).

CL/EM: m/z 429 $[MH]^+$, TR 3.14 min.

^1H RMN; (DMSO-d_6) δ: 0.87 (t, 3H1 J = 7.5 Hz), 1.65 (m, 2H), 2.02 (m, 2H), 2.91 (t, 2H, J = 7.5Hz), 3.86 (t, 2H, J = 7Hz), 3.97 (s, traslape de t, 4H), 7.27 (m, 5H) 14.46 (s, 1H).

b) 8-Cloro-7-(2-propen-1-il)-3-propil-3,7-dihidro-1*H*-purino-2,6-diona



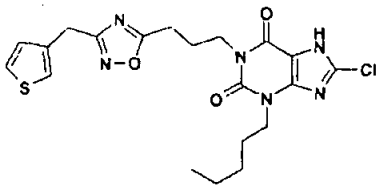
Una mezcla de 8-cloro-7-(2-propen-1-il)-3,7-dihidro-1*H*-purino-2,6-diona (1.5 g, 6.6 mmoles), 1-yodopropano (1.2 g, 6.9 mmoles) y carbonato de sodio (0.9 g, 8.5 mmoles) en DMF (40 ml) se calentó a 50°C durante 18 hr. La mezcla de reacción se concentró bajo vacío y el residuo se trató con agua (60 ml) y se extrajo con EtOAc (3x 80 ml). Los extractos orgánicos combinados se secaron ($MgSO_4$) se filtraron y se evaporaron. El residuo se trituró con éter/ciclohexano, el sólido se filtró y se secó para dar el compuesto del título (0.82 g, 46%).

CL/EM: m/z 269 $[MH]^+$.

EJEMPLO 91

8-Cloro-3-pentil-1-{3-[3-(3-tienilmetil)-1,2,4-oxadiazol-5-il]propil}-3,7-dihidro-1*H*-purino-2,6-diona

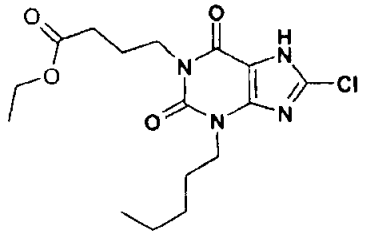
a) 8-Cloro-3-pentil-1-{3-[3-(3-tienilmetil)-1,2,4-oxadiazol-5-il]propil}-3,7-dihidro-1H-purino-2,6-diona



Una mezcla de 4-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)butanoato de etilo (70 mg, 0.19 mmoles), *N*-hidroxi-2-(3-tienil)etanimidamida (36 mg, 0.23 mmoles), solución al 21% de NaOEt en EtOH (78 µl, 0.21 mmoles) y EtOH (1.5 ml) se calentó en el microondas a 140°C durante 10 min. Después de enfriarse, la reacción se dividió entre HCl 2M (ac.) y EtOAc. La capa orgánica se separó y la capa acuosa se extrajo nuevamente con EtOAc. Los extractos combinados se concentraron y se purificaron por MDAP. El compuesto del título se secó por congelamiento a partir de 1,4-dioxano para dar un sólido blanco (27 mg, 31%).

CL/EM: m/z 463 $[MH]^+$, TR 3.4 min.

b) 4-(8-Cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1*H*-purin-1-il)butanoato de etilo

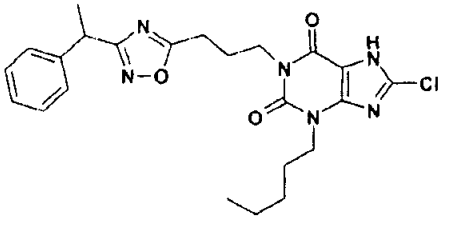


Una solución de 8-cloro-3-pentil-7-(2-propen-1-il)-3,7-dihidro-1*H*-purino-2,6-diona (3.0 g, 10.1 mmoles) en DMF anhidro (35 ml) se trató con Cs_2CO_3 (3.6 g, 11.1 mmoles) y 4-bromobutirato de etilo (1.6 ml, 11.1 mmoles). La mezcla se agitó a t.a. durante 18 hr, después se desgasificó bajo un vacío suave, después se introdujo nitrógeno. Esto se repitió dos veces. Se añadió $Pd(PPh_3)_4$ (1.17g, 1.0 mmoles) y la mezcla se desgasificó una vez más. Se añadió morfolina (8.8 ml, 101 mmoles) y se dejó agitar durante 3 hr a t.a. La mezcla se dividió entre HCl 2M (ac.) y EtOAc. La capa orgánica se separó, se lavó con salmuera, se secó ($MgSO_4$) y se concentró, dando un sólido amarillo (5.16 g). El residuo se recogió en MeOH y se dividió en dos porciones iguales, y después cada una se hizo pasar por un SPE de aminopropilo (20 g), eluyendo con MeOH seguido por 5% de AcOH/MeOH. Las fracciones de producto se combinaron y se concentraron dando el compuesto del título como un sólido casi blanco (3.01 g, 80%).

CL/EM: m/z 371 $[MH]^+$, TR 3.2 min.

EJEMPLO 92

8-Cloro-3-pentil-1-{3-[3-(1-feniletil)-1,2.4-oxadiazol-5-il]propil)-3,7-dihidro-1*H*-purino-2,6-diona



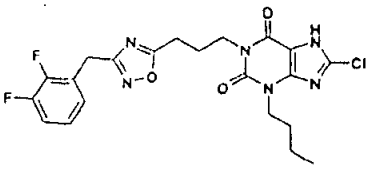
Una mezcla de 4-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1*H*-purin-1-il)butanoato de etilo (70 mg, 0.19 mmoles), N-hidroxi-2-fenilpropanimidamida (38 mg, 0.23 mmoles), solución al 21% de NaOEt en EtOH (78 µl, 0.21 mmoles) y EtOH (1.5 ml) se calentó en el microondas a 140°C durante 10 min. Después de enfriarse, la reacción se dividió entre HCl 2M (ac.) y EtOAc. La capa orgánica se separó y la capa acuosa se extrajo nuevamente con EtOAc. Los extractos combinados se concentraron y se purificaron por MDAP. El compuesto del título se secó por congelamiento a partir de 1,4-dioxano para dar un sólido blanco (44 mg, 49%).

CL/EM: m/z 471 $[MH]^+$, TR 3.6 min.

EJEMPLO 93

3-Butil-8-cloro-1-{3-[3-(2,3-difluorobencil)-1,2,4-oxadiazol-5-il]propil}-3,7-dihidro-1*H*-purino-2,6-diona

a) 3-Butil-8-cloro-1-{3-[3-(2,3-difluorobencil)-1,2,4-oxadiazol-5-il]propil}-3,7-dihidro-1*H*-purino-2,6-diona



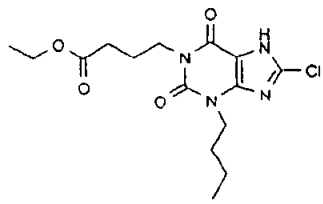
2,3-Difluorofenilacetonitrilo (23 mg, 0.15 mmoles) se disolvió en EtOH (1 ml). Se añadió clorhidrato de hidroxilamina (14 mg, 0.20 mmoles) seguido por agua (0.5 ml) y carbonato de potasio (41 mg, 0.3 mmoles). La mezcla se calentó a reflujo durante la noche y después se enfrió y se dividió entre EtOAc y salmuera. La fase orgánica se evaporó y la amidoxima cruda así obtenida se disolvió en EtOH (1 ml). Se añadió 4-(3-butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1*H*-purin-1-il)butanoato de etilo (43 mg, 0.12 mmoles) y 21% en peso de etóxido de sodio etanólico (0.067 ml, 0.18 mmoles) y la mezcla se calentó en el reactor de microondas a 140°C durante 10 min. La mezcla se dividió entre EtOAc y HCl 2M, la fase orgánica se evaporó y el producto se purificó por MDAP para proveer el compuesto del título como un sólido (13 mg).

CL/EM: m/z 479 $[MH]^+$, TR 3.52 min.

^{1}H RMN (MeOH-d_4) δ: 0.96 (t, 3H, J = 7Hz), 1.34-1.45 (m, 2H),

1.65-1.75 (m, 2H), 2.13-2.22 (m, 2H), 2.97 (t, 2H, J = 7Hz), 4.00 (t, 2H, J = 7Hz), 4.05 (s, 2H), 4.12 (t, 2H, J = 7Hz), 7.03-7.25 (m, 3H).

b) 4-(3-butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1*H*-purin-1-il)butanoato de etilo



A 3-butil-8-cloro-7-(2-propen-1-il)-3,7-dihidro-1*H*-purino-2,6-diona (6.0 g, 21.24 mmoles) en DMF seco (100 ml) se añadió Cs_2CO_3 (7.62 g, 23.36 mmoles) seguido por 4-bromobutirato de etilo (4.556 g, 23.36 mmoles). La mezcla se calentó a 55°C durante 18 hr y se dejó enfriar, después se desgasificó mediante evacuación repetida y radmitiendo nitrógeno. Se añadió morfolina (14.9 g, 171 mmoles) seguido por tetrakis(trifenilfosfin)paladio(0) (4.0 g, 3.46 mmoles) y la mezcla se agitó durante 4 hr. Se añadieron EtOAc (300 ml) y HCl 2M (150 ml) y agua (100 ml) y la fase orgánica se separó, se lavó con salmuera (3 x 100 ml) y se filtró. El filtrado se secó (Na_2SO_4) y se evaporó. El producto crudo (10 g) se purificó por SPE de aminopropilo (3 x 20 g), cargando en THF/MeOH (1:1), lavando con THF/MeOH (1:1) y MeOH neto y eluyendo el producto con DCM/MeOH (1:1) que contenía 5% de AcOH añadido para dar el compuesto del título (5.08 g).

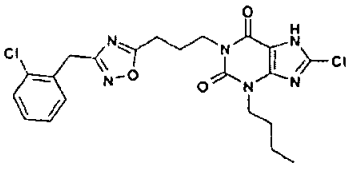
CL/EM: m/z 357 $[MH]^+$, TR 3.06 min.

^{1}H RMN (d^4 MeOH) 0.96 (3H, t, J = 7Hz), 1.33-1.42 (2H, m), 1.64-1.74 (2H, m), 2.12-2.21 (2H, m), 2.95 (2H, t, J = 8Hz), 3.99 (2H, t, J = 7Hz), 4.03 (2H, s), 4.11 (2H, t, J = 7Hz), 7.03-7.21 (3H, m).

260

EJEMPLO 94

3-Butil-8-cloro-1-{3-[3-(2-clorobencil)-1,2,4-oxadiazol-5-il]propil)-3,7-dihidro-1*H*-purino-2,6-diona



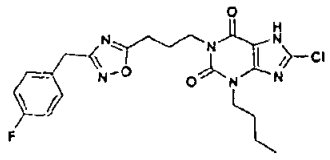
4-(3-butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1*H*-purin-1-il)butanoato de etilo (53 mg, 0.15 mmoles) y (1*Z*)-2-(2-clorofenil)-*N*-hidroxietanimidamida (30 mg, 0.18 mmoles; entrada 1, cuadro 7) se calentaron en EtOH (0.75 ml) con 21% de etóxido de sodio etanólico (0.083 ml, 0.22 mmoles) a 140°C durante 10 min. La mezcla después se dividió entre EtOAc y HCl 2M y la fase orgánica se evaporó. El producto se purificó por MDAP para dar el compuesto del título como un sólido (34.8 mg).

CL/EM: m/z 477 $[MH]^+$, TR 3.59 min.

^{1}H RMN (d^6 DMSO) 0.89 (3H, t, J = 8Hz), 1.24-1.34 (2H, m), 1.56-1.65 (2H, m), 1.98-2.07 (2H, m), 2.92 (2H, t, J = 7Hz), 3.89 (2H, t, J = 7Hz), 3.98 (2H, t, J = 7Hz), 4.09 (2H, s), 7.28-7.48 (4H, m).

EJEMPLO 95

3-Butil-8-cloro-1-{3-[3-(4-fluorobencil)-1,2,4-oxadiazol-5-il]propil}-3,7-dihidro-1*H*-purino-2,6-diona

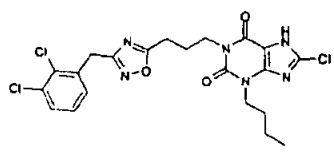


Empezando a partir de (1*Z*)-2-(4-fluorofenil)-*N*-hidroxietanimidamida (28 mg, 0.18 mmoles; entrada 2, cuadro 7) se obtuvo de manera similar el compuesto del título como un sólido (10.0 mg).

CL/EM: m/z 461 $[MH]^+$, TR 3.49 min.

EJEMPLO 96

3-Butil-8-cloro-1-{3-[3-(2,3-diclorobencil)-1,2,4-oxadiazol-5-il]propil}propil)-3,7-dihidro-1*H*-purino-2,6-diona



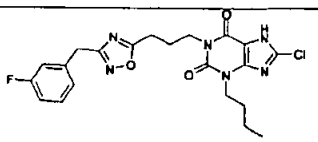
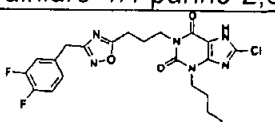
4-(3-butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1*H*-purin-1-il)butanoato de etilo (53 mg, 0.15 mmoles) y (1*Z*)-2-(2,3-diclorofenil)-*N*-hidroxietanimidamida (36 mg, 0.165 mmoles; entrada 3, cuadro 7) y 21% de etóxido de sodio etanólico (0.083 ml, 0.22 mmoles) se calentaron juntos en EtOH (0.75 ml) en el reactor de microondas a 140°C durante 10 min. La mezcla después se dividió entre EtOAc y HCl 2M, la fase orgánica se separó,

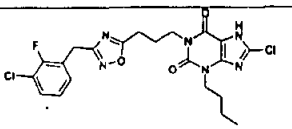
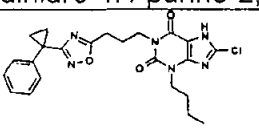
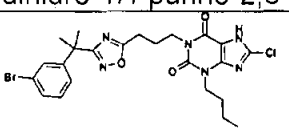
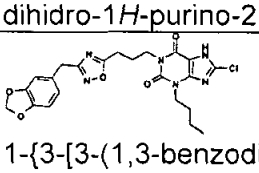
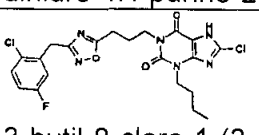
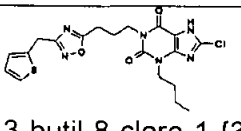
se evaporó y el producto se purificó por MDAP para dar el compuesto del título como un sólido (42.1 mg).

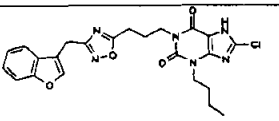
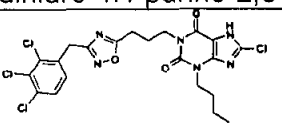
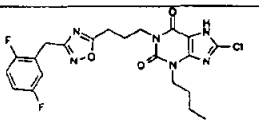
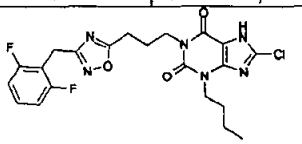
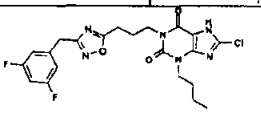
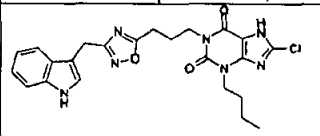
CL/EM: m/z 511, 513, 515 (isótopos) $[MH]^+$, TR 3.66 min.

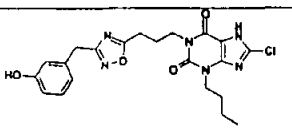
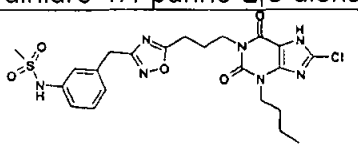
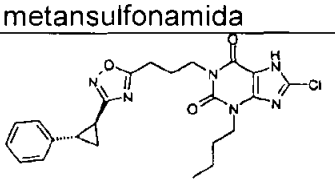
Los siguientes compuestos (cuadro 4) se prepararon usando un método análogo al del ejemplo 96, usando la amidoxima apropiada, (con las excepciones para el ejemplo 110 (cuadro 4) durante el tratamiento el pH se ajustó a 5 antes de la extracción con EtOAc; y en el caso del ejemplo 111 (cuadro 4) el producto crudo se agitó durante 18 hr con EtOH (1 ml) y NaOH 2M (0.5 ml) y ejemplo 112 (cuadro 4) se agitó durante 18 hr con EtOH (0.75 ml) y NaOH 2M (0.5 ml) antes de repetir el tratamiento y purificación por MDAP).

CUADRO 4

Ejemplo	Estructura	Amidoxima (véase cuadro 7)	Peso de amidoxima mg	Rend. mg	CL/EM:
97	 3-butil-8-cloro-1-{3-[3-(3-fluorobencil)-1,2,4-oxadiazol-5-il]propil}-3,7-dihidro-1*H*-purino-2,6-diona	4	28	32.4	m/z 461 $[MH]^+$ TR 3.41 min
98	 3-butil-8-cloro-1-{3-[3-(3,4-difluorobencil)-1,2,4-oxadiazol-5-il]propil}-3,7-dihidro-1*H*-purino-2,6-diona	5	31	28.3	m/z 479 $[MH]^+$ TR 3.46 min

99	 3-butil-8-cloro-1-{3-[3-(3-cloro-2-fluorobencil)-1,2,4-oxadiazol-5-il]propil}-3,7-dihidro-1*H*-purino-2,6-diona	6	33	32.3	m/z 495 $[MH]^+$ TR 3.55 min
100	 3-butil-8-cloro-1-{3-[3-(1-fenilciclopropil)-1,2,4-oxadiazol-5-il]propil}-3,7-dihidro-1*H*-purino-2,6-diona	8	29	3.5	m/z 469 $[MH]^+$ TR 3.43 min
101	 1-(3-{3-[1-(3-bromofenil)-1-metiletil]-1,2,4-oxadiazol-5-il}propil)-3-butil-8-cloro-3,7-dihidro-1*H*-purino-2,6-diona	9	42	2.6	m/z 551 $[MH]^+$ TR 3.71 min
102	 1-{3-[3-(1,3-benzodioxol-5-ilmetil)-1,2,4-oxadiazol-5-il]propil}-3-butil-8-cloro-3,7-dihidro-1*H*-purino-2,6-diona	10	32	30.5	m/z 487 $[MH]^+$ TR 3.27 min
103	 3-butil-8-cloro-1-(3-{3-[(2-cloro-5-fluorofenil)metil]-1,2,4-oxadiazol-5-il}propil)-3,7-dihidro-1*H*-purino-2,6-diona	19	33	26.2	m/z 495 $[MH]^+$ TR 3.47 min
104	 3-butil-8-cloro-1-{3-[3-(2-tienilmetil)-1,2,4-oxadiazol-5-il]propil}-3,7-dihidro-1*H*-purino-2,6-diona	21	26	33.4	m/z 449 $[MH]^+$ TR 3.23 min

105	 1-{3-[3-(1-benzofuranil-3-ilmetil)-1,2,4-oxadiazol-5-il]propil}-3-butil-8-cloro-3,7-dihidro-1*H*-purino-2,6-diona	22	31	27.3	m/z 483 $[MH]^+$ TR 3.47 min
106	 3-butil-8-cloro-1-(3-{3-[(2,3,4-triclorofenil)metil]-1,2,4-oxadiazol-5-il}propil)-3,7-dihidro-1*H*-purino-2,6-diona	15	42	29.8	m/z 545 $[MH]^+$ TR 3.79 min
107	 3-butil-8-cloro-1-(3-{3-[(2,5-difluorofenil)metil]-1,2,4-oxadiazol-5-il}propil)-3,7-dihidro-1*H*-purino-2,6-diona	16	31	34.8	m/z 479 $[MH]^+$ TR 3.35 min
108	 3-butil-8-cloro-1-(3-{3-[(2,6-difluorofenil)metil]-1,2,4-oxadiazol-5-il}propil)-3,7-dihidro-1*H*-purino-2,6-diona	17	31	38.2	m/z 479 $[MH]^+$ TR 3.31 min
109	 3-butil-8-cloro-1-(3-{3-[(3,5-difluorofenil)metil]-1,2,4-oxadiazol-5-il}propil)-3,7-dihidro-1*H*-purino-2,6-diona	18	31	35.4	m/z 479 $[MH]^+$ TR 3.39 min
110	 3-butil-8-cloro-1-{3-[3-(1*H*-indol-3-ilmetil)-1,2,4-oxadiazol-5-il]propil}-3,7-dihidro-1*H*-purino-2,6-diona	20	31	16.1	m/z 482 $[MH]^+$ TR 3.31 min

111	 3-Butil-8-cloro-1-(3-{3-[(3-hidroxifenil)metil]-1,2,4-oxadiazol-5-il}propil)-3,7-dihidro-1*H*-purino-2,6-diona	7	28	10	m/z 459 $[MH]^+$ TR 3.07 min
112	 *N*-[3-({5-[3-(3-butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1*H*-purin-1-il)propil]-1,2,4-oxadiazol-3-il}metil)fenil]-metansulfonamida	25	40	28.4	m/z 536 $[MH]^+$ TR 3.03 min
113	 3-butil-8-cloro-1-(3-{3-[(1S,2S)-2-fenilciclopropil]-1,2,4-oxadiazol-5-il}propil)-3,7-dihidro-1*H*-purino-2,6-diona	(1*S*,2*S*)-*N*-hidroxi-2-fenilciclo-propan-carboximi-damida	29	29.6	m/z 469 $[MH]^+$ TR 3.51 min

Detalles de RMN para ejemplos seleccionados del cuadro 4

EJEMPLO 97

3-Butil-8-cloro-1-{3-[3-(3-fluorobencil)-1,2,4-oxadiazol-5-il]propil}-3,7-dihidro-1*H*-purino-2,6-diona

^{1}H RMN (DMSO-d_6) δ: 0.90 (t, 3H, J = 7Hz), 1.25-1.36 (m, 2H), 1.56-1.67 (m, 2H), 2.0-2.1 (m, 2H), 2.94 (t, 2H, J = 7Hz), 3.90 (t, 2H, J = 7 Hz), 3.98 (t, 2H, J = 7Hz), 4.02 (s, 2H), 7.05-7.15 (m, 3H), 7.32-7.40 (m, 1H).

EJEMPLO 98

3-Butil-8-cloro-1-{3-[3-(3,4-difluorobencil)-1,2,4-oxadiazol-5-il]propil}-3,7-dihidro-1*H*-purino-2,6-diona

^{1}H RMN (DMSO-d_6) δ: 0.89 (t, 3H, J = 7.5Hz), 1.25-1.34 (m, 2H), 1.56-1.65 (m, 2H), 1.99-2.07 (m, 2H), 2.92 (t, 2H, J = 7Hz), 3.89 (t, 2H, J = 7 Hz), 3.98 (t, 2H, J = 7Hz), 4.02 (s, 2H), 7.10-7.15 (m, 1H), 7.32-7.39 (m, 2H), 14.45 (br s, 1H).

EJEMPLO 100

3-Butil-8-cloro-1-{3-[3-(1-fenilciclopropil)-1,2,4-oxadiazol-5-il]propil}-3,7-dihidro-1*H*-purino-2,6-diona

^{1}H RMN (MeOH-d_4) δ: 0.95 (t, 3H, J = 7Hz), 1.25-1.30 (m, 2H), 1.30-1.45 (m, 4H), 1.64-1.75 (m, 2H), 2.15-2.25 (m, 2H), 2.94 (t, 2H, J = 7Hz), 3.98 (t, 2H, J = 7Hz), 4.10 (t, 2H, J = 7Hz), 7.20-7.37 (m, 5H).

EJEMPLO 102

1-{3-[3-(1,3-benzodioxol-5-ilmetil)-1,2,4-oxadiazol-5-il]propil}-3-butil-8-cloro-3,7-dihidro-1*H*-purino-2,6-diona

^{1}H RMN (DMSO-d_6) δ: 0.90 (t, 3H, J = 7Hz), 1.25-1.36 (m, 2H), 1.58-1.68 (m, 2H), 1.98-2.09 (m, 2H), 2.92 (t, 2H, J = 7Hz), 3.88-3.95 (m, 4H),

3.99 (t, 2H, J = 7Hz), 5.98 (s, 2H), 6.70-6.86 (m, 3H).

EJEMPLO 110

3-Butil-8-cloro-1-{3-[3-(1*H*-indol-3-ilmetil)-1,2,4-oxadiazol-5-il]propil}-3,7-dihidro-1*H*-purino-2,6-diona

^{1}H RMN (DMSO-d_6) δ: 0.89 (t, 3H, J = 7Hz), 1.23-1.36 (m, 2H), 1.56-1.67 (m, 2H), 1.96-2.08 (m, 2H), 2.90 (t, 2H, J = 7Hz), 3.90 (t, 2H, J = 7 Hz), 3.99 (t, 2H, J = 7Hz), 4.04 (s, 2H), 6.92-7.50 (m, 5H), 10.95 (s, 1H).

EJEMPLO 111

3-Butil-8-cloro-1-(3-{3-[(3-hidroxifenil)metil]-1,2,4-oxadiazol-5-il}propil)-3,7-dihidro-1*H*-purino-2,6-diona

^{1}H RMN (DMSO-d_6) δ: 0.90 (t, 3H, J = 7Hz), 1.25-1.38 (m, 2H), 1.57-1.68 (m, 2H), 1.96-2.07 (m, 2H), 2.92 (t, 2H, J = 7Hz), 3.86 (s, 2H), 3.89 (t, 2H, J = 7Hz), 3.99 (t, 2H, J = 7Hz), 6.58-6.68 (m, 3H), 7.08 (m, 1H), 9.40 (s,1H).

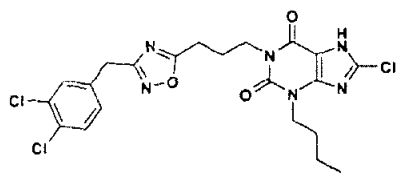
EJEMPLO 112

N-[3-({5-[3-(3-butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1*H*-purin-1-il)propil]-1,2,4-oxadiazol-3-il}metil)fenil]metansulfonamida

^{1}H RMN (DMSO-d_6) δ: 0.89 (t, 3H, J = 7.5Hz), 1.24-1.34 (m, 2H), 1.56-1.65 (m, 2H), 1.97-2.06 (m, 2H), 2.91 (t, 2H, J = 7.5Hz), 2.97 (s, 3H), 3.90 (t, 2H, J = 7.5Hz), 3.96 (s, 2H), 3.97 (t, 2H, J = 7Hz), 6.96-6.99 (m, 1H), 7.06-7.13 (m, 2H), 7.26 (t, 1H, J = 8Hz), 9.75 (s, 1H), 14.45 (br s, 1H).

EJEMPLO 114

3-Butil-8-cloro-1-(3-{3-[(3,4-diclorofenil)metil]-1,2,4-oxadiazol-5-il}propil)-3,7-dihidro-1*H*-purino-2,6-diona

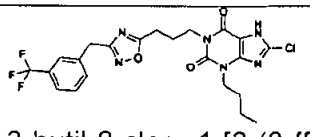
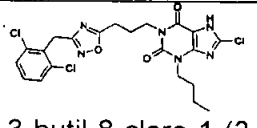
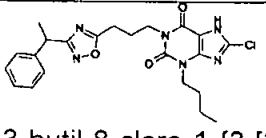


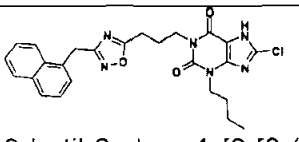
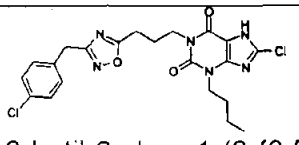
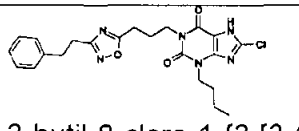
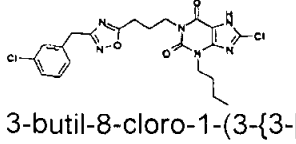
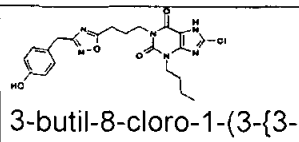
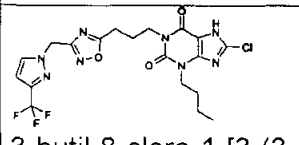
4-(3-butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1*H*-purin-1-il)butanoato de etilo (71 mg, 0.2 mmoles), (1*Z*)-2-(3,4-diclorofenil)-*N*-hidroxietanimidamida (48 mg, 0.22 mmoles) y 21% en peso de etóxido de sodio etanólico (0.111 ml, 0.3 mmoles) se calentaron juntos en EtOH (1 ml) en el reactor de microondas a 140°C durante 10 min. La mezcla después se dividió entre EtOAc y HCl 2M, la fase orgánica se separó y se evaporó, y el producto crudo se purificó por MDAP para dar el compuesto del título como un sólido (48.8 mg).

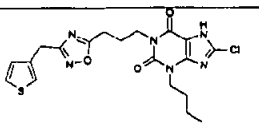
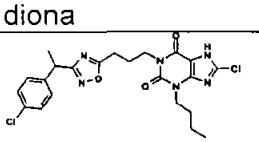
CL/EM: m/z 511 , 513 $[MH]^+$, TR 3.65 min.

Los siguientes compuestos (cuadro 5) se prepararon usando un método análogo al del ejemplo 114, usando la amidoxima apropiada (con la excepción de que para el ejemplo 115 y ejemplo 125, se añadieron 0.185 ml, (0.5 mmoles) de 21% de etóxido de sodio para permitir que las amidoximas fueran las sales de clorhidrato).

CUADRO 5

Ejemplo	Estructura	Amidoxima	Peso de amidoxima mg	Rend. mg	CL/EM:
115	 3-butil-8-cloro-1-[3-(3-{[3-trifluorometil)fenil]metil}-1,2,4-oxadiazol-5-il)propil]-3,7-dihidro-1*H*-purino-2,6-diona	Clorhidrato de (1*Z*)-*N*-hidroxi-2-[3-(trifluoro-metil)fenil]-etanimida-mina	56	46.5	m/z 511 $[MH]^+$ TR 3.63 min
116	 3-butil-8-cloro-1-(3-{3-[(2,6-diclorofenil)metil]-1,2,4-oxadiazol-5-il}propil]-3,7-dihidro-1*H*-purino-2,6-diona	(1*Z*)-2-(2,6-diclorofenil)-*N*-hidroxita-nimidamida	3148	53.8	m/z 511 $[MH]^+$ TR 3.64 min
117	 3-butil-8-cloro-1-{3-[3-(1-feniletil)-1,2,4-oxadiazol-5-il]propil}-3,7-dihidro-1*H*-purino-2,6-diona	(1*Z*)-*N*-hidroxi-2-fenilpropa-nimidamida	36	45.4	m/z 457 $[MH]^+$ TR 3.51 min

118	 3-butil-8-cloro-1-{3-[3-(1-naftalenilmetil)-1,2,4-oxadiazol-5-il]propil}-3,7-dihidro-1*H*-purino-2,6-diona	(1*Z*)-*N*-hidroxi-2-(1-naftalenil)-etanimidamida	44	48.6	m/z 493 $[MH]^+$ TR 3.67 min
119	 3-butil-8-cloro-1-(3-{3-[(4-clorofenil)metil]-1,2,4-oxadiazol-5-il}propil)-3,7-dihidro-1*H*-purino-2,6-diona	(1*Z*)-2-(4-clorofenil)-*N*-hidroxietanimidamida	41	35.6	m/z 477 $[MH]^+$ TR 3.60 min
120	 3-butil-8-cloro-1-{3-[3-(2-feniletil)-1,2,4-oxadiazol-5-il]propil}-3,7-dihidro-1*H*-purino-2,6-diona	(1*Z*)-*N*-hidroxi-3-fenilpropanimidamida	36	29.6	m/z 457 $[MH]^+$ TR 3.55 min
121	 3-butil-8-cloro-1-(3-{3-[(3-clorofenil)metil]-1,2,4-oxadiazol-5-il}propil)-3,7-dihidro-1*H*-purino-2,6-diona	(1*Z*)-2-(3-clorofenil)-*N*-hidroxietanimidamida	41	39.4	m/z 477 $[MH]^+$ TR 3.64 min
122	 3-butil-8-cloro-1-(3-{3-[(4-hidroxifenil)metil]-1,2,4-oxadiazol-5-il}propil)-3,7-dihidro-1*H*-purino-2,6-diona	(1*Z*)-*N*-hidroxi-2-(4-hidroxifenil)-etanimidamida	36	53.5	m/z 459 $[MH]^+$ TR 3.08 min
123	 3-butil-8-cloro-1-[3-(3-{(3-(trifluorometil)1H-pirazol-1-*il*]*metil*}-1,2,4-oxadiazol-5-il)propil}-3,7-dihidro-1*H*-purino-2,6-diona	(1*Z*)-*N*-hidroxi-2-[3-(trifluorometil)-1H-pirazol-1-il]etanimidamida	46	58.1	m/z 501 $[MH]^+$ TR 3.33 min

124	 3-butil-8-cloro-1-{3-[3-(3-tienilmetil)-1,2,4-oxadiazol-5-il]propil}-3,7-dihidro-1*H*-purino-2,6-diona	(1*Z*)-*N*-hidroxi-2-(3-tienil)etanimidamida	34	32.6	m/z 449 $[MH]^+$ TR 3.31 min
125	 3-butil-8-cloro-1-(3-{3-[1-(4-clorofenil)etil]1,2,4-oxadiazol-5-il}propil)-3,7-dihidro-1*H*-purino-2,6-diona	Clorhidrato de (1*Z*)-2-(4-clorofenil)-*N*-hidroxipropanimidamida	52	30.3	m/z 491 $[MH]^+$ TR 3.67 min

Detalles de RMN para ejemplos seleccionados del cuadro 5

EJEMPLO 115

^{1}H RMN (d^6 DMSO) 0.88 (3H, t, J = 7Hz), 1.24-1.33 (2H, m), 1.56-1.65 (2H, m), 1.98-2.06 (2H, m), 2.92 (2H, t, J = 7Hz), 3.89 (2H, t, J = 7Hz), 3.97 (2H, t, J = 7Hz), 4.14 (2H, s), 7.52-7.70 (4H, m).

EJEMPLO 117

3-Butil-8-cloro-1-{3-[3-(1-feniletil)-1,2,4-oxadiazol-5-il]propil}-3,7-dihidro-1*H*-purino-2,6-diona

^{1}H RMN (DMSO-d_6) δ: 0.89 (t, 3H, J = 7Hz), 1.22-1.35 (m, 2H),

1.52 (d, 3H, J = 8Hz), 1.56-1.68 (m, 2H), 1.95-2.08 (m, 2H), 2.91 (t, 2H, J = 7Hz), 3.89 (t, 2H, J = 7Hz), 3.95 (t, 2H, J = 7Hz), 4.18 (q, 1H, J = 8Hz), 7.17-7.32 (m, 5H).

EJEMPLO 119

3-Butil-8-cloro-1-(3-{3-[(4-clorofenil)metil]-1,2,4-oxadiazol-5-il}propil)-3,7-dihidro-1*H*-purino-2,6-diona

^{1}H RMN (DMSO-d_6) δ: 0.89 (t, 3H, J = 7Hz), 1.23-1.37 (m, 2H), 1.55-1.67 (m, 2H), 1.97-2.09 (m, 2H), 2.90 (t, 2H, J = 7Hz), 3.88 (t, 2H, J = 7Hz), 3.97 (t, 2H, J = 7Hz), 4.00 (s, 2H), 7.27-7.40 (m, 4H).

EJEMPLO 122

3-Butil-8-cloro-1-(3-{3-[(4-hidroxifenil)metil]-1,2,4-oxadiazol-5-il}propil)-3,7-dihidro-1*H*-purino-2,6-diona

^{1}H RMN (DMSO-d_6) δ: 0.90 (t, 3H, J = 7Hz), 1.23-1.37 (m, 2H), 1.57-1.68 (m, 2H), 1.96-2.08 (m, 2H), 2.90 (t, 2H, J = 7Hz), 3.82 (s, 2H), 3.90 (t, 2H, J = 7Hz), 3.98 (t, 2H, J = 7Hz), 6.68 (d, 2H, J = 9Hz), 7.04 (d, 2H, J = 9Hz), 9.32 (s, 1H).

EJEMPLO 123

3-Butil-8-cloro-1-[3-(3-{[3-(trifluorometil)-1*H*-pirazol-1-il]metil}-1,2,4-oxadiazol-5-il)propil]-3,7-dihidro-1*H*-purino-2,6-diona

^{1}H RMN (DMSO-d_6) δ: 0.90 (t, 3H, J = 7Hz), 1.23-1.36 (m, 2H), 1.57-1.69 (m, 2H), 1.95-2.08 (m, 2H), 2.95 (t, 2H, J = 7Hz), 3.91 (t, 2H, J = 7Hz), 3.97 (t, 2H, J = 7Hz), 5.62 (s, 2H), 6.79 (s, 1H), 8.10 (s, 1H).

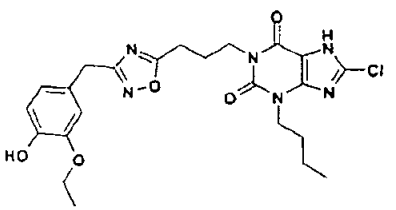
EJEMPLO 125

3-Butil-8-cloro-1-(3-{3-[1-(4-clorofenil)etil]-1,2,4-oxadiazol-5-il}propil)-3,7-dihidro-1*H*-purino-2,6-diona

^{1}H RMN (DMSO-d_6) δ: 0.90 (t, 3H, J = 7Hz), 1.23-1.38 (m, 2H), 1.51 (d, 3H1 J = 6Hz), 1.55-1.69 (m, 2H), 1.96-2.10 (m, 2H), 2.92 (t, 2H, J = 7Hz), 3.89 (t, 2H, J = 7Hz), 3.98 (t, 2H, J = 7Hz), 4.24 (q, 1H, J = 6Hz), 7.27-7.40 (m, 4H).

EJEMPLO 126

3-Butil-8-cloro-1-[3-(3-{[3-(etiloxi)-4-hidroxifenil]metil}-1.2,4-oxadiazol-5-il)propil]-3,7-dihidro-1*H*-purino-2,6-diona



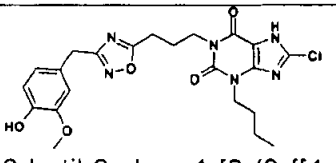
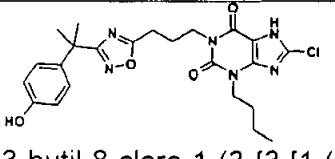
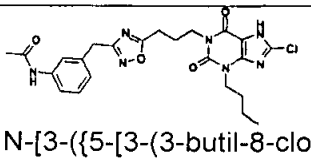
4-(3-Butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1*H*-purin-1-il)butanoato de etilo (53 mg, 0.15 mmoles) y (1Z)-2-[3-(etiloxi)-4-hidroxifenil]-*N*-hidroxietanimidamida (35 mg, 0.165 mmoles; entrada 11, cuadro 7) se mezclaron en EtOH (0.75 ml). Se añadió etóxido de sodio etanólico (21% en peso, 0.083 ml, 0.22 mmoles) y la mezcla se calentó en el microondas a 140°C durante 10 min. 0.055 ml adicionales (0.15 mmoles) de solución de NaOEt se añadió después y la mezcla se calentó durante un periodo de 10 min adicionales a 140°C. La mezcla se dividió entre EtOAc y HCl 2M y la fase orgánica se evaporó y se purificó por MDAP para dar el compuesto del título como un sólido (29.6 mg).

CL/EM: m/z 503 $[MH]^+$, TR 3.15 min.

Los siguientes compuestos (cuadro 6) se prepararon usando un método análogo al del ejemplo 126, usando la amidoxima apropiada (con la excepción de que para el ejemplo 127 (cuadro 6), el producto crudo, después de tratamiento, se agitó con EtOH (1 ml) y NaOH 2M (0.5 ml) durante la noche a fin de hidrolizar éster de partida residual, antes de repetir tratamiento con

HCl y purificación por MDAP).

CUADRO 6

Ejemplo	Estructura	Amidoxima (véase cuadro 7)	Peso de amidoxima mg	Rend. mg	CL/EM:
127	 3-butil-8-cloro-1-[3-(3-{[4-hidroxi-3-(metiloxi)fenil]metil}-1,2,4-oxadiazol-5-il)propil]-3,7-dihidro-1*H*-purino-2,6-diona	12	32	37.2	m/z 489 $[MH]^+$ TR 2.98 min
128	 3-butil-8-cloro-1-(3-{3-[1-(4-hidroxifenil)-1-metiletil]-1,2,4-oxadiazol-5-il}propil)-3,7-dihidro-1*H*-purino-2,6-diona	13	32	23.6	m/z 487 $[MH]^+$ TR 3.23 min
129	 N-[3-({5-[3-(3-butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1H-purin-1-il)propil]1,2,4-oxadiazol-3-il}metil)fenil]acetamida	14	34		m/z 500 $[MH]^+$ TR 2.94 min

Detalles de RMN para ejemplos seleccionados del cuadro 6

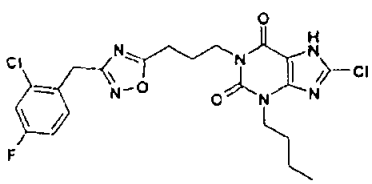
EJEMPLO 129

***N*-[3-({5-[3-(3-butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1*H*-purin-1-il)propil]-1,2,4-oxadiazol-3-il}metil)fenil]acetamida**

^{1}H RMN (DMSO-d_6) δ: 0.90 (t, 3H, J = 7Hz), 1.25-1.38 (m, 2H), 1.57-1.68 (m, 2H), 1.95-2.07 (m, 5H), 2.92 (t, 2H, J = 7Hz), 3.91 (t, 2H, J = 7Hz), 3.94 (s, 2H), 3.98 (m, 2H), 6.88-7.50 (m, 4H), 9.90 (s, 1H).

EJEMPLO 130

3-Butil-8-cloro-1-(3-{3-[(2-cloro-4-fluorofenil)metil]-1,2,4-oxadiazol-5-il}propil)-3,7-dihidro-1*H*-purino-2,6-diona



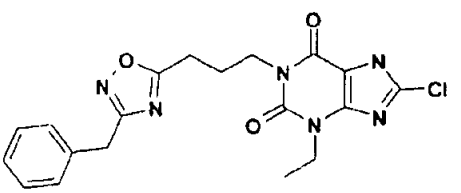
4-(3-Butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1*H*-purin-1-il) butanoato de etilo (100 mg, 0.28 mmoles) y (1*Z*)-2-(2-cloro-4-fluorofenil)-*N*-hidroxietanimidamida (62.4 mg, 0.308 mmoles) y 21% en peso de etóxido de sodio etanólico (0.157 ml, 0.42 mmoles) se calentaron juntos en un reactor de microondas en EtOH (1.5 ml) a 140°C durante 10 min. La mezcla se trató dividiendo entre EtOAc y HCl 2M. La fase orgánica se evaporó y se purificó por MDAP para dar el compuesto del título como un sólido (73 mg).

CL/EM: m/z 495 $[MH]^+$, TR 3.55 min.

EJEMPLO 131

8-Cloro-3-etil-1-{3-[3-(fenilmetil)-1,2,4-oxadiazol-5-il]propil}-3,7-dihidro-1*H*-purino-2,6-diona

a) 8-Cloro-3-etil-1-{3-[3-(fenilmetil)-1,2,4-oxadiazol-5-il]propil}-3,7-dihidro-1*H*-purino-2,6-diona



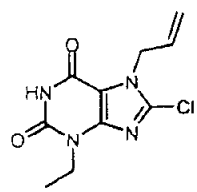
Una solución de 8-cloro-3-etil-7-(2-propen-1-il)-3,7-dihidro-1*H*-purino-2,6-diona (150 mg, 0.59 mmoles) en THF anhidro (4 ml) se trató con 3-[3-(fenilmetil)-1,2,4-oxadiazol-5-il]-1-propanol (154 mg, 0.71 mmoles) y trifenilfosfina (200 mg, 0.76 mmoles). Se añadió DBAD (162 mg, 0.71 mmoles) en una porción y la mezcla se dejó agitar a t.a., bajo nitrógeno durante 18 hr. La mezcla se desgasificó por alto vacío, después se añadieron $Pd(PPh_3)_4$ (68 mg, 0.059 mmoles) y morfolina (515 µl, 5.9 mmoles). La mezcla se dejó agitar a t.a., bajo nitrógeno, durante 3 hr. La mezcla se dividió entre EtOAc y HCl 2M (ac.). La capa orgánica se separó, se lavó con salmuera, se secó ($MgSO_4$) y se concentró por alto vacío. El material crudo se purificó por un SPE de aminopropilo usando MeOH para cargar el compuesto en la columna y para

lavar las impurezas, después con 2% de AcOH/MeOH para eluir el compuesto. Las fracciones activas UV se combinaron y se concentraron por alto vacío. El producto además se purificó por MDAP. Las fracciones de producto se combinaron y se concentraron para dar el compuesto del título como un sólido blanco (61 mg, 25%).

CL/EM: m/z 415 $[MH]^+$, TR 3.01 min

^{1}H RMN; (DMSO-d_6) δ: 1.19 (t, 3H, J = 7Hz), 2.93 (m, 2H), 2.91 (t, 2H, J = 7.5Hz), 3.96 (m, 6H), 7.27 (m, 5H) 14.46 (s, 1H).

b) 8-Cloro-3-etil-7-(2-propen-1-il)-3,7-dihidro-1*H*-purino-2,6-diona

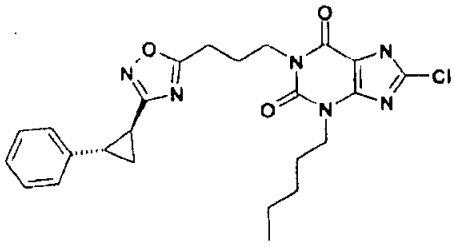


Una solución de 8-cloro-7-(2-propen-1-il)-3,7-dihidro-1*H*-purino-2,6-diona (10 g, 0.044 moles) en DMF anhidro (100 ml) se trató con yodoetano (5.4 ml, 0.068 moles) y Na_2CO_3 (4.9 g, 0.046 moles). La mezcla de reacción se dejó agitar a t.a. bajo nitrógeno durante 2 días. Se añadió yodoetano (0.35 ml, 0.0044 moles) y la mezcla se dejó agitar a t.a. durante 1 día. La mezcla se dividió entre EtOAc y HCl 2M. La capa orgánica se separó, se lavó secuencialmente con solución de sulfito de sodio saturada y salmuera, se secó ($MgSO_4$) y se concentró. El sólido crudo se lavó con Et_2O para dar el compuesto del título como un sólido blanco (8.37 g, 75%).

CL/EM: m/z 255 $[MH]^+$, TR 2.35 min.

EJEMPLO 132

8-Cloro-3-pentil-1-(3-{3-[(1*S*,2*S*)-2-fenilciclopropil]-1,2,4-oxadiazol-5-il}propil)-3,7-dihidro-1*H*-purino-2,6-diona



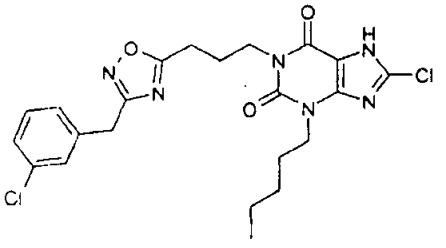
5-(8-Cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1*H*-purin-1-il) pentanoato de etilo (70 mg, 0.19 mmoles) se disolvió en EtOH (1.5 ml). La solución se trató con a solución al 21% de NaOEt en EtOH (78 µl, 0.21 mmoles) y (1*S*,2*S*)-*N*-hidroxi-2-fenilciclopropancarboximidamida (37 mg, 0.21 mmoles). La reacción se calentó en el microondas a 140°C durante 10 min. La mezcla se dividió entre EtOH y HCl 2M (ac.). La capa orgánica se separó y se concentró, el producto crudo resultante se purificó por MDAP. Las fracciones de producto se combinaron y se concentraron para dar el compuesto del título como un sólido blanco (35 mg, 38%).

CL/EM: m/z 483 $[MH]^+$, TR 3.67 min.

EJEMPLO 133

480

8-Cloro-1-(3-{3-[(3-clorofenil)metil]-1,2,4-oxadiazol-5-il}propil)-3-pentil-3,7-dihidro-1*H*-purino-2,6-diona



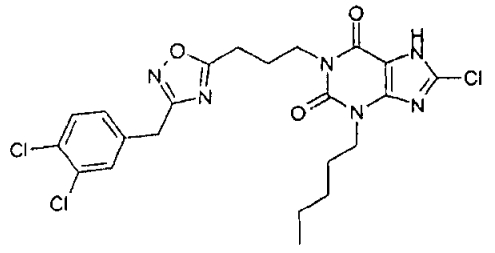
5-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1*H*-purin-1-il) pentanoato de etilo (70 mg, 0.19 mmoles) se disolvió en EtOH. La solución se trató con a solución al 21% de NaOEt en EtOH (78 µl, 0.21 mmoles) y (1*Z*)-2-(3-clorofenil)-*N*-hidroxietanimidamida (38 mg, 0.21 mmoles). La reacción se calentó en el microondas a 140°C durante 10 min. La mezcla se dividió entre EtOH y HCl 2M (ac.). La capa orgánica se decantó y se concentró. El producto crudo se purificó sobre MDAP. Las fracciones de producto se combinaron y se concentraron para dar el compuesto del título como un sólido blanco (46 mg, 49%).

CL/EM: m/z 491 $[MH]^+$, TR 3.64 min.

^{1}H RMN (DMSO-d_6) δ: 0.85 (t, 3H, J = 7Hz), 1.27 (m, 4H), 1.62 (m, 2H), 2.02 (m, 2H), 2.92 (t, 2H, J = 7.5Hz), 3.88 (t, 2H, J=7 Hz), 3.97 (t, 2H, J = 6.5Hz), 4.02 (s, 2H), 7.23 (d, 1H, J = 7Hz), 7.34 (m, 3H).

EJEMPLO 134

8-Cloro-1-(3-{3-[(3,4-diclorofenil)metil]-1,2.4-oxadiazol-5-il}propil)-3-pentil-3,7-dihidro-1*H*-purino-2,6-diona

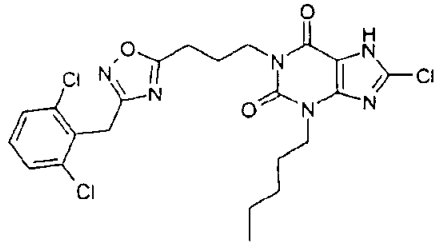


5-(8-Cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1*H*-purin-1-il) pentanoato de etilo (70 mg, 0.19 mmoles) se disolvió en EtOH. La solución se trató con a solución al 21% de NaOEt en EtOH (78 µl, 0.21 mmoles) y (1*Z*)-2-(3,4-diclorofenil)-*N*-hidroxietanimidamida (46 mg, 0.21 mmoles). La reacción se calentó en el microondas a 140°C durante 10 min. La mezcla se dividió entre EtOH y HCl 2M (ac.). La capa orgánica se decantó y se concentró. El producto crudo se purificó sobre MDAP. Las fracciones de producto se combinaron y se concentraron para dar el compuesto del título como un sólido blanco (66 mg, 66%).

CL/EM: m/z 527 $[MH]^+$, TR 3.80 min.

EJEMPLO 135

8-Cloro-1-(3-{3-[(2,6-diclorofenil)metil]1,2,4-oxadiazol-5-il}propil)-3-pentil-3,7-dihidro-1*H*-purino-2,6-diona

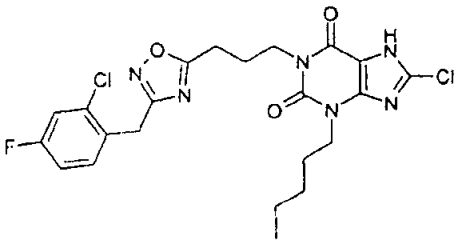


5-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1*H*-purin-1-il)pentanoato de etilo (70 mg, 0.19 mmoles) se disolvió en EtOH. La solución se trató con a solución al 21% de NaOEt en EtOH (78 µl, 0.21 mmoles) y (1*Z*)-2-(2,6-diclorofenil)-*N*-hidroxietanimidamida (46 mg, 0.21 mmoles). La reacción se calentó en el microondas a 140°C durante 10 min. La mezcla se dividió entre EtOH y HCl 2M (ac.). La capa orgánica se decantó y se concentró mediante soplado de nitrógeno. El producto crudo se purificó sobre MDAP. Las fracciones de producto se combinaron y se concentraron para dar el compuesto del título como un sólido blanco (80 mg, 80%).

CL/EM: m/z 526 $[MH]^+$, TR 3.6 min.

EJEMPLO 136

8-Cloro-1-(3-{3-[(2-cloro-4-fluorofenil)metil]-1,2,4-oxadiazol-5-il}propil)-3-pentil-3,7-dihidro-1*H*-purino-2,6-diona

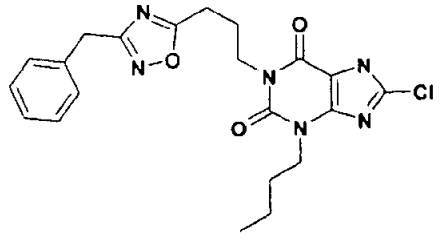


5-(8-Cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1*H*-purin-1-il) pentanoato de etilo (70 mg, 0.19 mmoles) se disolvió en EtOH. La solución se trató con a 21% de solución de NaOEt en EtOH (78 µl, 0.21 mmoles) y (1*Z*)-2-(2-cloro-4-fluorofenil)-*N*-hidroxietanimidamida (42 mg, 0.21 mmoles). La reacción se calentó en el microondas a 140°C durante 10 min. La mezcla se dividió entre EtOH y HCl 2M (ac.). La capa orgánica se decantó y se concentró. El producto crudo se purificó sobre MDAP. Las fracciones de producto se combinaron y se concentraron para dar el compuesto del título como un sólido blanco (65 mg, 67%).

CL/EM: m/z 509 $[MH]^+$, TR 3.63 min.

EJEMPLO 137

3-Butil-8-cloro-1-{3-[3-(fenilmetil)-1,2,4-oxadiazol-5-il]propil}-3,7-dihidro-1*H*-purino-2,6-diona



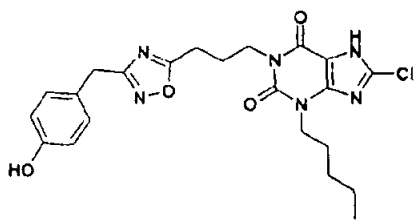
Una solución de 3-butil-8-cloro-7-(2-propen-1-il)-3,7-dihidro-1*H*-purino-2,6-diona (205 mg, 0.73 mmoles) en THF anhidro (4 ml) se trató con 3-[3-(fenilmetil)-1,2,4-oxadiazol-5-il]-1-propanol (190 mg, 0.87 mmoles) y PPh_3 (247 mg, 0.94 mmoles). Se añadió DBAD (217 mg, 0.94 mmoles) en una porción y la mezcla se agitó a t.a. bajo nitrógeno durante 18 hr. La mezcla se desgasificó por alto vacío, después se añadieron $Pd(PPh_3)_4$ (84 mg, 0.073 mmoles) y morfolina (636 µl, 7.3 mmoles). La mezcla se agitó a t.a. bajo nitrógeno durante 3 hr. La mezcla se dividió entre EtOAc y HCl 2M (ac.) y la capa orgánica se separó, se lavó con salmuera, se secó ($MgSO_4$) y se concentró. El material crudo se purificó mediante una columna de aminopropilo usando MeOH para cargar el compuesto en la columna y para lavar las impurezas, después con gradiente de 2-4% de AcOH/MeOH para remover el compuesto de la columna. La purificación adicional se llevó a cabo por MDAP para dar el compuesto del título como un sólido blanco (75 mg, 23%).

CL/EM: m/z 443 $[MH]^+$, TR 3.37 min.

^{1}H RMN; (DMSO-d_6) δ: 0.89 (t, 3H, J = 7.5 Hz), 1.29 (m, 2H), 1.61 (m, 2H), 2.02 (m, 2H), 2.91 (t, 2H, J = 7.5Hz), 3.89 (t, 2H, J = 7Hz), 3.97 (m, 4H), 7.27 (m, 5H) 14.46 (s, 1H).

EJEMPLO 138

8-Cloro-1-(3-{3-[(4-hidroxifenil)metil]-1,2,4-oxadiazol-5-il}propil)-3-pentil-3,7-dihidro-1*H*-purino-2,6-diona



5-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1*H*-purin-1-il) pentanoato de etilo (29 mg, 0.078 mmoles) y (1*Z*)-*N*-hidroxi-2-(4-hidroxifenil)etanimidamida (14 mg, 0.084 mmoles) se calentaron en EtOH (1 ml) con 21% de etóxido de sodio etanólico (0.043 ml, 0.117 mmoles) bajo irradiación de microondas a 140°C durante 10 min. La mezcla se dividió entre EtOAc y HCl 2M y la fase orgánica se evaporó. Este material se agitó con EtOH (1 ml) y NaOH 2M (0.5 ml) durante 18 hr, antes de ser tratado nuevamente al dividir entre EtOAc y HCl 2M. La purificación por MDAP dio el compuesto del título (6.5 mg).

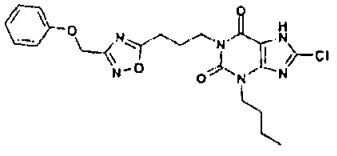
CL/EM: m/z 473 $[MH]^+$, TR 3.34 min.

^{1}H RMN (MeOH-d_4) δ: 0.92 (t, 3H, J = 7Hz), 1.25-1.45 (m, 4H), 1.68-1.78 (m, 2H), 2.11- 2.21 (m, 2H), 2.93 (t, 2H, J = 7Hz), 3.82 (s, 2H), 3.98

(t, 2H, J = 7Hz), 4.10 (t, 2H, J = 7Hz), 6.70 (d, 2H, J = 10Hz), 7.02 (d, 2H, J = 10Hz).

EJEMPLO 139

3-Butil-8-cloro-1-(3-{3-[(feniloxi)metil]-1,2.4-oxadiazol-5-il}propil)-3,7-dihidro-1*H*-purino-2,6-diona



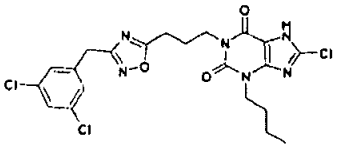
A 4-(3-butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1*H*-purin-1-il) butanoato de etilo (26 mg, 0.073 mmoles) y clorhidrato de (1*Z*)-*N*-hidroxi-2-(feniloxi)etanimidamida (16 mg, 0.079 mmoles) en EtOH (1 ml) se añadió 21% en peso de solución de etóxido de sodio etanólico (0.068 ml, 0.183 mmoles) y la mezcla se calentó bajo irradiación de microondas a 140°C durante 10 min. La mezcla se dividió entre EtOAc y HCl 2M, la fase orgánica se secó (Na_2SO_4) se evaporó y se purificó por MDAP para dar el compuesto del título como una goma que se solidificó al triturar con éter (5.9 mg).

CL/EM: m/z 459 $[MH]^+$, TR 3.39 min.

^{1}H RMN (DMSO-d_6) δ: 0.90 (t, 3H, J = 8Hz), 1.22-1.36 (m, 2H), 1.57-1.68 (m, 2H), 2.02-2.14 (m, 2H), 3.00 (t, 2H, J = 8Hz), 3.90 (t, 2H, J = 7Hz), 4.00 (t, 2H, J = 7Hz), 5.18 (s, 2H), 6.95-7.35 (m, 5H).

EJEMPLO 140

3-Butil-8-cloro-1-{3-{3-[(3,5-diclorofenil)metil]-1,2,4-oxadiazol-5-il}propil}-3,7-dihidro-1*H*-purino-2,6-diona

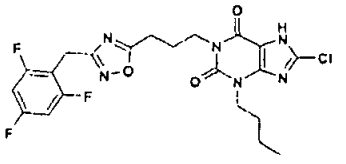


A 4-(3-butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1*H*-purin-1-il) butanoato de etilo (185 mg, 0.52 mmoles) y (1*Z*)-2-(3,5-diclorofenil)-*N*-hidroxietanimidamida (126 mg, 0.58 mmoles; entrada 23, cuadro 7) en EtOH seco (2 ml) se añadió 21% en peso de solución de etóxido de sodio etanólico (0.29 ml, 0.78 mmoles) y la mezcla se calentó por microondas a 140°C durante 10 min. La reacción se trató dividiendo entre EtOAc y HCl 2M y evaporando la fase orgánica. La purificación por MDAP dio el compuesto del título como un sólido (135 mg).

CL/EM: m/z 511 $[MH]^+$, TR 3.71 min.

EJEMPLO 141

3-Butil-8-cloro-1-(3-{3-[(2,4,6-trifluorofenil)metil]-1,2,4-oxadiazol-5-il}propil)-3,7-dihidro-1*H*-purino-2,6-diona



Se preparó de manera similar empezando a partir de (1*Z*)-*N*-

hidroxi-2-(2,4,6-trifluorofenil)etanimidamida (119 mg, 0.58 mmoles; entrada 24, cuadro 7) en un rendimiento de 135 mg.

CL/EM: m/z 497 $[MH]^+$, TR 3.39 min.

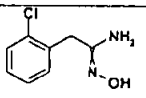
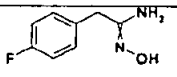
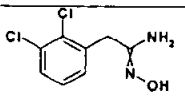
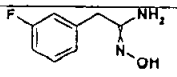
^{1}H RMN (DMSO-d_6) δ: 0.90 (t, 3H, J = 7Hz), 1.24-1.36 (m, 2H), 1.55-1.66 (m, 2H), 1.96-2.06 (m, 2H), 2.91 (t, 2H, J = 8Hz), 3.91 (t, 2H, J = 8 Hz), 3.94-4.02 (m, 4H), 7.18-7.28 (m, 2H).

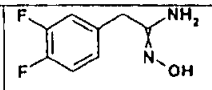
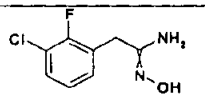
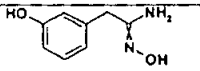
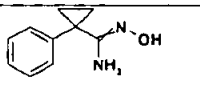
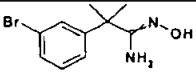
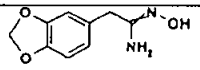
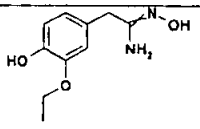
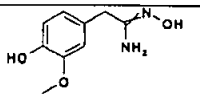
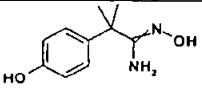
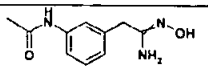
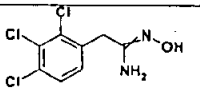
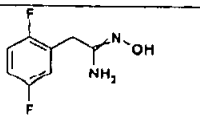
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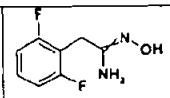
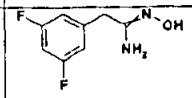
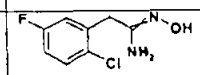
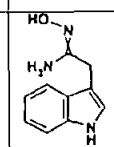
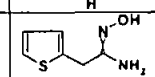
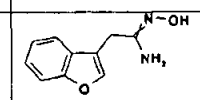
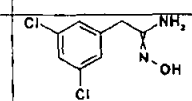
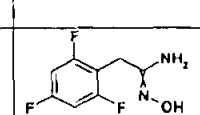
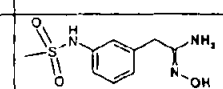
Estas están disponibles por los métodos detallados a continuación e ilustrados por análogos en el cuadro 7.

CUADRO 7

(Intermediarios)

Entrada	Estructura	Nombre	Método	Rend. mg	CL/EM
1		(1Z)-2-(2-clorofenil)-*N*-hidroxietanimidamida	G	38	m/z 185 $[MH]^+$ TR 1.04 min
2		(1Z)-2-(4-fluorofenil)-*N*-hidroxietanimidamida	G	42	m/z 169 $[MH]^+$ TR 0.72 min
3		(1Z)-2-(2,3-diclorofenil)-*N*-hidroxietanimidamida	B	64	m/z 219 $[MH]^+$ TR 1.83 min
4		(1Z)-2-(3-fluorofenil)-*N*-hidroxietanimidamida	A	78	m/z 169 $[MH]^+$ TR 0.62 min

5		(1*Z*)-2-(3,4-difluorofenil)-*N*-hidroxietanimidamida	A	88	m/z 187 $[MH]^+$ TR 0.74 min
6		(1*Z*)-2-(3-cloro-2-fluorofenil)-*N*-hidroxietanimidamida	A	92	m/z 203 $[MH]^+$ TR 1.40 min
7		(1*Z*)-*N*-hidroxi-2-(3-hidroxifenil)-hidroxi-etanimidamida	A	67	m/z 167 $[MH]^+$ TR 0.46 min
8		*N*-hidroxi-1-fenilciclopropan-carboximidamida	C	75	m/z 177 $[MH]^+$ TR 1.06 min
9		(1*Z*)-2-(3-bromofenil)-*N*-hidroxi-2-metilpropanimidamida	D	74	m/z 257 $[MH]^+$ TR 2.04 min
10		(1*Z*)-2-(1,3-benzodioxol-5-il)-*N*-hidroxi-etanimidamida	C	98	m/z 195 $[MH]^+$ TR 0.73 min
11		(1*Z*)-2-[3-(etiloxi)-4-hidroxifenil]-*N*-hidroxi-etanimidamida	C	109	m/z 211 $[MH]^+$ TR 0.76 min
12		(1*Z*)-*N*-hidroxi-2-[4-hidroxi-3-(metiloxi)fenil]-etanimidamida	C	98	m/z 197 $[MH]^+$ TR 0.50 min
13		(1*Z*)-*N*-hidroxi-2-[4-hidroxifenil)-2-metilpropanimidamida	D	66	m/z 195 $[MH]^+$ TR 0.85 min
14		*N*-{[(2*Z*)-2-(hidroxiamino)-2-iminoetil]fenil}acetamida	C	91	m/z 208 $[MH]^+$ TR 0.73 min
15		(1*Z*)-*N*-hidroxi-2-(2,3,4-triclorofenil)etanimida-mida	C	124	m/z 253 $[MH]^+$ TR 2.29 min
16		(1*Z*)-2-(2,5-difluorofenil)-*N*-hidroxietanimidamida	C	89	m/z 187 $[MH]^+$ TR 0.66 min

17		(1Z)-2-(2,6-difluorofenil)-*N*-hidroxietanimidamida	C	86	m/z 187 $[MH]^+$ TR 0.62 min
18		(1Z)-2-(3,5-difluorofenil)-*N*-hidroxietanimidamida	C	96	m/z 187 $[MH]^+$ TR 0.80 min
19		(1Z)-2-(2-cloro-5-fluorofenil)-*N*-hidroxietanimidamida	C	97	m/z 203 $[MH]^+$ TR 0.90 min
20		(1Z)-*N*-hidroxi-2-(1*H*-indol-3-il)etanimidamida	C	95	m/z 190 $[MH]^+$ TR 0.90 min
21		(1Z)-*N*-hidroxi-2-(2-tienil)etanimidamida	C	74	m/z 157 $[MH]^+$ TR 0.38 min
22		(1Z)-2-(1-benzofuran-3-il)-*N*-hidroxietanimidamida	C	87	m/z 191 $[MH]^+$ TR 1.46 min
23		(1Z)-2-(3,5-diclorofenil)-*N*-hidroxietanimidamida	E	165	m/z 219 $[MH]^+$ TR 2.03 min
24		(1Z)-*N*-hidroxi-2-(2,4,6-trifluorofenil)etanimidamida	F	297	m/z 205 $[MH]^+$ TR 0.66 min
25		(1Z)-*N*-hidroxi-2-(3-[(metilsulfonil)amino]fenil}etanimidamida	C	125	m/z 244 $[MH]^+$ TR 0.63 min

Método A

El nitrilo correspondiente (0.5 mmoles) se agitó en EtOH (1.5 ml) con solución de hidroxilamina acuosa al 50% (0.08 ml, 1.3 mmoles) y se calentó a 65°C durante 4.5 hr. Después de enfriarse, la mezcla de reacción cruda se cargó en un cartucho SPE SCX (2 g) y se lavó con MeOH, después

el producto de amidoxima se eluyó con amoniaco 2M en MeOH.

Método B

Similar al método A excepto que el producto se cristalizó a partir de la mezcla de reacción cruda y se aisló por filtración y no por SCX.

Método C

Similar al método A excepto que el producto se purificó en un cartucho SCX 5g.

Método D

Similar al método C excepto que el periodo de caletamiento fue de 18 hr.

Método E

Similar al método C excepto que la escala fue de 0.753 mmoles de nitrilo.

Método F

Similar al método A excepto que la escala fue de 1.5 mmoles de nitrilo y la purificación fue sobre un cartucho SCX de 10 g.

Método G

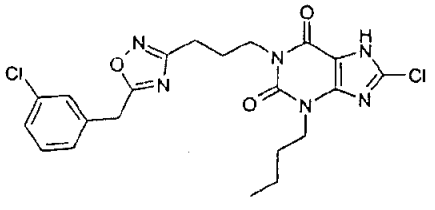
Similar al método A excepto que el tiempo de calentamiento fue 2.75 hr y la escala fue de 0.25 mmoles de nitrilo.

Cabe notar que la asignación anterior de estereoquímica (*Z*) no ha sido confirmada por datos experimentales. El experto en la técnica también reconocerá que puede haber interconversión entre los isómeros E y Z. (Dondoni, Alessandro; Lunazzi, Lodovico; Giorgianni, Patrizia; Macciantelli, Dante. Carbon-nitrogen rotational barrier as a stereochemical probe of benzamidoximes. Journal of Organic Chemistry (1975), 40(20), 2979-80).

EJEMPLO 142

3-Butil-8-cloro-1-(3-{5-[(3-clorofenil)metil-1,2,4-oxadiazol-3-il}propil)-3,7-dihidro-1*H*-purino-2,6-diona

a) 3-Butil-8-cloro-1-(3-{5-[(3-clorofenil)metil]-1,2,4-oxadiazol-3-il}propil)-3,7-dihidro-1H-purino-2,6-diona



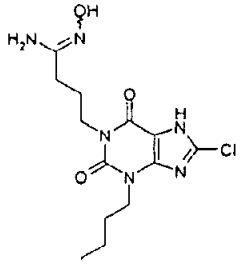
Acido (3-clorofenil)acético (0.1 mmoles), clorhidrato de *N*-[3-(dimetilamino)propil]-*N'*-etilcarbodiimida (21 mg, 0.11 mmoles) y 1*H*-1,2,3-benzotriazol-1-ol (15 mg, 0.11 mmoles) se agitaron en 1-metil-2-pirrolidinona

(1 ml). A esto se añadió (1*Z*)-4-(3-butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1*H*-purin-1-il)-*N*-hidroxibutanimidamida (34 mg, 0.1 mmoles) y la mezcla se agitó a t.a. durante 17 hr y después a 80°C durante 24 hr. La mezcla de reacción se purificó, sin modificación adicional, por CLAR preparativa (auto prep) para dar el compuesto del título (13 mg, 27%).

CL/EM: m/z 477, 479 $[MH]^+$, TR 3.5 min.

^{1}H RMN ($CDCl_3$) δ: 0.96 (t, 3H, J = 7Hz), 1.32-1.47 (m, 2H), 1.68-1.80 (m, 2H), 2.12-2.24 (m, 2H), 2.83 (t, 2H, J = 7.5Hz), 4.05-4.24 (m, 6H), 7.16-7.30 (m, 4H).

b) (1*Z*)-4-(3-butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1*H*-purin-1-il)-*N*-hidroxibutanimidamida

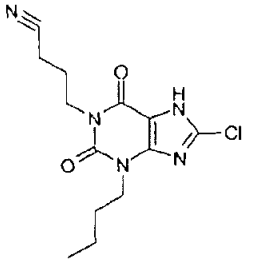


4-(3-Butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1*H*-purin-1-il) butanonitrilo (1 g, 0.0032 moles) se agitó en EtOH (3.5 ml) y agua (1.8 ml). Se añadieron clorhidrato de hidroxilamina (344 mg, 0.0049 moles) y carbonato de potasio (652 mg, 0.0049 moles) y la mezcla se calentó a 80°C durante 3 días. Después de enfriarse, la mezcla de reacción cruda se evaporó. El producto crudo se disolvió en agua, se neutralizó a pH 7 con HCl, y se cargó en un

cartucho Oasis™ (2g). Este se eluyó con agua para remover las sales y después con MeOH, para dar el compuesto del título (957 mg, 86%).

CL/EM: m/z 343, 345 $[MH]^+$, TR 2.04 min.

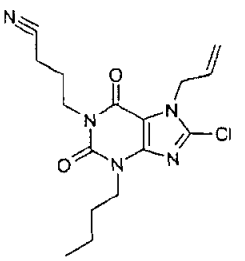
c) 4-(3-Butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1*H*-purin-1-il) butanonitrilo



4-[3-Butil-8-cloro-2,6-dioxo-7-(2-propen-1-il)-2,3,6,7-tetrahidro-1*H*-purin-1-il] butanonitrilo (2.1 g, 6 mmoles) se agitó en una mezcla de DCM desgasificado con nitrógeno (20 ml) y AcOH (2 ml). Tetrakis(trifenilfosfin)-paladio (675 mg, 0.6 mmoles) y fenilsilano (7.4 ml, 60 mmoles) se añadieron y la mezcla se agitó a t.a. durante 2 días. Esta después se evaporó y el residuo se trituró con una mezcla de éter dietílico:ciclohexano (1:1) para dar el compuesto del título (1.47 g, 60%) como un sólido blanco.

CL/EM: m/z 310 $[MH]^+$, TR 2.66 min.

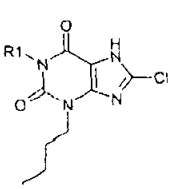
d) 4-[3-Butil-8-cloro-2,6-dioxo-7-(2-propen-1-il)-2,3,6,7-tetrahidro-1*H*-purin-1-il]butanonitrilo



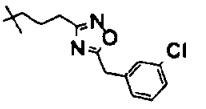
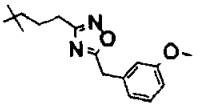
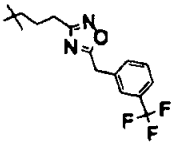
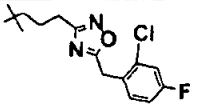
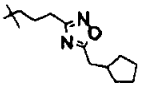
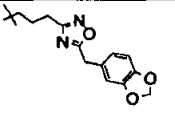
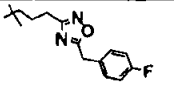
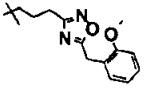
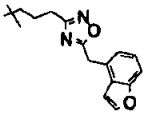
A 3-butil-8-cloro-7-(2-propen-1-il)-3,7-dihidro-1*H*-purino-2,6-diona (2.0 g, 0.0072 moles) en MeCN seco (20 ml) se añadió Cs_2CO_3 (4.68 g, 0.0144 moles) seguido por bromobutironitrilo (1.38 g, 0.0094 moles). La mezcla se calentó a 80°C durante 18 hr y después se dejó enfriar. La mezcla de reacción se evaporó y el producto crudo se dividió entre EtOAc y HCl (2N). La fase orgánica se separó y se lavó con salmuera, se secó ($MgSO_4$) y se evaporó para dar el producto crudo. Este se purificó por SPE de sílice (50 g), eluyendo con ciclohexano:acetato de etilo (2:1 a 1:1) para dar el compuesto del título como un aceite claro (2.1 g, 85%).

CL/EM: m/z 350 $[MH]^+$, TR 3.10 min.

Los siguientes compuestos (cuadro 8) se prepararon usando un método análogo al del ejemplo 142, a partir de los ácidos correspondientes y (1*Z*)-4-(3-butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1*H*-purin-1-il)-*N*-hidroxibutanimidamida.



CUADRO 8

Ejemplo		Compuesto: R1 =	Rend. %	CL/EM:
143	3-butil-8-cloro-1-(3-{5-[(3-clorofenil)metil-1,2,4-oxadiazol-3-il}propil)-3,7-dihidro-1*H*-purino-2,6-diona		27	m/z 477 $[MH]^+$ TR 3.5 min
144	3-butil-8-cloro-1-(3-{5-[(3-metiloxi)fenil]metil}-1,2,4-oxadiazol-3-il)propil}-3,7-dihidro-1*H*-purino-2,6-diona		22	m/z 473 $[MH]^+$ TR 3.3 min
145	3-butil-8-cloro-1-(3-(5-{(3-(trifluorometil)fenil]metil}-1,2,4-oxadiazol-3-il)propil]-3,7-dihidro-1*H*-purino-2,6-diona		23	m/z 511 $[MH]^+$ TR 3.5 min
146	3-butil-8-cloro-1-(3-{5-[(2-cloro-4-fluorofenil)metil]-1,2,4-oxadiazol-3-il}propil)-3,7-dihidro-1*H*-purino-2,6-diona		28	m/z 495 $[MH]^+$ TR 3.5 min
147	3-butil-8-cloro-1-{3-[5-(ciclopentilmetil)-1,2,4-oxadiazol-3-il]propil}-3,7-dihidro-1*H*-purino-2,6-diona		15	m/z 435 $[MH]^+$ TR 3.5 min
148	1-{3-[5-(1,3-benzodioxol-5-ilmetil)-1,2,4-oxadiazol-3-il]propil}-3-butil-8-cloro-3,7-dihidro-1*H*-purino-2,6-diona		27	m/z 487 $[MH]^+$ TR 3.3 min
149	3-butil-8-cloro-1-(3-{5-[(4-fluorofenil)metil]-1,2,4-oxadiazol-3-il}propil]-3,7-dihidro-1*H*-purino-2,6-diona		28	m/z 461 $[MH]^+$ TR 3.3 min
150	3-butil-8-cloro-1-[3-(5-{(2-(metiloxi)fenil]metil}-1,2,4-oxadiazol-3-il)propil]-3,7-dihidro-1*H*-purino-2,6-diona		21	m/z 473 $[MH]^+$ TR 3.3 min
151	1-{3-[5-(1-benzofuran-4-ilmetil)-1,2,4-oxadiazol-3-il]propil}-3-butil-8-cloro-3,7-dihidro-1*H*-purino-2,6-diona		24	m/z 483 $[MH]^+$ TR 3.4 min

Detalles de RMN para ejemplos seleccionados del cuadro 8

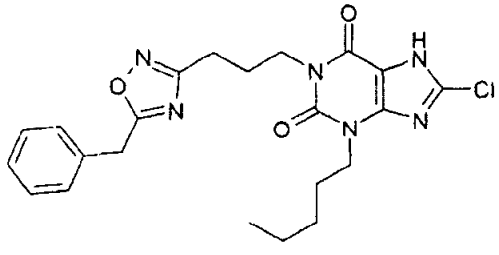
EJEMPLO 145

^{1}H RMN ($CDCl_3$) 0.96 (3H, t, J = 7.5Hz), 1.32-1.47 (2H, m), 1.65-1.81 (2H, m), 2.12-2.25 (2H, m), 2.84 (2H, t, J = 7.5 Hz), 4.02 (2H, t, 7.5Hz), 4.22 (2H, t, 7Hz), 4.24 (2H, s), 7.40-7.62 (4H, m).

EJEMPLO 152

8-Cloro-3-pentil-1-{3-[5-(fenilmetil)-1,2,4-oxadiazol-3-il]propil}-3,7-dihidro-1*H*-purino-2,6-diona

a) 8-Cloro-3-pentil-1-{3-[5-(fenilmetil)-1,2,4-oxadiazol-3-il]propil}-3,7-dihidro-1H-purino-2,6-diona

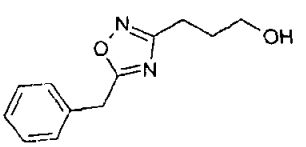


A una solución agitada de 8-cloro-3-pentil-7-(2-propen-1-il)-3,7-dihidro-1*H*-purino-2,6-diona (0.20, 0.67 mmoles) en THF (5 ml) se añadió 3-[5-(fenilmetil)-1,2,4-oxadiazol-3-il]-1-propanol (0.162 g, 0.74 mmoles), DBAD (0.186 g, 0.81 mmoles) y trifenilfosfina (0.212 g, 0.81 mmoles) y la solución se agitó durante 18 hr. A la solución se añadió $Pd(PPh_3)_4$ (75 mg, 0.067 mmoles)

y morfolina (600 µl, 6.7 mmoles) y se agitó durante a t.a. bajo nitrógeno durante 3 hr adicionales. 75 mg de $Pd(PPh_3)_4$ se añadieron y la mezcla se dejó agitar durante otras 3 hr. La mezcla se dividió entre EtOAc y HCl 2M (ac.). La capa orgánica se separó, se lavó con salmuera, se secó ($MgSO_4$) y se concentró. El material crudo se purificó por un SPE de aminopropilo usando MeOH para cargar el compuesto en la columna y para lavar las impurezas, después con 2-4% de AcOH/MeOH para eluir el compuesto. Las fracciones de producto se combinaron y se concentraron, después se purificó adicionalmente por MDAP. Las fracciones de producto se combinaron y se concentraron dando el compuesto del título como un sólido blanco (51 mg, 20%).

CL/EM: m/z 457 $[MH]^+$, TR 3.54 min.

b) 3-[5-(Fenilmetil)-1,2,4-oxadiazol-3-il]-1-propanol



Una mezcla de (1*E*)-4,4-bis(etiloxi)-*N*-hidroxibutanimidamida (3.2 g, 16.8 mmoles), fenilacetato de etilo (2.3 ml, 14.4 mmoles) y etóxido de sodio (solución al 21% en EtOH, 6.4 ml) se calentó en un microondas a 140°C durante 10 min. El material se combinó con el de una segunda reacción (usando 1.2 g de (1*E*)-4,4-bis(etiloxi)-*N*-hidroxibutanimidamida y se condujo como antes) y se dividió entre solución de HCl 1M y EtOAc. La capa orgánica

se separó, se lavó con salmuera, se secó y se concentró para proveer 5-[3,3-bis(etiloxi)propil]-5-(fenilmetil)-1,2,4-oxadiazol que se usó sin purificación en la siguiente etapa.

3-[3,3-Bis(etiloxi)propil]-5-(fenilmetil)-1,2,4-oxadiazol crudo (5.63 g, 19.4 mmoles) en EtOH (75 ml) se agitó con ácido p-toluensulfónico (0.738 g, 3.9 mmoles) durante 21 hr y la mezcla se dividió entre EtOAc y agua. Los compuestos orgánicos se aislaron, se lavaron con agua y salmuera, se secaron y se concentraron a un aceite rojo. Este material contenía cantidades significativas de acetal, por lo tanto el aceite se disolvió en THF (15 ml) y se trató con solución de HCl 2M durante 2 hr, después se dividió entre EtOAc y agua. Los compuestos orgánicos se aislaron, se lavaron con salmuera, se secaron y se concentraron para dar 3-[5-(fenilmetil)-1,2,4-oxadiazol-3-il]propanal como un aceite rojo/café (3.77 g) que se usó crudo en el siguiente paso.

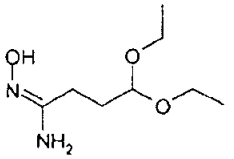
Una solución de 3-[5-(fenilmetil)-1,2,4-oxadiazol-3-il]propanal crudo (3.76 g, 17.4 mmoles) en MeOH (60 ml) se enfrió a 0°C y borhidruro de sodio (0.724 g, 19.1 mmoles) se añadió en porciones durante 30 min. El baño de enfriamiento se removió y la solución se agitó durante 1 hr adicional, después se dividió entre HCl 1M y EtOAc. La capa orgánica se separó y la capa acuosa se extrajo con EtOAc. Los extractos combinados se lavaron con salmuera, se secaron y se concentraron a un líquido anaranjado. Este se purificó en un SPE de sílice de 50g eluyendo con ciclohexano/EtOAc (elución por gradiente de 20% a 80%) para proveer el compuesto del título como un

aceite amarillo (2.24 g).

CL/EM: m/z 210 $[MH]^+$.}

A50

c) (1*E*)-4,4-bis(etiloxi)-*N*-hidroxibutanimidamida

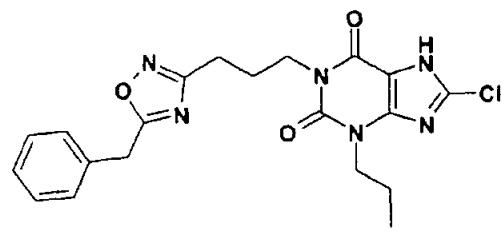


Una mezcla de dietilacetal de 3-cinopropionaldehído (6.12 g, 39 mmoles), clorhidrato de hidroxilamina (4.06 g, 58.4 mmoles), carbonato de potasio (10.76 g, 77.9 mmoles) en agua (20 ml) y EtOH (40 ml) se puso a reflujo durante 24 hr. La mezcla se dejó enfriar y después se dividió entre agua y EtOAc. La capa orgánica se separó y la capa acuosa se extrajo con EtOAc. Las fracciones orgánicas combinadas se lavaron con salmuera, se secaron y se concentraron para proveer el compuesto del título como un aceite incoloro contaminado con-20% del nitrilo de partida (6.03 g, 81%).

CL/EM: m/z 191 $[MH]^+$.

EJEMPLO 153

8-Cloro-1-{3-[5-(fenilmetil)-1,2,4-oxadiazol-3-il]propil}-3-propil-3,7-dihidro-1*H*-purino-2,6-diona



Una solución de 8-cloro-7-(2-propen-1-il)-3-propil-3,7-dihidro-1*H*-purino-2,6-diona (200 mg, 0.74 mmoles) en THF (4 ml) se trató con 3-[5-(fenilmetil)-1,2,4-oxadiazol-3-il]-1-propanol (195 mg, 0.89 mmoles) y PPh_3 (254 mg, 0.96 mmoles). Se añadió DBAD (223 mg, 0.96 mmoles) en una porción y la mezcla se dejó agitar a t.a. bajo nitrógeno durante 18 hr. La mezcla se dividió entre EtOAc y HCl 2M (ac.). La capa orgánica se separó, se lavó con salmuera, se secó ($MgSO_4$) y se concentró por alto vacío. El producto crudo se purificó sobre una columna de SPE de sílice usando un gradiente de 0-70% de ciclohexano/EtOAc. Las fracciones de producto se combinaron, se concentraron por alto vacío y se purificaron en una columna de SPE de sílice usando un gradiente de 0-60% de ciclohexano/EtOAc. Las fracciones de producto se combinaron y se concentraron, después se disolvieron en THF anhidro (4 ml). La solución se desgasificó por alto vacío, después se añadieron $Pd(PPh_3)_4$ (61 mg, 0.053 mmoles) y morfolina (460 µl, 5.3 mmoles) y la mezcla se dejó agitar a t.a. bajo nitrógeno durante 1 día. La mezcla se dividió entre EtOAc y HCl 2M (ac.). La capa orgánica se separó, se

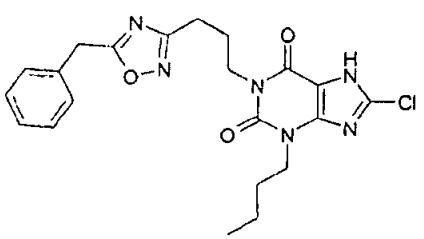
lavó con salmuera, se secó ($MgSO_4$) y se concentró por alto vacío. El producto crudo se purificó por un SPE de aminopropilo usando MeOH para cargar el compuesto en la columna y para lavar las impurezas, después un gradiente de 2-4% de AcOH/MeOH para eluir el producto. Las fracciones de producto se combinaron y se concentraron para dejar el compuesto del título como un sólido blanco (36 mg, 11%).

CL/EM: m/z 429 $[MH]^+$, TR 3.14 min.

^1H RMN (DMSO-d_6) δ: 0.86 (t, 3H, J = 7.5Hz), 1.65 (m, 2H), 1.93 (m, 2H), 2.70 (t, 2H, J = 7.5Hz), 3.86 (t, 2H, J = 7Hz), 3.96 (t, 2H, J = 7Hz), 4.28 (s, 2H), 7.32 (m, 5H).

EJEMPLO 154

3-Butil-8-cloro-1-(3-[5-(fenilmetil)-1,2,4-oxadiazol-3-il]propil}-3,7-dihidro-1*H*-purino-2,6-diona



Una solución de 3-[5-(fenilmetil)-1,2,4-oxadiazol-3-il]-1-propanol (594 mg, 2.7 mmoles) en THF (25 ml) se trató con 3-butil-8-cloro-7-(2-propen-1-il)-3,7-dihidro-1*H*-purino-2,6-diona (700 mg, 2.48 mmoles) y PPh_3 (779 mg, 2.97 mmoles) bajo nitrógeno. Se añadió DBAD (684 mg, 2.97 mmoles) en una porción y la reacción se dejó reaccionar durante 60 hr. La mezcla se dividió

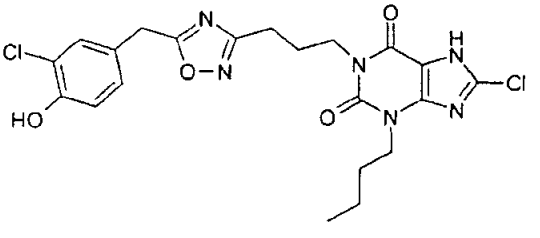
entre HCl 2M (ac.) y EtOAc. La capa orgánica se separó, se lavó con salmuera, se secó ($MgSO_4$) y se concentró. MeOH se añadió al residuo y después se hizo pasar una columna de aminopropilo eluyendo el producto con 2-4% de AcOH/MeOH. Las fracciones de producto se combinaron y se concentraron. El residuo blanquecino se recristalizó a partir de EtOAc:ciclohexano (1:1), dando el compuesto del título como un sólido blanco (696 mg, 63%).

CL/EM: m/z 443 $[MH]^+$, TR 3.4 min.

^{1}H RMN (DMSO-d_6) δ: 0.89 (t, 3H, J = 7Hz), 1.29 (m, 2H), 1.61 (m, 2H), 1.93 (m, 2H), 2.70 (t, 2H, J = 7.5Hz), 3.90 (t, 2H, J = 7Hz), 3.96 (t, 2H, J = 7Hz), 4.28 (2H, s), 7.31 (m, 5H), 14.4 (br s, 1H).

EJEMPLO 155

3-Butil-8-cloro-1-(3-{5-[(3-cloro-4-hidroxifenil)metil]-1,2,4-oxadiazol-3-il}propil)-3,7-dihidro-1*H*-purino-2,6-diona



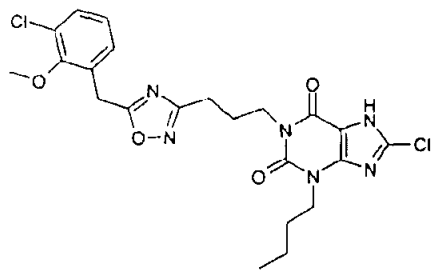
Una solución de ácido 3-cloro-4-hidroxifenilacético (24 mg, 0.13 mmoles) en DMSO (1 ml) se trató con CDI (21 mg, 0.13 mmoles) y se dejó reaccionar durante 30 min. Se añadió (1*Z*)-4-(3-butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1*H*-purin-1-il)-N-hidroxibutanimidamida (50 mg, 0.15 mmoles) y la

mezcla se calentó en el microondas a 120°C durante 15 min. La solución se purificó directamente por MDAP para obtener el compuesto del título como un sólido blanco (12 mg, 17%).

CL/EM: m/z 493 $[MH]^+$, TR 3.2 min.

EJEMPLO 156

3-Butil-8-cloro-1-[3-(5-{[3-cloro-2-(metiloxi)fenil]metil}-1,2,4-oxadiazol-3-il)propil]-3,7-dihidro-1*H*-purino-2,6-diona

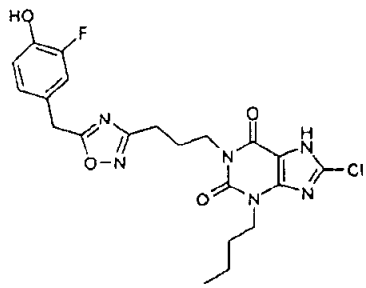


Una mezcla de ácido [3-cloro-2-(metiloxi)fenil]acético (32 mg, 0.16 mmoles) en DMF (1.5 ml) se trató con CDI (26 mg, 0.16 mmoles) y se dejó reaccionar durante 45 min. Se añadió (1*Z*)-4-(3-butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1*H*-purin-1-il)-*N*-hidroxibutanimidamida (60 mg, 0.18 mmoles) y la mezcla se calentó en el microondas a 140°C durante 15 min. Después de enfriarse, la reacción se dividió entre HCl 2M (ac.) y EtOAc. La capa orgánica se separó, después se concentró y se purificó por MDAP. El compuesto del título se obtuvo como un sólido blanco (25 mg, 28%).

CL/EM: m/z 507 $[MH]^+$, TR 3.5 min.

EJEMPLO 157

3-Butil-8-cloro-1-(3-{5-[(3-fluoro-4-hidroxifenil)metil]-1,2,4-oxadiazol-3-il}propil)-3,7-dihidro-1*H*-purino-2,6-diona



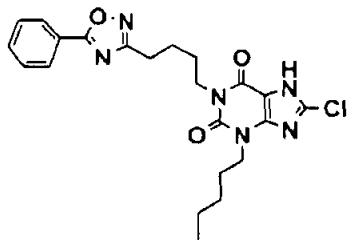
Una mezcla de ácido (3-fluoro-4-hidroxifenil)acético (27 mg, 0.16 mmoles) en DMF (1.5 ml) se trató con CDI (26 mg, 0.16 mmoles) y se dejó reaccionar durante 45 min. Se añadió (1*Z*)-4-(3-butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1*H*-purin-1-il)-N-hidroxibutanimidamida (60 mg, 0.18 mmoles) y la mezcla se calentó en el microondas a 140°C durante 15 min. Después de enfriarse, la reacción se dividió entre HCl 2M (ac.) y EtOAc. La capa orgánica se separó, después se concentró y se purificó por MDAP. El compuesto del título se obtuvo como un sólido blanco (10 mg, 12%).

CL/EM: m/z 477 $[MH]^+$, TR 3.2 min.

EJEMPLO 158

8-Cloro-3-pentil-1-[4-(5-fenil-1,2,4-oxadiazol-3-il)butil]-3,7-dihidro-1*H*-purino-2,6-diona

a) Preparación de 8-cloro-3-pentil-1-[4-(5-fenil-1,2,4-oxadiazol-3-il)butil]-3,7-dihidro-1*H*-purino-2,6-diona



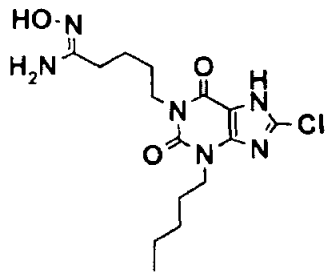
Acido benzoico (18 mg, 0.15 mmoles) se trató con una solución de 1H-1,2,3-benzotriazol-1-ol hidratado (25 mg, 0.19 mmoles) en DMSO (0.3 ml). A este se añadió una solución/suspensión de clorhidrato de N-[3-(dimetilamino)propil]-N'-etilcarbodiimida (29 mg, 0.15 mmoles) en DMSO (0.3 ml) seguido por una solución de 5-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)-N-hidroxipentanimidamida (55 mg, 0.15 mmoles) en DMSO (0.3 ml). La mezcla se calentó a 40°C durante 1 hr, después a 80°C durante 5 hr y después se enfrió. La mezcla se sometió a purificación por MDAP. Las fracciones que contenían producto se soplaron a sequedad por una corriente de nitrógeno para dar el compuesto del título como un sólido blanco (17.2 mg, 25%).

CL/EM: m/z 457 $[MH]^+$, TR 3.67 min.

^{1}H RMN ($CDCl_3$) δ: 0.90 (t, 3H1 J = 6.8Hz), 1.35 (m, 4H), 1.76

(m, 2H), 1.89 (m, 4H), 2.88 (t, 2H, J = 7.2Hz), 4.08 (t, 2H, J = 7.5Hz), 4.17 (t, 2H, J = 6.7Hz), 7.50 (m, 2H), 7.57 (m, 1H), 8.08, (d, 2H, J = 7.3Hz).

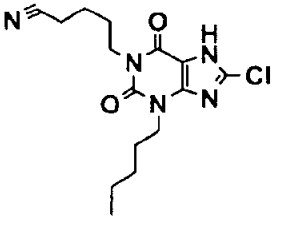
b) 5-(8-Cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1*H*-purin-1-il)-N-hidroxipentanimidamida



Una solución de 5-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1*H*-purin-1-il)pentanonitrilo (3.0 g, 8.9 mmoles) en EtOH (30 ml) se trató con agua (15 ml), carbonato de potasio (1.48 g, 10.7 mmoles) y clorhidrato de hidroxilamina (0.74 g, 10.7 mmoles) y después se calentó a 70°C durante la noche. arbonato de potasio adicional (1.5 g, 10.9 mmoles) y clorhidrato de hidroxilamina (1.0 g, 14.5 mmoles) se añadieron cuidadosamente a la mezcla que después se calentó a 90°C durante 24 hr. La mezcla se enfrió y se concentró bajo vacío para remover la mayor parte de EtOH. La mezcla residual se trató con agua (30 ml) y se acidificó a pH 7 mediante la adición cuidadosa de ácido clorhídrico acuoso 2M. El sólido precipitado se filtró, se lavó con agua, después con éter dietílico y se secó completamente para dar el compuesto del título como un sólido blanco (2.80 g, 85%).

CL/EM: m/z 371 $[MH]^+$, TR 2.27 min.

c) 5-(8-Cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1*H*-purin-1-il)pentanonitrilo

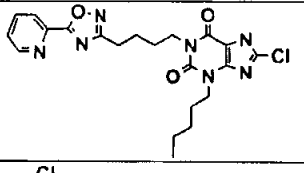
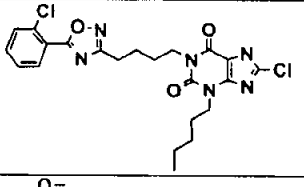
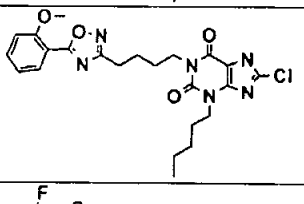
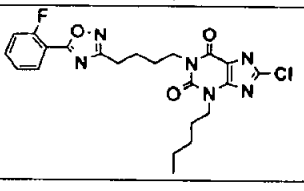


Una solución de 8-cloro-3-pentil-7-(2-propen-1-il)-3,7-dihidro-1*H*-purino-2,6-diona (4.0 g, 13.5 mmoles) en DMF (100 ml) se trató con carbonato de cesio (4.83 g, 14.8 mmoles) y 5-bromopentanonitrilo (1.73 ml, 14.8 mmoles). La mezcla se calentó a 50°C en una atmósfera de nitrógeno durante 19 hr y después se enfrió. La mezcla se desgasificó después mediante la aplicación sucesiva repetida de un vacío y después de presión de nitrógeno. La mezcla después se trató con tetrakis(trifenilfosfin)paladio(0) (1.1 g, 0.94 mmoles) y morfolina (11.8 ml, 136 mmoles). La mezcla se agitó en una atmósfera de nitrógeno durante 3 hr y después se dividió entre EtOAc y ácido clorhídrico acuoso 2M. La capa orgánica se separó, se lavó con salmuera, se secó ($MgSO_4$) y se concentró para revelar un residuo amarillo, oleoso. Este se disolvió en MeOH, se dividió igualmente en cuatro porciones y cada porción se aplicó a un SPE de aminopropilo de 20 g que después se lavó con MeOH. El producto deseado se eluyó del cartucho con una solución al 5% v/v de AcOH en MeOH. Las fracciones que contenían producto se combinaron y se concentraron para dar el compuesto del titulo como un sólido amarillo pálido (4.03 g, 88%).

CL/EM: m/2 338 $[MH]^+$, TR 3.05 min.

Los siguientes compuestos se prepararon usando un método análogo al del ejemplo 158 (8-cloro-3-pentil-1-[4-(5-fenil-1,2,4-oxadiazol-3-il)butil]-3,7-dihidro-1H-purino-2,6-diona) a partir de los ácidos correspondientes:

CUADRO 9

No.	Estructura	Nombre	Rend.	CL/EM:
159		8-cloro-3-pentil-1-{4-[5-(2-piridinil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purina-2,6-diona	7.3 mg (11%)	m/z 458 $[MH]^+$ TR 3.21 min
160		8-cloro-1-{4-[5-(2-clorofenil)-1,2,4-oxadiazol-3-il]butil}-3-pentil-3,7-dihidro-1H-purina-2,6-diona	12.8 mg (17%)	m/z 491 $[MH]^+$ TR 3.77 min
161		8-cloro-1-(4-{5-[2-metiloxi)fenil]-1,2,4-oxadiazol-3-il}butil)-3-pentil-3,7-dihidro-1H-purina-2,6-diona	21.7 mg (30%)	m/z 487 $[MH]^+$ TR 3.54 min
162		8-cloro-1-{4-[5-(2-fluorofenil)-1,2,4-oxadiazol-3-il]butyl}-3-pentil-3,7-dihidro-1H-purina-2,6-diona	16.6 mg (23%)	m/z 475 $[MH]^+$ TR 3.62 min

Además el ejemplo 159, 8-cloro-3-pentil-1-{4-[5-(2-piridinil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purino-2,6-diona tiene los siguientes datos del espectro:

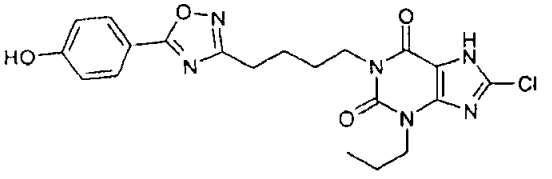
^{1}H RMN ($CDCl_3$) δ: 0.89 (t, 3H, J = 6.9Hz), 1.75 (m, 4H), 1.89 (m,

6H), 2.92 (t, 2H, J = 7.1Hz), 4.07 (t, 2H, J = 7.4Hz), 4.16 (t, 2H, J = 6.9Hz), 7.52 (m, 1H), 7.92 (m, 1H), 8.18 (m, 1H), 8.83 (m, 1H), 13.40 (br s, 1H).

A60

EJEMPLO 163

8-Cloro-1-{4-[5-(4-hidroxifenil)-1,2,4-oxadiazol-3-il]butil}-3-propil-3,7-dihidro-1*H*-purino-2,6-diona

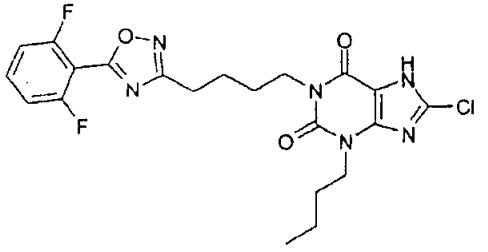


Acido 4-hidroxibenzoico (18 mg, 0.13 mmoles) y CDI (24 mg, 0.15 mmoles) se agitaron en DMSO anhidro (0.9 ml) a t.a. durante 1 hr. (1*Z*)-5-(8-cloro-2,6-dioxo-3-propil-2,3,6,7-tetrahidro-1*H*-purin-1-il)-*N*-hidroxipentanimidamida (50 mg, 0.15 mmoles; preparada de manera similar a (1*Z*)-5-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)-*N*-hidroxipentanimidamida preparada como se describió en el ejemplo 158(b)) se añadió y la mezcla se agitó a 90°C durante 2 hr. La mezcla de reacción se purificó por MDAP. La fracción de producto se combinó y se concentró bajo alto vacío para dar el compuesto del título como un sólido blanco (7 mg, 11%).

CL/EM: m/z 443 $[MH]^+$, TR 3.28 min.

EJEMPLO 164

3-Butil-8-cloro-1-{4-[5-(2,6-difluorofenil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1*H*-purino-2,6-diona

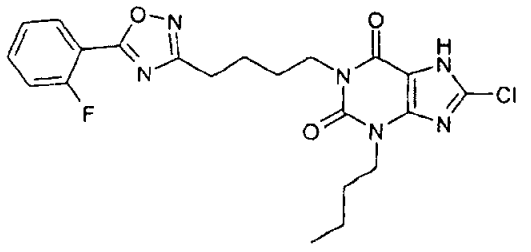


Acido 2,6-difluorobenzoico (40 mg, 0.25 mmoles) y CDI (45 mg, 0.28 mmoles) se agitaron en DMSO anhidro (0.9 ml) a t.a. durante 1 hr. Se añadió (1*Z*)-5-(3-butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1*H*-purin-1-il)-*N*-hidroxipentani-midamida (100 mg, 0.28 mmoles) y la mezcla se agitó a 90°C durante 16 hr. La mezcla de reacción se purificó por MDAP. La fracción de producto se combinó y se concentró para dar el compuesto del título como un sólido blanco (18 mg, 15%).

CL/EM: m/z 479 $[MH]^+$, TR 3.40 min.

EJEMPLO 165

3-Butil-8-cloro-1-{4-[5-(2-fluorofenil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1*H*-purino-2,6-diona

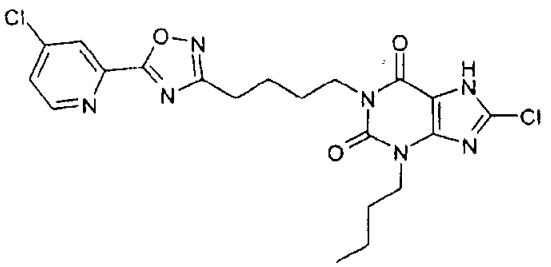


Acido 2-fluorobenzoico (36 mg, 0.25 mmoles) y CDI (45 mg, 0.28 mmoles) se agitaron en DMSO anhidro (0.9 ml) a t.a. durante 1 hr. Se añadió (1*Z*)-5-(3-butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1*H*-purin-1-il)-*N*-hidroxi-pentanimidamida (100 mg, 0.28 mmoles) y la mezcla se agitó a 90°C durante 16 hr. La mezcla se purificó por MDAP. La fracción de producto se combinó y se concentró para dar el compuesto del título como un sólido blanco (33 mg, 29%).

CL/EM: m/z 461 $[MH]^+$, TR 3.44 min.

EJEMPLO 166

3-Butil-8-cloro-1-{4-[5-(4-cloro-2-piridinil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1*H*-purino-2,6-diona



Acido 4-cloro-2-piridincarboxílico (40 mg, 0.25 mmoles) y CDI (45 mg, 0.28 mmoles) se agitaron en DMSO anhidro (0.9 ml) a t.a. durante 1 hr. Se añadió (1*Z*)-5-(3-butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1*H*-purin-1-il)-*N*-hidroxipentanimidamida (100 mg, 0.28 mmoles) y la mezcla se agitó a 90°C durante 16 hr. La mezcla de reacción se purificó por MDAP. La fracción de producto se combinó y se concentró para dar el compuesto del título como un

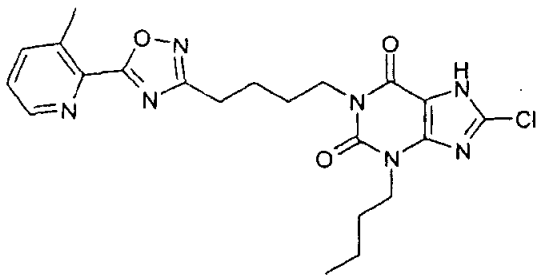
sólido blanco (13 mg, 11%).

CL/EM: m/z 478 $[MH]^+$, TR 3.31 min.

^{1}H RMN (DMSO-d_6) δ_H 14.4 (br. s, 1H), 8.79 (d, 1H, J=6Hz), 8.24 (d, 1H, J=2Hz), 7.88 (dd, 1H, J=6Hz y 2Hz), 3.91 (m, 4H), 2.85 (t, 2H, J=7.5Hz), 1.56-1.76 (m, 6H), 1.28 (m, 2H), 0.87 (t, 3H, J=7.5Hz) ppm.

EJEMPLO 167

3-Butil-8-cloro-1-{4-[5-(3-metil-2-piridinil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1*H*-purino-2,6-diona



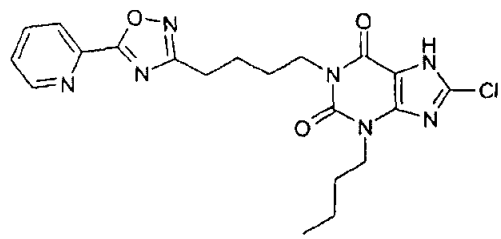
Acido 3-metil-2-piridincarboxílico (35 mg, 0.25 mmoles) y CDI (45 mg, 0.28 mmoles) se agitaron en DMSO anhidro (0.9 ml) a t.a. durante 1 hr. Se añadió (1*Z*)-5-(3-butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1*H*-purin-1-il)-*N*-hidroxipentanimidamida (100 mg, 0.28 mmoles) y la mezcla se agitó a 90°C durante 16 hr. La mezcla de reacción se purificó por MDAP. La fracción de producto se combinó y se concentró para dar el compuesto del título como un sólido blanco (14 mg, 12%).

CL/EM: m/z 458 $[MH]^+$, TR 3.13 min.

EJEMPLO 168

3-Butil-8-cloro-1-{4-[5-(2-piridinil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1*H*-purino-2,6-diona

Método A

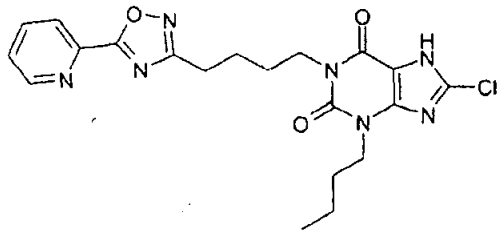


Acido 2-piridincarboxílico (31 mg, 0.25 mmoles) y CDI (45 mg, 0.28 mmoles) se agitaron en DMSO anhidro (0.5 ml) a t.a. durante 1 hr. Una solución de (1*Z*)-5-(3-butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1*H*-purin-1-il)-*N*-hidroxipentanimidamida (100 mg, 0.28 mmoles) en DMSO (0.4 ml) se añadió y la mezcla se agitó a 90°C durante 16 hr. La mezcla de reacción se purificó directamente por MDAP. Las fracciones de producto se combinaron y se concentraron para dar el compuesto del título como un sólido blanco (14 mg, 12%).

CL/EM: m/z 444 $[MH]^+$, TR 3.01 min.

^{1}H RMN (DMSO-d_6) δ: 0.87 (t, 3H, J = 7 Hz), 1.27 (m, 2H), 1.65 (m, 6H), 2.84 (t, 2H, J = 7 Hz), 3.91 (m, 4H), 7.70 (dd 1H, J = 5 y 7Hz), 8.07 (m, 1H), 8.19 (d, 1H, J = 8Hz), 8.81 (d, 1H, J = 5Hz), 14.5 (br. s, 1H).

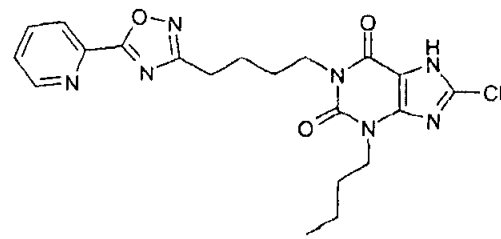
Método B



Acido 2-piridincarboxílico (675 mg, 5.3 mmoles) y CDI (909 mg, 5.6 mmoles) se agitaron en DMF anhidro (30 ml) a t.a. bajo nitrógeno durante 90 min. Se añadieron (1*Z*)-5-(3-butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1*H*-purin-1-il)-*N*-hidroxipentanimidamida (2.0 g, 5.6 mmoles) y DMF (10 ml) y la mezcla se agitó a 100°C durante 20 hr. La mezcla de reacción se enfrió a t.a. después se dividió entre solución de NH4Cl (ac.) saturada y EtOAc. La capa orgánica se separó, y la solución acuosa se extrajo con EtOAc. Los extractos combinados se lavaron con salmuera, se secaron $MgSO_4$ y se concentraron dando un líquido anaranjado. Este se purificó usando el sistema Companion™ dando dos sólidos blancos idénticos (649 mg; 240 mg).

CL/EM: m/z 444 $[MH]^+$, TR 3.04 min.

Método C



Un matraz de fondo redondo, de 12 litros se equipó con una

cabeza, agitador mecánico, una sonda de temperatura con un controlador de temperatura J-KEM, un condenser y un adaptador de entrada de nitrógeno. El matraz se cargó con ácido picolínico (0.180 kg, 1.46 moles), MIBK (4.0 l), 1,1'-carbonildiimidazol (0.23 kg, 1.42 moles) y más MIBK (0.66 l). La mezcla se agitó y se calentó a 50°C durante aproximadamente 1 hora, y la temperatura se elevó a 56°C. Los sólidos se disolvieron durante el calentamiento a 50°C y se generó dióxido de carbono. Después de 1 hora a 50°C, se añadió (1*Z*)-5-(3-butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1*H*-purin-1-il)-*N*-hidroxi-pentanimidamida (0.467 kg, 1.31 moles) a la reacción. La mezcla se calentó después a 90°C durante 1 hora. El análisis por CLAR de la reacción después de calentamiento a 90°C durante 5.5 horas indicó que la reacción se completó. El calentamiento se apagó, y se añadió solución de ácido ácido clorhídrico 1.0 N (2.33 l). La temperatura cayó a 61°C. Depués de agitarse durante la noche, el producto se precipitó y se filtró. La torta de filtro se lavó con agua (1 x 2.23 l, 1 x 2.43 l) y heptanos (1.40 l). La torta húmeda se secó en un horno de vacío a 50°C durante 22 horas para dar 396 g de producto (68%), análisis por CLAR 97.7% (AUC) t_R = 18.6 min.

Método D

Formación de 3-Butil-8-cloro-1-{4-[5-(2-piridinil)-1,2,4-oxadiazol-3-il] butil}-3,7-dihidro-1*H*-purino-2,6-diona Forma 1

El recipiente de reacción se cargó con 3-butil-8-cloro-1-{4-[5-(2-piridinil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1*H*-purino-2,6-diona (1% en peso), acetona (20% en vol.) y agua (0.6% en vol.). La mezcla se agitó y se calentó a 50-60°C y se agitó durante un mínimo de 1 hora. Se formó una solución que se clarificó a esta temperatura por filtración a través de un filtro de 1 micra en un segundo recipiente de reacción. La solución se enfrió durante aproximadamente 3 horas a 33-38°C y se sembró a esta temperatura con 3-butil-8-cloro-1-{4-[5-(2-piridinil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1*H*-purino-2,6-diona (Forma 1, 0.01% en peso). Esta suspensión delgada se agitó a esta temperatura durante un mínimo de 1 hora, después se enfrió a 20-25°C y se mantuvo a esta temperatura durante un mínimo de 12 horas. La suspensión así formada se enfrió a 13-17°C y se mantuvo a esta temperatura durante un mínimo de 1 hora. La suspensión después se muestreó, y el sólido se recogió por filtración en el laboratorio. El sólido se secó y se analizó por xrpd/DSC para verificar la forma. Si la forma es como se requiere (Forma 1) el lote se filtra, se lava (2x3 vol. de acetona) y se seca en un horno de vacío a 50°C. El lote es descargado una vez que el análisis muestra que los niveles de solvente (acetona, agua) son aceptables.

Rendimiento esperado (75-80% p/p).

Si la forma de la muestra tomada muestra se otra distinta de la

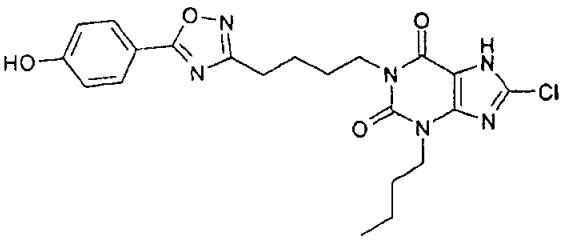
forma 1 pura, entonces **el lote se vuelve a calentar a 35-45°C y se agita a esta temperatura durante un mínimo de 1 hora. La suspensión delgada después se enfría a 20-25°C y se mantiene a esta temperatura durante un mínimo de 12 horas. La suspensión así formada después se enfría a 13-17°C y se mantienea esta temperatura durante un mínimo de 1 hora. La suspensión después se muestrea y el sólido se recoge por filtración en el laboratorio. El sólido se seca y se analiza por xrpd/DSC para verificar la forma. Si la forma es como se requiere (forma 1) el lote se filtra, se lava y se seca como se describió antes. Si la forma no es la forma 1 pura, entonces la forma de ciclo** se repite hasta que se obtiene un resultado satisfactorio.

Difracción de Rayos X en polvo (XRPD)

Los datos de difracción de rayos X en polvo (XRPD) se muestran en las figuras 1-3. Los datos se adquirieron en un difractómetro de polvo PANalytical X'Pert Pro, modelo PW3040/60, número de serie DY1850 usando un detector X'Celerator. Las condiciones de adquisicón fueron: radiación: Cu Ka, tensión del generador: 40 kV, corriente del generador: 45 mA, ángulo de inicio: 2.0°2θ, ángulo de terminación: 40.0°2 θ, tamaño de paso: 0.0167 °2 θ, tiempo por paso: 31.75 segundos. Las muestras se prepararon montando unos cuantos miligramos de muestra sobre placas de oblea de Si (fondo de cero), dando por resutado una capa delgada de polvo.

EJEMPLO 169

3-Butil-8-cloro-1-{4-[5-(4-hidroxifenil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1*H*-purino-2,6-diona

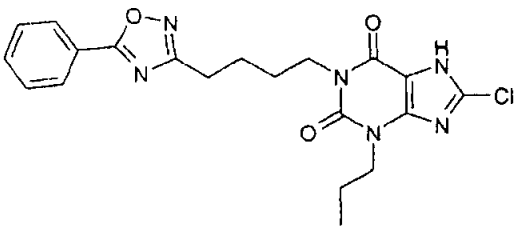


Acido 4-hidroxibenzoico (35 mg, 0.25 mmoles) y CDI (45 mg, 0.28 mmoles) se agitaron en DMSO anhidro (0.9 ml) a t.a. durante 1 hr. Se añadió (1*Z*)-5-(3-butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1*H*-purin-1-il)-*N*-hidroxipentanimidamida (100 mg, 0.28 mmoles) y la mezcla se agitó a 90°C durante 16 hr. La mezcla se purificó por MDAP para dar el compuesto del título como un sólido blanco (5 mg, 4%).

CL/EM: m/z 459 $[MH]^+$, TR 3.24 min.

EJEMPLO 170

8-Cloro-1-[4-(5-fenil-1,2,4-oxadiazol-3-il)butil]-3-propil-3,7-dihidro-1*H*-purino-2,6-diona



Acido benzoico (9 mg, 0.074 mmoles) y CDI (13 mg, 0.081

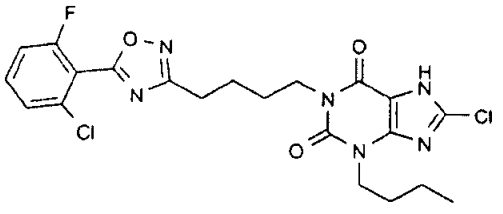
mmoles) se agitaron en DMSO anhidro (0.9 ml) a t.a. durante 1 hr. Se añadió (1Z)-5-(8-cloro-2,6-dioxo-3-propil-2,3,6,7-tetrahidro-1H-purin-1-il)-N-hidroxi-pentanimidamida (28 mg, 0.081 mmoles) y la mezcla se agitó a 80°C durante 4 hr. La mezcla se purificó por MDAP para dar el compuesto del título como un sólido blanco (0.6 mg, 2%).

CL/EM: m/z 429 $[MH]^+$, TR 3.21 min.

^{1}H RMN (MeOH-d_4) δ: 0.93 (t, 3H, J = 7.5Hz), 1.74 (m, 4H), 1.84 (m, 2H), 2.84 (t, 2H, J = 7Hz), 3.97 (t, 2H, J = 7.5Hz), 4.08 (t, 2H, J = 7Hz), 7.57 (dd, 2H, J = 7 y 7.5Hz), 7.65 (dd, 1H, J = 7 y 7.5Hz), 8.08 (d, 2H, J = 7.5Hz).

EJEMPLO 171

3-Butil-8-cloro-1-{4-[5-(2-cloro-6-fluorofenil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1*H*-purino-2,6-diona



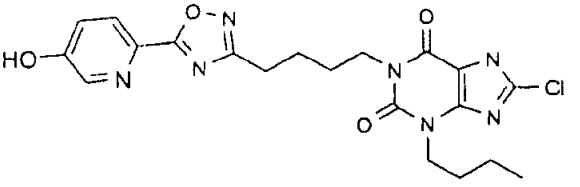
Acido 2-cloro-6-fluorobenzoico (44 mg, 0.25 mmoles) y CDI (45 mg, 0.28 mmoles) se agitaron en DMSO anhidro (0.9 ml) a t.a. durante 1 hr. Se añadió (1Z)-5-(3-butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1H-purin-1-il)-N-hidroxipentanimidamida (100 mg, 0.28 mmoles) y la mezcla se agitó a 90°C durante 16 hr. La mezcla se purificó por MDAP. La fracción de producto se

combinó y se concentró para dar el compuesto del título como un sólido blanco (6.4 mg, 5%).

CL/EM: m/z 495 $[MH]^+$, TR 3.58 min.

EJEMPLO 172

3-Butil-8-cloro-1-{4-[5-(5-hidroxi-2-piridinil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1*H*-purino-2,6-diona

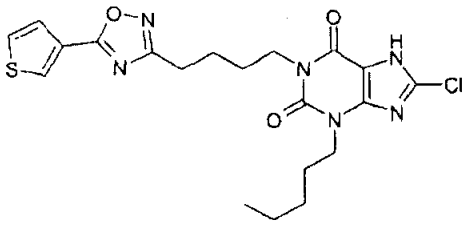


Acido 5-hidroxi-2-piridincarboxílico (24 mg, 0.17 mmoles) y CDI (31 mg, 0.19 mmoles) se agitaron en DMSO anhidro (0.9 ml) a t.a. durante 1 hr. Se añadió (1Z)-5-(3-butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1H-purin-1-il)-N-hidroxipentanimidamida (68 mg, 0.19 mmoles) y la mezcla se agitó a 90°C durante 16 hr. La mezcla se purificó por MDAP y las fracciones de producto se concentraron para dar el compuesto del título como un sólido blanco (19 mg, 24%).

CL/EM: m/z 459 $[MH]^+$, TR 3.03 min.

EJEMPLO 173

8-Cloro-3-pentil-1-{4-[5-(3-tienil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1*H*-purino-2,6-diona

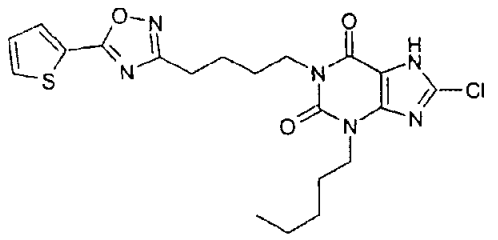


Una solución de (1Z)-5-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1*H*-purin-1-il)-N-hidroxipentanimidamida (50 mg, 0.13 mmoles) en EtOH (1 ml) se trató con una solución al 21% de NaOEt en EtOH (55 µl, 0.21 mmoles) y 3-tiofencarboxilato de etilo (18 µl, 0.13 mmoles). La mezcla se calentó en el microondas a 150°C durante 10 min. Después de enfriarse, la reacción se dividió entre HCl 2M (ac.) y EtOAc. La capa orgánica se separó y la capa acuosa se extrajo nuevamente con EtOAc. Los extractos combinados se concentraron y se purificaron por MDAP. El compuesto del título se obtuvo como un sólido blanquecino (20 mg, 32%).

CL/EM: m/z 463 $[MH]^+$, TR 3.6 min.

EJEMPLO 174

8-Cloro-3-pentil-1-{4-[5-(2-tienil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1*H*-purino-2,6-diona

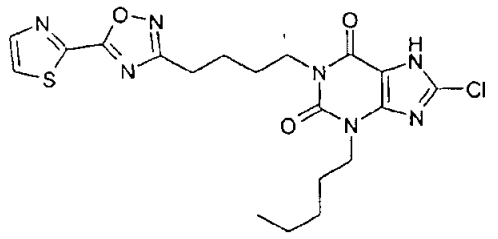


Acido 2-tiofencarboxílico (14 mg, 0.11 mmoles) se disolvió en NMP (0.9 ml) y se trató con CDI (18 mg, 0.11 mmoles). Después de 1 hr, se añadió (1Z)-5-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1*H*-purin-1-il)-N-hidroxipentanimidamida (50 mg, 0.13 mmoles) y la mezcla se calentó en el microondas a 150°C durante 15 min. La solución se purificó directamente por MDAP para obtener el compuesto del título que después se secó por congelamiento a partir de 1,4-dioxano para dar el compuesto del título como un sólido blanco (19 mg, 31%).

CL/EM: m/z 463 $[MH]^+$, TR 3.5 min.

EJEMPLO 175

8-Cloro-3-pentil-1-{4-[5-(1,3-tiazol-2-il)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1*H*-purino-2,6-diona



Una solución de (1Z)-5-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1*H*-purin-1-il)-*N*-hidroxipentanimidamida (50 mg, 0.13 mmoles) en EtOH (1.5 ml) se trató con una solución al 21% de NaOEt en EtOH (50 µl, 0.13 mmoles) y 1,3-tiazol-2-carboxilato de etilo (18 mg, 0.11 mmoles). La mezcla se calentó en el microondas a 170°C durante 10 min. Después de enfriarse, la reacción se dividió entre HCl 2M (ac.) y EtOAc. La capa orgánica se separó, después se concentró y se purificó por MDAP. El compuesto del título se obtuvo como un sólido blanco (13 mg, 21%).

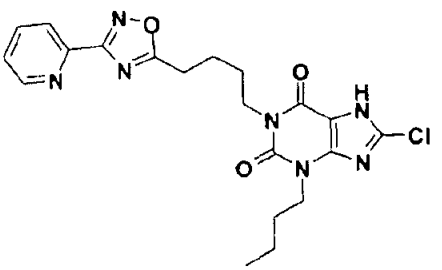
CL/EM: m/z 464 $[MH]^+$, TR 3.3 min.

^{1}H RMN (DMSO-d_6) δ: 0.83 (t, 3H, J = 7Hz), 1.21-1.32 (m, 4H), 1.60-1.77 (m, 6H), 2.84 (t, 2H, J = 7Hz), 3.91 (m, 4H), 8.23 (d, 1H1 J = 3Hz), 8.27 (d, 1H, J = 3Hz),14.4 (br s, 1H).

EJEMPLO 176

3-Butil-8-cloro-1-{4-[3-(2-piridinil)-1,2,4-oxadiazol-5-il]butil}-3,7-dihidro-1H-purino-2,6-diona

a) Preparación de 3-butil-8-cloro-1-{4-[3-(2-piridinil)-1,2,4-oxadiazol-5-il]butil}-3,7-dihidro-1H-purino-2,6-diona

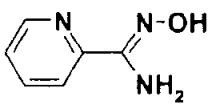


A una mezcla de 5-(3-butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1H-purin-1-il)pentanoato de etilo (120 mg, 0.32 mmoles) y de N-hidroxi-2-piridinacarboximidamida (50 mg, 0.36 mmoles) en EtOH (2 ml) se añadió una solución al 21% (p/v) de etóxido de sodio en EtOH (0.225 ml, 0.62 mmoles) y después se calentó en un vial sellado en un horno de microondas a 140°C durante 10 min. La mezcla enfriada se evaporó a sequedad y el residuo se dividió entre cloroformo (5 ml) y cloruro de amonio acuoso saturado (5 ml). La fase orgánica se evaporó a sequedad y el producto crudo se sometió a purificación por MDAP. Las fracciones que contenían producto se combinaron y se evaporaron a sequedad. El producto se trituró a un sólido en una pequeña cantidad de éter dietílico, después se secó para revelar el compuesto del título como un sólido blanco (44 mg, 31%).

CL/EM: m/z 444 $[MH]^+$, TR 3.03 min.

^{1}H RMN ($CDCl_3$) δ: 0.96 (t, 3H, J = 7.3Hz), 1.40 (m, 2H), 1.74 (m, 2H), 1.88 (m, 2H), 1.99 (m, 2H), 3.07 (t, 2H, J = 7.5Hz), 4.09 (t, 2H, J = 7.5Hz), 4.17 (t, 2H, J = 7.0Hz), 7.43 (m, 1H), 7.64 (m, 1H), 8.10 (m, 1H), 8.79 (m, 1H).

b) Preparación de N-hidroxi-2-piridincarboximidamida



A una mezcla de 2-piridincarbonitrilo (3 g, 29 mmoles) y carbonato de potasio (4.1 g, 30 mmoles) en EtOH (30 ml) se añadió agua (15 ml) y, cuidadosamente, clorhidrato de hidroxilamina (2.9 g, 42 mmoles) y después se calentó a reflujo durante 6 hr, se enfrió y se evaporó a sequedad. El residuo se trató con agua (100 ml) y el producto sólido suspendido se filtró, se lavó con agua y se secó para dar el compuesto del título como un sólido blanco (2.28g, 57%).

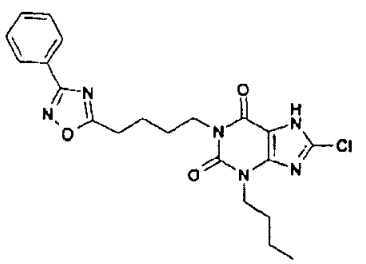
^{1}H RMN (DMSO-d_6) δ: 5.85 (br s, 2H), 7.40 (m, 1H), 7.79 (m, 1H), 7.86 (m, 1H), 8.55 (m, 1H), 9.92 (s, 1H)

EJEMPLO 177

3-Butil-8-cloro-1-[4-(3-fenil-1,2,4-oxadiazol-5-il)butil]-3,7-dihidro-1*H*-purino-2,6-diona

Método A

a) 3-Butil-8-cloro-1-[4-(3-fenil-1,2,4-oxadiazol-5-il)butil]-3,7-dihidro-1*H*-purina- 2,6-diona

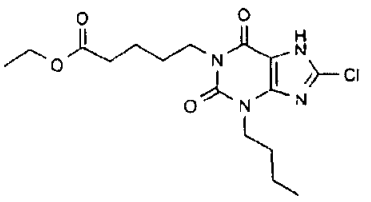


5-(3-Butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1*H*-purin-1-il) pentanoato de etilo (74 mg, 0.2 mmoles) y benzamidoxima (30 mg, 0.22 mmoles) se suspendieron en EtOH seco (1 ml) y se añadió etóxido de sodio etanólico (21% en peso, 0.111 ml, 0.3 mmoles). La mezcla se calentó suavemente hasta que los sólidos se disolvieron y después se calentó en el reactor de microondas a 140°C durante 10 min. La mezcla después se dividió entre EtOAc y HCl 2M y la fase orgánica se secó (Na_2SO_4) y se evaporó. MDAP dio el compuesto del título puro (40.7 mg).

CL/EM: m/z 443 $[MH]^+$, TR 3.67 min.

^{1}H RMN (DMSO-d_6) δ: 0.89 (t, 3H, J = 7Hz), 1.22-1.34 (m, 2H), 1.57-1.75 (m, 4H), 1.75-1.86 (m, 2H), 3.05 (t, 2H, J = 7 Hz), 3.88-3.98 (m, 4H), 7.52-7.63 (m, 3H), 7.95-8.0 (m, 2H).

b) 5-(3-butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1*H*-purin-1-il)pentanoato de etilo

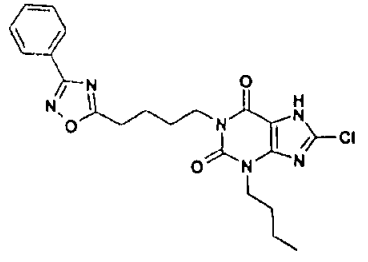


A 3-butil-8-cloro-7-(2-propen-1-il)-3,7-dihidro-1*H*-purino-2,6-diona (1.5 g, 5.31 mmoles) en DMF seco (25 ml) se añadió Cs_2CO_3 (1.905 g, 5.84 mmoles), seguido por 5-bromovalerato de etilo (1.46 g, 6.99 mmoles). La mezcla se calentó a 55°C durante 18 hr, después se dejó enfriar. Esta se desgasificó mediante evacuación repetida y radmitiendo nitrógeno, después se añadieron morfolina (3.70 ml, 42.5 mmoles) y tetrakis(trifenilfosfin)-paladio(0) (1.0 g, 0.865 mmoles) y la mezcla se agitó durante 5 hr. EtOAc (75 ml), HCl 2M (40 ml) y agua (20 ml) se añadieron y la fase orgánica se separó, se lavó con salmuera (3 x 25 ml), se filtró para remover algo del sólido amarillo insoluble, se secó (Na_2SO_4) y se evaporó. El residuo (2.5 g) se purificó por SPE de aminopropilo (20g), cargando en THF-MeOH (1:1), lavando con MeOH y eluyendo el producto con DCM-MeOH (1:1) que contenía 5% de AcOH añadido para dar el compuesto del título (1.53 g).

CL/EM:, m/z 371 MH^+, TR 3.18 min

Método B

a) 3-Butil-8-cloro-1-[4-(3-fenil-1,2,4-oxadiazol-5-il)butil]-3,7-dihidro-1*H*-purino-2,6-diona

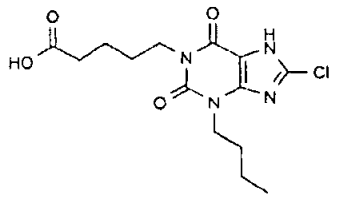


CDI (0.98 g, 6.1 mmoles) se añadió a una solución de ácido 5-(3-butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1*H*-purin-1-il)pentanoico (1.89 g, 5.5 mmoles) en DMF (15 ml) y se agitó bajo nitrógeno durante 1.5 hr. Se añadió benzamidoxima (0.91 g, 6.1 mmoles) y la mezcla se agitó a 110°C durante la noche. La mezcla de reacción se dividió entre EtOAc y HCl 2M. La capa orgánica se separó, se lavó con salmuera, se secó ($MgSO_4$) y se evaporó. El producto crudo se cristalizó a partir de metanol y después se purificó adicionalmente usando el sistema Companion™ y un gradiente de elución de ciclohexano a EtOAc. Las fracciones que contenían producto se combinaron y se evaporaron para dar el compuesto del título como un sólido blanco (850 mg).

CL/EM: m/z 443 $[MH]^+$, TR 3.52 min.

^{1}H RMN (MeOH-d_4) δ: 0.94 (t, 3H, J = 7.5Hz), 1.31-1.41 (m, 2H), 1.65-1.73 (m, 2H), 1.75-1.83 (m, 2H), 1.87-1.96 (m, 2H), 3.04 (t, 2H, J = 7.5Hz), 4.01 (t, 2H, J = 7.5Hz), 4.06 (t, 2H, J = 7Hz), 7.46-7.55 (m, 3H), 7.98-8.02 (m, 2H).

b) Acido 5-(3-butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1*H*-purin-1-il)pentanoico

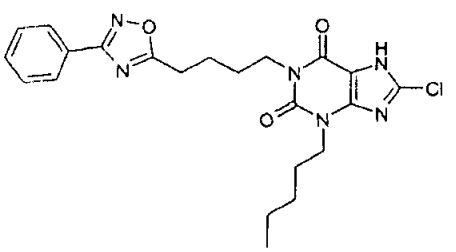


Una mezcla de 5-(3-butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1*H*-purin-1-il)pentanoato de etilo (2.8 g, 7.55 mmoles), LiOH (542 mg, 22.7 mmoles), agua (2.5 ml) y metanol (50 ml) se agitó a t.a. durante 60 hr. La mezcla se dividió entre agua y EtOAc y el pH de la fase acuosa se ajustó a pH 4-5. La capa orgánica se separó, se lavó con salmuera, se secó ($MgSO_4$) y se evaporó para dar el compuesto del título como un sólido blanco (2.18 g).

CL/EM: m/z 343 $[MH]^+$, TR 2.69 min.

EJEMPLO 178

8-Cloro-3-pentil-1-[4-(3-fenil-1,2,4-oxadiazol-5-il)butil]-3,7-dihidro-1*H*-purino-2,6-diona



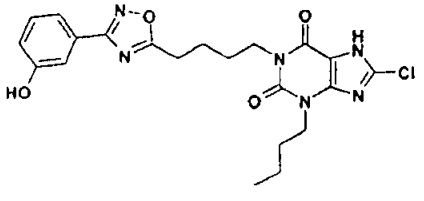
(20 mg, 0.15 mmoles) y una solución al 21% de NaOEt en EtOH (76 µl, 0.20 mmoles) en EtOH (1.5 ml) se calentó en el microondas a 140°C durante 10 min. Después de enfriarse, la reacción se dividió entre HCl 2M (ac.) y EtOAc. La capa orgánica se separó, se secó ($MgSO_4$) y se concentró. Lapurificación por MDAP dio el compuesto del título como un sólido blanco (25 mg, 41%).

CL/EM: m/z 457 $[MH]^+$, TR 3.7 min.

^{1}H RMN (DMSO-d_6) δ: 0.82 (t, 3H1 J = 7 Hz), 1.25 (m, 4H), 1.66 (m, 4H), 1.79 (m, 2H), 3.04 (t, 2H, J = 7Hz), 3.92 (4H,m), 7.57 (m, 3H), 7.97 (m, 2H), 14.5 (br s, 1H).

EJEMPLO 179

3-Butil-8-cloro-1-{4-[3-(3-hidroxifenil)-1,2,4-oxadiazol-5-il]butil}-3,7-dihidro-1*H*-purino-2,6-diona



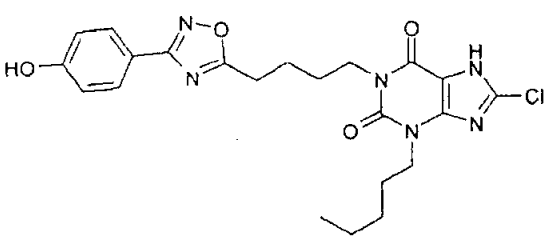
Una mezcla de 5-(3-butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1H-purin-1-il)pentanoato de etilo (50 mg, 0.13 mmoles), *N*,3-dihidroxibencen-carboximidamida (25 mg, 0.16 mmoles), solución al 21% de NaOEt en EtOH (55 µl, 0.15 mmoles) y EtOH (1.5 ml) se calentó en el microondas a 180°C durante 10 min. Otra alícuota de solución al 21% de NaOEt en EtOH (55 µl, 0.21 mmoles) se añadió y la mezcla se calentó en el microondas a 175°C

durante 30 min. Después de enfriarse, la reacción se dividió entre HCl 2M (ac.) y EtOAc. La capa orgánica se separó, se concentró y se purificó por MDAP. El compuesto del título se obtuvo como un sólido blanquecino (20 mg, 32%).

CL/EM: m/z 459 $[MH]^+$, TR 3.3 min.

EJEMPLO 180

8-Cloro-1-{4-[3-(4-hidroxifenil)-1,2,4-oxadiazol-5-il]butil}-3-pentil-3,7-dihidro-1*H*-purino-2,6-diona

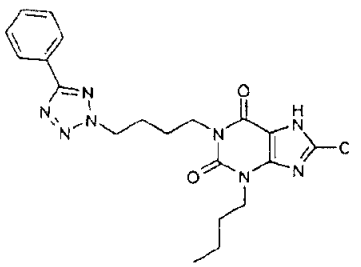


Una solución de ácido 5-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)pentanoico (50 mg, 0.14 mmoles) en DMF (2 ml) se trató con CDI (23 mg, 0.14 mmoles) y se agitó a t.a. durante 30 min. Se añadió *N*,4-dihidroxibencencarboximidamida (26 mg, 0.17 mmoles) y la mezcla se calentó en el microondas a 120°C durante 15 min. Después de enfriarse, la reacción se dividió entre HCl 2M (ac.) y EtOAc. La capa orgánica se separó, se concentró y se purificó por MDAP. El compuesto del título se obtuvo como un sólido blanquecino (17 mg, 26%).

CL/EM: m/z 473 $[MH]^+$,TR 3.5 min.

EJEMPLO 181

3-Butil-8-cloro-1-[4-(5-fenil-2*H*-tetrazol-2-il)butil]-3,7-dihidro-1*H*-purino-2,6-diona



Una mezcla de metansulfonato de 4-[3-butil-8-cloro-2,6-dioxo-7-(2-propen-1-il)-2,3,6,7-tetrahidro-1H-purin-1-il]butilo (50 mg, 0.12 mmoles), Cs_2CO_3 (45 mg, 0.14 mmoles) y DMF (3 ml) se trató con 5-fenil-1*H*-tetrazol (20 mg, 0.14 mmoles) y se agitó durante 60 hr a 50°C. Después de enfriarse, la mezcla se desgasificó aplicando un vacío y después se introdujo nitrógeno. Se añadió $Pd(PPh_3)_4$ (20 mg, 0.017 mmoles) y la mezcla se desgasificó una vez más. Morfolina (150 µl, 1.7 mmoles) se añadió y la mezcla se agitó bajo nitrógeno durante 18 hr, después se dividió entre HCl 2M (ac.) y EtOAc. La capa orgánica se separó y la capa acuosa se extrajo nuevamente con EtOAc. Los extractos combinados se concentraron, dando un residuo amarillo. Se añadió MeOH y después se hizo pasar una columna de NH_2-propilo eluyendo el producto con 2% de AcOH/MeOH. La purificación adicional por MDAP dio el compuesto del título como un sólido blanquecino (15 mg, 29%).

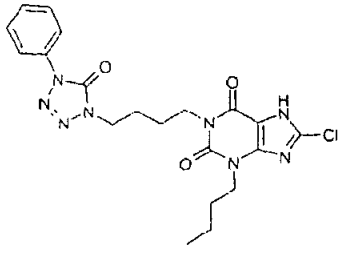
CL/EM: m/z 443 $[MH]^+$, TR 3.4 min.

^{1}H RMN (DMSO-d_6) δ: 0.86 (t, 3H, J = 7Hz), 1.26 (m, 2H), 1.59 (m, 4H), 1.97 (m, 2H), 3.90 (m, 4H), 4.76 (t, 2H, J = 7Hz), 7.54 (m, 3H), 8.02

(m, 2H), 14.4 (br s, 1H).

EJEMPLO 182

3-Butil-8-cloro-1-[4-(5-oxo-4-fenil-4,5-dihidro-1*H*-tetrazol-1-il)butil]-3,7-dihidro-1*H*-purino-2,6-diona



Una mezcla de metansulfonato de 4-[3-butil-8-cloro-2,6-dioxo-7-(2-propen-1-il)-2,3,6,7-tetrahidro-1H-purin-1-il]butilo (50 mg, 0.12 mmoles), Cs_2CO_3 (45 mg, 0.14 mmoles) y DMF (3 ml) se trató con 1-fenil-1,2-dihidro-5H-tetrazol-5-ona (23 mg, 0.14 mmoles) y se agitó durante 60 hr a 50°C. Después de enfriarse, la mezcla se desgasificó aplicando un vacío y después se introdujo nitrógeno. Se añadió $Pd(PPh_3)_4$ (20 mg, 0.017 mmoles) y la mezcla se desgasificó una vez más. Se añadió morfolina (150 µl, 1.7 mmoles) y la mezcla se agitó bajo nitrógeno durante 18 hr, después se dividió entre HCl 2M (ac.) y EtOAc. La capa orgánica se separó y la capa acuosa se extrajo nuevamente con EtOAc. Los extractos combinados se concentraron, dando un residuo amarillo. MeOH se añadió y después se hizo pasar una columna de aminopropilo eluyendo el producto con 2% de AcOH/MeOH. La purificación adicional por MDAP dio el compuesto del título como un sólido blanquecino (27 mg, 51%). NB. aprox. 10% de material O-alquilado presente.

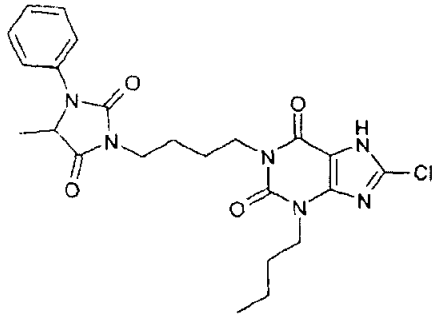
CL/EM: m/z 459 [MH]+, TR 3.1 min.

^{1}H RMN (DMSO-d_6) δ: 0.88 (t, 3H, J = 7Hz), 1.28 (m, 2H), 1.62 (m, 4H), 1.79 (m, 2H), 3.91 (m, 4H), 4.03 (m, 2H), 7.44 (m, 1H), 7.57 (m, 2H), 7.85 (m, 2H), 14.5 (br s, 1H).

EJEMPLO 183

3-Butil-8-cloro-1-[4-(4-metil-2,5-dioxo-3-fenil-1-imidazolidinil)butil]-3,7-dihidro-1H-purino-2,6-diona

a) 3-Butil-8-cloro-1-[4-(4-metil-2,5-dioxo-3-fenil-1-imidazolidinil) butil]-3,7-dihidro-1*H*-purino-2,6-diona

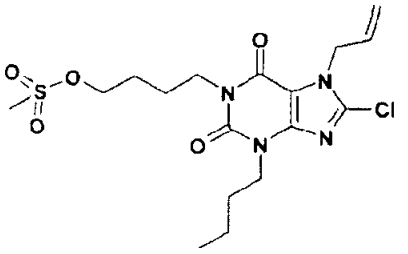


Una mezcla de metansulfonato de 4-[3-butil-8-cloro-2,6-dioxo-7-(2-propen-1-il)-2,3,6,7-tetrahidro-1H-purin-1-il]butilo (88 mg, 0.20 mmoles), Cs_2CO_3 (80 mg, 0.24 mmoles) y DMF (2 ml) se trató con 5-metil-1-fenil-2,4-imidazolidindiona (46 mg, 0.24 mmoles) y se agitó durante 18 hr a 70°C. Después de enfriarse, la mezcla se desgasificó aplicando un vacío y después se introdujo nitrógeno. $Pd(PPh_3)_4$ (25 mg, 0.022 mmoles) se añadió y la mezcla se desgasificó una vez más. Se añadió morfolina (174 µl, 2.0 mmoles)

y la mezcla se agitó bajo nitrógeno durante 5 hr, después se dividió entre HCl 2M (ac.) y EtOAc. La capa orgánica se separó y la capa acuosa se extrajo nuevamente con EtOAc. Los extractos combinados se concentraron, dando un residuo amarillo. MeOH se añadió y después se hizo pasar un SPE de aminopropilo eluyendo el producto con 2% de AcOH/MeOH. La purificación adicional por MDAP dio el compuesto del título como un sólido (70 mg, 71%).

CL/EM: m/z 487 $[MH]^+$, TR 3.2 min.

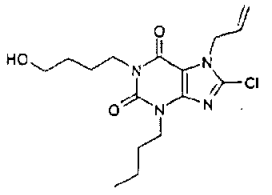
b) Metansulfonato de 4-[3-butil-8-cloro-2,6-dioxo-7-(2-propen-1-il)-2,3,6,7-tetrahidro-1*H*-purin-1-il]butilo



Una solución de 3-butil-8-cloro-1-(4-hidroxibutil)-7-(2-propen-1-il)-3,7-dihidro-1H-purino-2,6-diona (1.30 g, 3.66 mmoles) en DCM (10 ml) se trató con trietilamina (0.77 ml, 5.50 mmoles) seguido por la adición en porciones de anhídrido metansulfónico (702 mg, 4.03 mmoles). CUIDADO, efervescencia. La mezcla de reacción se agitó a t.a. durante 10 min, después se dividió entre solución de NaHCO3 (ac.) saturada y DCM. La capa orgánica se separó y se lavó con HCl 1M (ac.) y después con salmuera. Esta se secó ($MgSO_4$) y se concentró, dando el compuesto del título como un aceite viscoso (1.60 g, cuant.).

CL/EM: m/z 433 $[MH]^+$, TR 3.3 min.

c) 3-Butil-8-cloro-1-(4-hidroxibutil)-7-(2-propen-1-il)-3,7-dihidro-1*H*-purina-2,6- diona

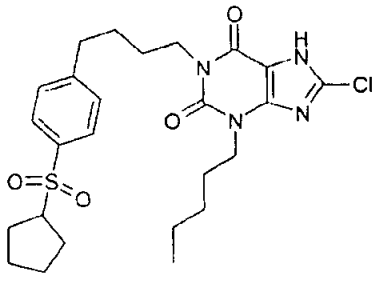


Una solución agitada de 3-butil-8-cloro-7-(2-propen-1-il)-3,7-dihidro-1*H*-purino-2,6-diona (5.0 g, 17.7 mmoles) en DMF (100 ml) se trató con Cs_2CO_3 (6.3 g, 19.5 mmoles) y 4-bromo-1-butanol (3.0 ml, 21.2 mmoles). La mezcla se calentó a 50°C durante 5 hr, después se dividió entre HCl 2M (ac.) y EtOAc. La capa orgánica se separó, se lavó con salmuera, se secó ($MgSO_4$) y se concentró, dando un sólido amarillo. Lapurificación por SPE de sílice (mezclas de EtOAc/ciclohexano como el eluyente) y después por el sistema Companion™ (mezclas de IPA/DCM como el eluyente) dio el compuesto del título como un aceite incoloro (1.35 g, 21%).

CL/EM: m/z 355 $[MH]^+$, TR 2.9 min.

EJEMPLO 184

8-Cloro-1-{4-[4-(ciclopentilsulfonil)fenil]butil}-3-pentil-3,7-dihidro-1*H*-purino-2,6-diona

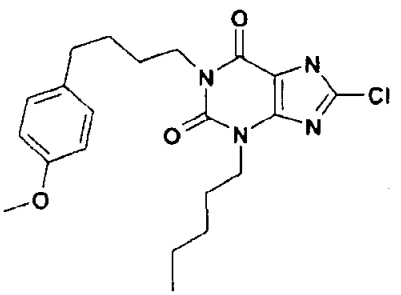


8-Cloro-3-pentil-7-(2-propen-1-il)-3,7-dihidro-1*H*-purino-2,6-diona (100 mg, 0.34 mmoles) se disolvió en DMF (1 ml) y secuencialmente se trató con 4-[4-(ciclopentilsulfonil)fenil]-1-butanol (105 mg, 0.37 mmoles), PPh_3 (404 µl de una solución 1M en DMF) y DBAD (404 µl de una solución 1M en DMF). Depués de agitarse durante 24 hr bajo nitrógeno, la mezcla se desgasificó aplicando un vacío y después se introdujo nitrógeno. $Pd(PPh_3)_4$ (39 mg, 0.034 mmoles) se añadió y la mezcla se desgasificó una vez más. Se añadió morfolina (297 µl, 3.4 mmoles) y la mezcla se agitó bajo nitrógeno durante 63 hr, después se dividió entre HCl 2M (ac.) y EtOAc. La capa orgánica se separó, se lavó con salmuera, se secó ($MgSO_4$) y se concentró, dando un residuo amarillo. MeOH se añadió y después se hizo pasar un SPE de aminopropilo eluyendo el producto con 2% de AcOH/MeOH. El producto además se purificó por MDAP dando el compuesto del título como un sólido color beige (5 mg, 3%).

CL/EM: m/z 521 $[MH]^+$, TR 3.7 min.

EJEMPLO 185

8-Cloro—1-{4-[4-(metiloxi)fenil]butil}-3-pentil-3,7-dihidro-1*H*-purino-2,6-diona



Una solución de éter 4-(4-bromobutil)fenilmetílico (88 mg, 0.36 mmoles) en DMF (3 ml) se hizo reaccionar con 8-cloro-3-pentil-7-(2-propen-1-il)-3,7-dihidro-1*H*-purino-2,6-diona (90 mg, 0.30 mmoles) y Cs_2CO_3 (109 mg, 0.33 mmoles) durante 5 hr a 50°C. La mezcla se desgasificó aplicando un vacío y después se introdujo nitrógeno. $Pd(PPh_3)_4$ (35 mg, 0.030 mmoles) se añadió y la mezcla se desgasificó una vez más. Se añadió morfolina (0.26 ml, 3.0 mmoles) y la mezcla se agitó bajo nitrógeno durante 3 hr. Otra alícuota de $Pd(PPh_3)_4$ (35 mg, 0.030 mmoles) se añadió y se dejó durante 3 hr adicionales. La mezcla se dividió entre HCl 2M (ac.) y EtOAc. La capa orgánica se separó y la capa acuosa se extrajo nuevamente con EtOAc. Los extractos combinados se concentraron, dando un residuo amarillo. MeOH se añadió y después se hizo pasar un SPE de aminopropilo eluyendo el producto con 3% de AcOH/MeOH. El producto además se purificó por MDAP dando el compuesto del título como un sólido (2 mg, 1.5%).

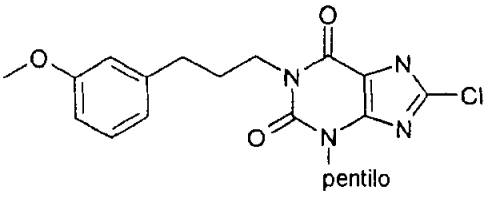
CL/EM: m/z 419 $[MH]^+$, TR 3.7 min.

^{1}H RMN; (MeOH-d_4) δ: 0.90 (t, 3H, J = 7Hz), 1.28-1.40 (m, 4H), 1.57-1.75 (m, 6H), 2.57 (t, 2H, J = 7Hz), 3.73 (s, 3H), 3.97-4.02 (4H, m), 6.77 (m, 2H), 7.06 (m, 2H).

EJEMPLO 186

8-Cloro-3-pentil-1-{3-[3-(metiloxi)fenillpropil}-3,7-dihidro-1*H*-purino-2,6-diona

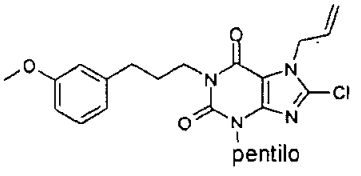
a) 8-Cloro-3-pentil-1-{3-[3-(metiloxi)fenil]propil}-3,7-dihidro-1*H*-purina-2,6- diona



8-Cloro-3-pentil-1-{3-[3-(metiloxi)fenil]propil}-7-(2-propen-1-il)-3,7-dihidro-1H-purino-2,6-diona (2.94 g) se disolvió en THF anhidro (40 ml). La solución se desgasificó usando una purga de nitrógeno/vacío 6 veces. Se añadió tetrakis(trifenilfosfina)paladio (0.66 g) seguido por morfolina (5 ml). Depués de agitarse durante 18 hr, la mezcla de reacción se diluyó con EtOAc y se lavó con HCl 1N y salmuera (x2), se secó ($MgSO_4$) y se evaporó bajo vacío. Este material crudo se purificó sobre un SPE de aminopropilo (70g) eluyendo con MeOH, después MeOH que contenía 3% de AcOH para dar el compuesto del título como un sólido amarillo pálido (1.56 g).

CL/EM: m/z 405 $[MH]^+$, TR 3.51 min.

b) 8-Cloro-3-pentil-1-{3-[3-(metiloxi)fenil]propil}-7-(2-propen-1-il)-3,7-dihidro- 1H-purino-2,6-diona

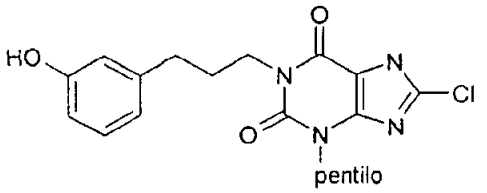


8-Cloro-3-pentil-7-(2-propen-1-il)-3,7-dihidro-1*H*-purino-2,6-diona (1.76 g, 5.94 mmoles) y 3-[3-(metiloxi)fenil]-1-propanol (1.00 g, 6.04 mmoles) se disolvieron en THF anhidro (50 ml) bajo una atmósfera de nitrógeno. Después de 5 min, se añadió trifenilfosfina (1.87 g, 7.12 mmoles). Después de 5 min adicionales, se añadió azodicarboxilato de di-ter-butilo (1.64 g, 7.1 mmoles). La solución se agitó durante 20 hr a t.a. La solución turbia se concentró bajo vacío y se purificó en un SPE de sílice II de 50 g (IST) usando Biotage FlashMaster™ Personal, eluyendo con ciclohexano/EtOAc 5:1. Las fracciones apropiadas se concentraron bajo vacío para dar el compuesto del título como un aceite cremoso pálido que contenía impurezas menores (2.94 g).

CL/EM:, m/z 445 $[MH]^+$, TR 3.88 min.

EJEMPLO 187

8-Cloro-1-[3-(3-hidroxifenil)propil]-3-pentil-3,7-dihidro-1*H*-purino-2,6-diona



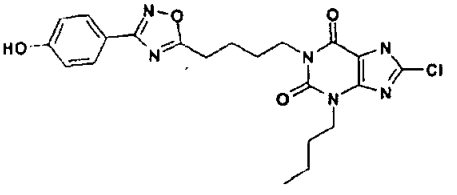
A una suspensión de 8-cloro-3-pentil-1-{3-[3-(metiloxi) fenil]propil}-3,7-dihidro-1*H*-purino-2,6-diona (1.52 g, 3.86 mmoles) en DCM anhidro (40 ml) a –73°C se añadió lentamente tribromuro de boro 1N en DCM (4.6 ml). La mezcla de reacción se agitó a –70°C durante 2 horas y después a t.a. durante 96 hr. La mezcla de reacción se enfrió en hielo y se añadió lentamente agua (6.8 ml). La mezcla de reacción después se diluyó con EtOAc y agua, y la fase orgánica se lavó con bicarbonato de sodio saturado (x3) y salmuera, después se secó ($MgSO_4$) y se evaporó bajo vacío. Una porción de este material crudo (90 mg) se purificó por MDAP para dar el compuesto del título, después de secado por congelamiento, como un sólido blanco (40 mg).

CL/EM:, m/z 391 $[MH]^+$, TR 3.43 min.

^{1}H RMN (DMSO-d_6) δ: 0.85 (t, 3H, J = 7Hz); 1.27 (m, 4H); 1.63 (m, 2H); 1.80 (m, 2H); 2.50 (m, 2H); 3.89 (m, 4H); 6.57 (m, 3H); 7.02 (t, 1H, J = 8Hz); 9.22 (s, 1H); 14.39 (s, 1H).

EJEMPLO 188

3-Butil-8-cloro-1-{4-[3-(4-hidroxifenil)-1,2,4-oxadiazol-5-il]butil}-3,7-dihidro-1*H*-purino-2,6-diona

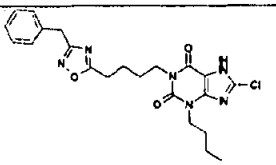
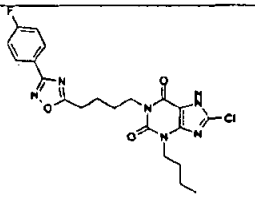
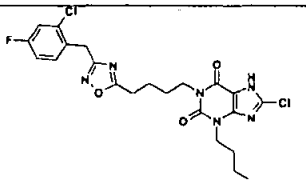


Una solución agitada de ácido 5-(3-butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1*H*-purin-1-il)pentanoico (100 mg, 0.29 mmoles) en DMF (4 ml) se trató con CDI (52 mg, 0.32 mmoles). Después de 1 hr, se añadió *N*,4-dihidroxibencencarboximidamida se añadió y la mezcla se calentó a 100°C durante 6 hr. Durante el enfriamiento, la mezcla de reacción se dividió entre HCl 2M (ac.) y EtOAc. La capa orgánica se separó, se lavó con salmuera, se secó ($MgSO_4$) y se concentró. La purificación por MDAP dio el compuesto del título como un sólido gris pálido (72 mg).

CL/EM: m/z 459 $[MH]^+$, TR 3.27 min.

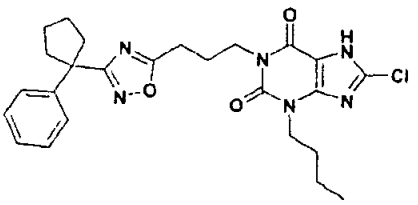
Los siguientes compuestos (cuadro 10) se prepararon usando un método análogo al del ejemplo 177, usando la amidoxima apropiada.

CUADRO 10

Ejemplo	Estructura	Rend. (mg)	CL/EM:
189	 3-butil-8-cloro-1-{4-[3-(fenilmetil)-1,2,4-oxadiazol-5-il]butil}-3,7-dihidro-1H-purina-2,6-diona	48.4	m/z 458 $[MH]^+$ TR 3.21 min
190	 3-butil-8-cloro-1-{4-[3-(4-fluorofenil)-1,2,4-oxadiazol-5-il]butil}-3,7-dihidro-1H-purina-2,6-diona	12.8 mg (17%)	m/z 491 $[MH]^+$ TR 3.77 min
191	 3-butil-8-cloro-1-(4-{3-[(2-cloro-4-fluorofenil)metil]-1,2,4-oxadiazol-5-il}butil)-3,7-dihidro-1H-purina-2,6-diona	21.7 mg (30%)	m/z 487 $[MH]^+$ TR 3.54 min

EJEMPLO 192

3-Butil-8-cloro-1-{3-[3-(1-fenilciclopentil)-1,2,4-oxadiazol-5-il]propil}-3,7-dihidro-1*H*-purino-2,6-diona

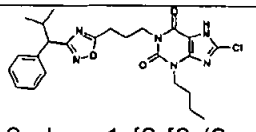


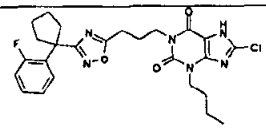
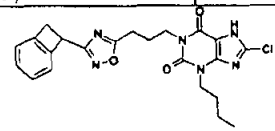
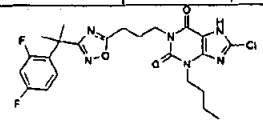
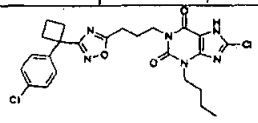
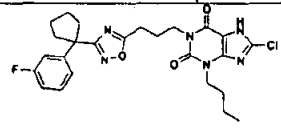
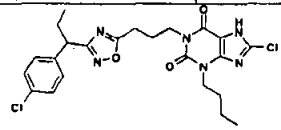
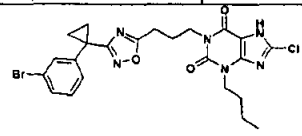
4-(3-Butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1*H*-purin-1-il) butanoato de etilo (53 mg, 0.15 mmoles), *N*-hidroxi-1-fenilciclopentano-carboximidamida (34 mg, 0.165 mmoles) y metóxido de sodio (20 mg, 0.37 mmoles) en MeOH seco (0.75 ml) se calentaron a 140°C en el reactor de microondas durante 10 min. La mezcla después se dividió entre acetato de etilo y HCl 2M, la fase orgánica se evaporó y el producto se purificó por MDAP para dar el compuesto del título como un sólido (29.1 mg).

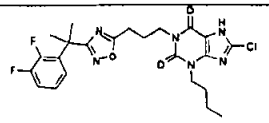
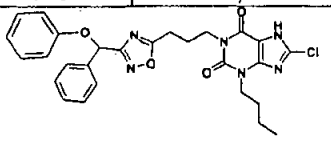
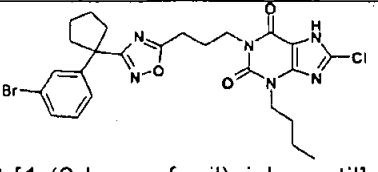
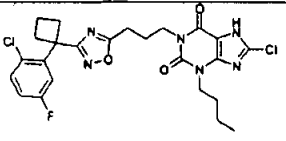
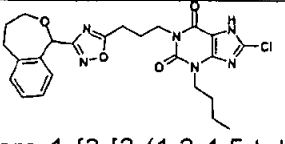
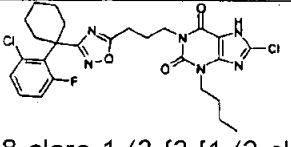
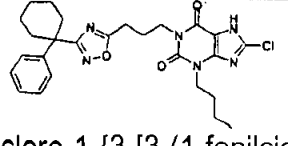
CL/EM: m/z 497 $[MH]^+$, TR 3.76 min.

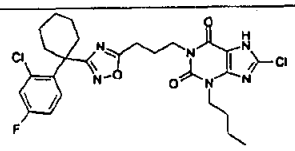
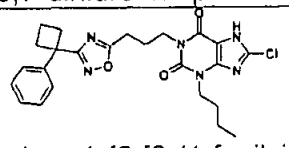
Los siguientes compuestos (cuadro 11) se prepararon usando un método análogo al del ejemplo 192, usando la amidoxima apropiada [con la excepción de que para los ejemplos 210, 211 y 212, se usó EtOH como solvente de reacción; para los ejemplos 210, 211 y 212 las reacciones se trataron añadiendo HCl 2M hasta que se hicieron neutras y evaporando el solvente; para el ejemplo 206 la escala fue de 32 mg de éster etílico de partida; para el ejemplo 208 la escala fue de 42 mg de éster etílico de partida].

CUADRO 11

Ejemplo	Estructura	Rend. (mg)	CL/EM:
193	 3-butil-8-cloro-1-{3-[3-(2-metil-1-fenilpropil)-1,2,4-oxadiazol-5-il]propil}-3,7-dihidro-1H-purina-2,6-diona	17.4	m/z 485 $[MH]^+$ TR 3.74 min

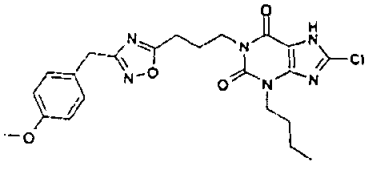
194	 3-butil-8-cloro-1-(3-{3-[1-(2-fluorofenil)ciclopentil]-1,2,4-oxadiazol-5-il}propil)-3,7-dihidro-1H-purina-2,6-diona	33.7	m/z 515 $[MH]^+$ TR 3.73 min
195	 1-[3-(3-biciclo[4.2.0]octa-1,3,5-trien-7-il-1,2,4-oxadiazol-5-il)propil]-3-butil-8-cloro-3,7dihidro-1H-purina-2,6-diona	28.8	m/z 455 $[MH]^+$ TR 3.43 min
196	 3-butil-8-cloro-1-(3-{3-[1-(2,4-difluorofenil)-1-metiletil]-1,2,4-oxadiazol-5-il}propil)-3,7-dihidro-1H-purina-2,6-diona	33.4	m/z 507 $[MH]^+$ TR 3.59 min
197	 3-butil-8-cloro-1-(3-{3-[1-(4-clorofenil)ciclobutil]-1,2,4-oxadiazol-5-il}propil)-3,7-dlhidro-1H-purina-2,6-diona	33.8	m/z 517 $[MH]^+$ TR 3.85 min
198	 3-butil-8-cloro-1-(3-{3-[1-(3-fluorofenii)ciclopentil]-1,2,4-oxadiazol-5-il}propil)-3,7-dihidro-1H-purina-2,6-diona	34.2	m/z 515 $[MH]^+$ TR 3.80 min
199	 3-butil-8-cloro-1-(3-{3-[1-(4-clorofenil)propil]-1,2,4-oxadiazol-5-il}propil)-3,7-dihidro1H-purina-2,6-diona	16.3	m/z 505 $[MH]^+$ TR 3.80 min
200	 1-(3-{3-[1-(3-bromofenil)ciclopropil]-1,2,4-oxadiazol-5-il}propil)-3-butil-8-cloro-3,7-dihidro-1H-purina-2,6-diona	34.9	m/z 549 $[MH]^+$ TR 3.72 min

201	 3-butil-8-cloro-1-(3-{3-[1-(2,3-difluorofenil)-1-metiletil]-1,2,4-oxadiazol-5-il}propil)-3,7-dihidro-1H-purina-2,6-diona	30.4	m/z 507 $[MH]^+$ TR 3.59 min
202	 3-butil-8-cloro-1-(3-{3-[fenoxi(fenil)metil]-1,2,4-oxadiazol-5-il}propil)-3,7-dihidro-1H-purina-2,6-diona	3	m/z 535 $[MH]^+$ TR 3.69 min
203	 1-(3-{3-[1-(3-bromofenil)ciclopentil]-1,2,4-oxadiazol-5-il}-propil)-3-butil-8-cloro-3,7-dihidro-1H-purina-2,6-diona	38.8	m/z 577 $[MH]^+$ TR 3.99 min
204	 3-butil-8-cloro-1-(3-{3-[1-(2-cloro-5-fluorofenil)ciclobutil]-1,2,4-oxadiazol-5-il}propil)-3,7-dihidro-1H-purina-2,6-diona	41.4	m/z 535 $[MH]^+$ TR 3.79 min
205	 3-butil-8-cloro-1-{3-[3-(1,3,4,5-tetrahidro-2-benzoxepin-1-il)-1,2,4-oxadiazol-5-il]propil]-3,7-dihidro-1H-purina-2,6-diona	27.4	m/z 499 $[MH]^+$ TR 3.42 min
206	 3-butil-8-cloro-1-(3-{3-[1-(2-cloro-6-fluorofenil)ciclohexil]-1,2,4-oxadiazol-5-il}propil)-3,7-dihidro-1H-purina-2,6-diona	12.9	m/z 563 $[MH]^+$ TR 4.02 min
207	 3-butil-8-cloro-1-{3-[3-(1-fenilciclohexil)-1,2,4-oxadiazol-5-il]propil}-3,7-dihidro-1H-purina-2,6-diona	34.8	m/z 511 $[MH]^+$ TR 3.88 min

208	 3-butil-8-cloro-1-(3-{3-[1-(2-cloro-4-fluorofenil)ciclohexil]-1,2,4-oxadiazol-5-il}propil)-3,7-dihidro-1H-purino-2,6-diona	19	m/z 563 $[MH]^+$ TR 4.00 min
209	 3-butil-8-cloro-1-{3-[3-(1-fenilciclobutil)-1,2,4-oxadiazol-5-il]propil}-3,7-dihidro-1H-purina-2,6-diona	30.5	m/z 483 $[MH]^+$ TR 3.64 min

EJEMPLO 210

3-Butil-8-cloro-1-[3-(3-{[4-(metiloxi)fenil]metil}-1,2,4-oxadiazol-5-il)-3,7-dihidro-1H-purina-2,5-diona



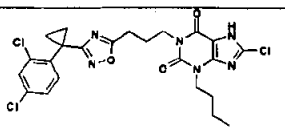
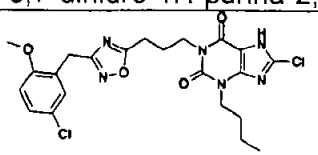
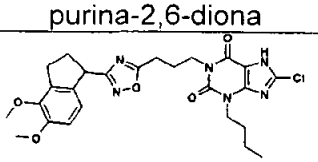
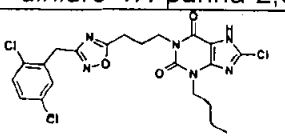
Se preparó usando un método análogo al usado para el ejemplo 93, excepto que se utilizó un paso de purificación final adicional usando CLAR. Rendimiento 6.0 mg.

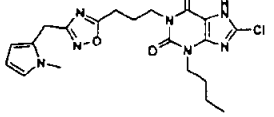
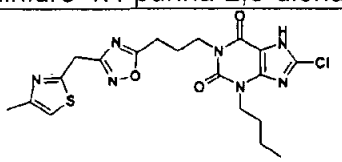
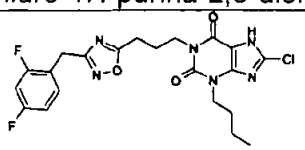
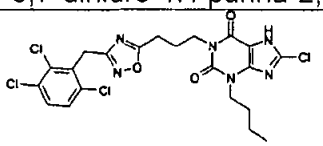
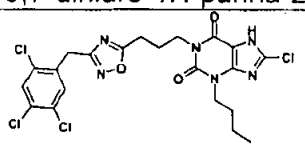
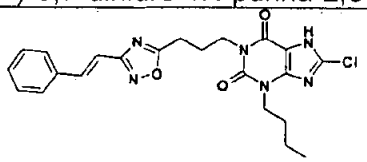
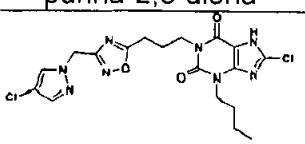
CL/EM: m/z 473 $[MH]^+$, TR 3.27 min.

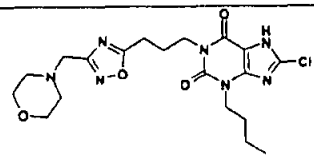
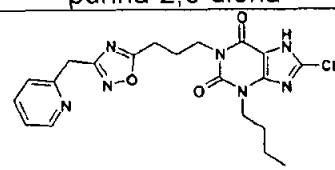
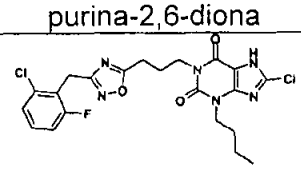
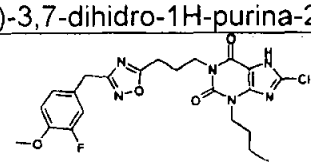
Los siguientes compuestos (cuadro 12) se prepararon usando un método análogo al del ejemplo 96, usando la amidoxima apropiada [con la excepción de que para el ejemplo 211 la escala fue de 0.12 mmoles en lugar de 0.15 mmoles; para el ejemplo 216 el producto crudo se agitó en EtOH (0.75 ml) con NaOH 2M (0.5 ml) durante la noche antes de tratamiento con

EtOAc/HCl usual y MDAP; el ejemplo 218 se aisló como una impureza a partir de la preparación del ejemplo 219 y se separó de esta por CLAR; para los ejemplos 221, 222 y 223 el pH durante tratamiento acuoso se ajustó a aproximadamente 5 antes de la extracción; de manera adicional el ejemplo 223 además se purificó por SPE de sílice (2 g, DCM-MeOH 40:1, después 20:1) después MDAP].

CUADRO 12

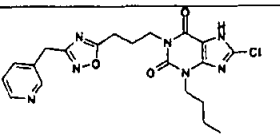
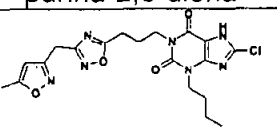
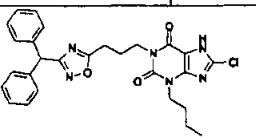
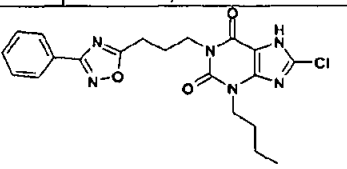
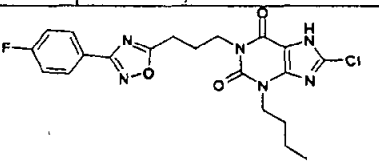
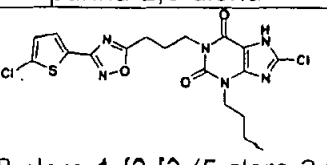
Ejemplo	Estructura	Rend. (mg)	CL/EM:
211	 3-butil-8-cloro-1-(3-{3-[1-(2,4-diclorofenil)ciclopropil]-1,2,4-oxadiazol-5-il}propil)-3,7-dihidro-1H-purina-2,6-diona	23.8	m/z 537 $[MH]^+$ TR 3.83 min
212	 3-butil-8-cloro-1-[3-(3-([5-cloro-2-(metiloxi)fenil)metil}-1,2,4-oxadiazol-5-il)propil]-3,7-dihidro-1H-purina-2,6-diona	39.5	m/z 507 $[MH]^+$ TR 3.58 min
213	 1-(3-{3-[4,5-bis(metiloxi)-2,3-dihidro-1H-inden-1-il]-1,2,4-oxadiazol-5-il}propil)-3-butil-8-cloro-3,7-dihidro-1H-purina-2,6-diona	35.8	m/z 529 $[MH]^+$ TR 3.41 min
214	 3-butil-8-cloro-1-(3-{3-[(2,5-diclorofenil)metil]-1,2,4-oxadiazol-5-il}propil)-3,7-dihidro-1H-purina-2,6-diona	9.7	m/z 511 $[MH]^+$ TR 3.63 min

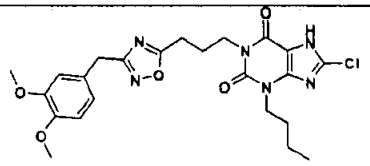
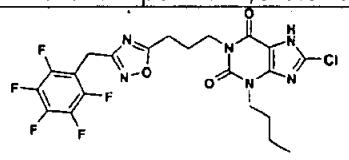
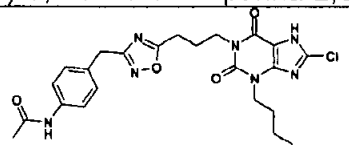
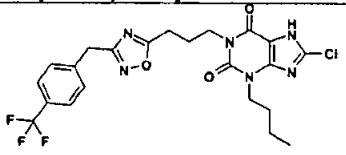
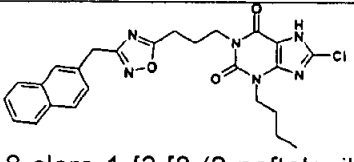
215	 3-butil-8-cloro-1-(3-{3-[(1-metil-1H-pirrol-2-il)metil]-1,2,4-oxadiazol-5-il}propil)-3,7-dihidro-1H-purina-2,6-diona	18.0	m/z 446 $[MH]^+$ TR 3.15 min
216	 3-butil-8-cloro-1-(3-{3-[(4-metil-1,3-tiazol-2-il)metil]-1,2,4-oxadiazol-5-il}propil)-3,7-dihidro-1H-purina-2,6-diona	15.5	m/z 464 $[MH]^+$ TR 2.94 min
217	 3-butil-8-cloro-1-(3-{3-[(2,4-difluorofenil)metil]-1,2,4-oxadiazol-5-il}propil)-3,7-dihidro-1H-purina-2,6-diona	33.5	m/z 479 $[MH]^+$ TR 3.35 min
218	 3-butil-8-cloro-1-(3-{3-[(2,3,6-triclorofenil)metil]-1,2,4-oxadiazol-5-il}propil)-3,7-dihidro-1H-purina-2,6-diona	4.6	m/z 545 $[MH]^+$ TR 3.71 min
219	 3-butil-8-cloro-1-(3-{3-[(2,4,5-triclorofenil)metil]-1,2,4-oxadiazol-5-il}propil)-3,7-dihidro-1H-purina-2,6-diona	17.7	m/z 545 $[MH]^+$ TR 3.79 min
220	 3-butil-8-cicro-1-(3-{3-[(*E*)-2-feniletenil)-1,2,4-oxadiazol-5-il}propil)-3,7-dihidro-1H-purina-2,6-diona	17.8	m/z 455 $[MH]^+$ TR 3.49 min
221	 3-butil-8-cloro-1-(3-{3-[(4-cloro-1H-pirazol-1-il)metil]-1,2,4-oxadiazol-5-il}propil)-3,7-dihidro-1H-purina-2,6-diona	39.2	m/z 467 $[MH]^+$ TR 3.24 min

222	 3-butil-8-cloro-1-{3-[3-(4-morfolinilmetil)-1,2,4-oxadiazol-5-il]propil}-3,7-dihidro-1H-purina-2,6-diona	27.0	m/z 452 $[MH]^+$ TR 2.56 min
223	 3-butil-8-cloro-1-{3-[3-(2-piridinilmetil)-1,2,4-oxadiazol-5-il-]propil}-3,7-dihidro-1H-purina-2,6-diona	23.6	m/z 444 $[MH]^+$ TR 2.92 min
224	 3-butil-8-cloro-1-(3-{3-[(2-cloro-6-fluorofenil)metil]-1,2,4-oxadiazol-5-il}propil)-3,7-dihidro-1H-purina-2,6-diona	38.8	m/z 495 $[MH]^+$ TR 3.43 min
225	 3-butil-8-cloro-1-[3-(3-{[3-fluoro-4(metiloxi)fenil]metil}-1,2,4-oxadiazol-5-il)propil]-3,7-dihidro-1H-purina-2,6-diona	27	m/z 491 $[MH]^+$ TR 3.31 min

Los siguientes compuestos (cuadro 13) se prepararon usando un método análogo al del ejemplo 114, usando la amidoxima apropiada [con la excepción de que el ejemplo 226 se condujo a la mitad de la escala del ejemplo 114 y durante el tratamiento, la fase acuosa se neutralizó antes de la extracción; el ejemplo 227 se condujo a la mitad de la escala del ejemplo 114 y el producto crudo se agitó con NaOH 2M (0.5 ml) en EtOH (1 ml) durante 5 hr antes de tratamiento y MDAP; para el ejemplo 232 se usaron 0.185 ml (0.5 mmoles) de 21% de NaOEt].

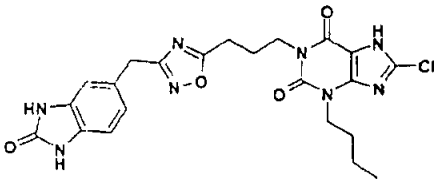
CUADRO 13

Ejemplo	Estructura	Rend. (mg)	CL/EM:
226	 3-butil-8-cloro-1-{3-[3-(3-piridinilmetil)-1,2,4-oxadiazol-5-il]propil}-3,7-dihidro-1H-purina-2,6-diona	20	m/z 444 $[MH]^+$ TR 2.74 min
227	 3-butil-8-cloro-1-(3-{3-[(5-metil-3-isoxazolil)metil]-1,2,4-oxadiazol-5-il}propil)-3,7-dihidro-1H-purina-2,6-diona	7.2	m/z 448 $[MH]^+$ TR 3.13 min
228	 3-butil-8-cloro-1-{3-[3-(difenilmetil)-1,2,4-oxadiazol-5-il]propil}-3,7-dihidro-1H-purina-2,6-diona	47.4	m/z 519 $[MH]^+$ TR 3.71 min
229	 3-butil-8-cloro-1-[3-(3-fenil-1,2,4-oxadiazol-5-il)propil]-3,7-dihidro-1H-purina-2,6-diona	36.7	m/z 429 $[MH]^+$ TR 3.36 min
230	 3-butil-8-cloro-1-{3-[3-(4-fluorofenil)1,2,4-oxadiazol-5-il]propil}-3,7-dihidro-1H-purina-2,6-diona	41.1	m/z 447 $[MH]^+$ TR 3.42 min
231	 3-butil-8-cloro-1-{3-[3-(5-cloro-2-tienil)-1,2,4-oxadiazol-5-il]propil)-3,7-dihidro-1H-purina-2,6-diona	36.7	m/z 469 $[MH]^+$ TR 3.60 min

232	 1-[3-(3-{[3,4-bis(metiloxi)fenil]metil}-1,2,4-oxadiazol-5-il)propil]-3-butil-8-cloro-3,7-dihidro-1H-purina-2,6-diona	47.0	m/z 503 $[MH]^+$ TR 3.14 min
233	 3-butil-8-cloro-1-(3-{3-[(pentafluorofenil)metil]-1,2,4-oxadiazol-5-il}propil)-3,7-dihidro-1H-purina-2,6-diona	29.2	m/z 533 $[MH]^+$ TR 3.62 min
234	 *N*-[4-({5-[3-(3-butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1H-purin-1-il)propil]1,2,4-oxadiazol-3-il}metil)fenil]acetamida	29.8	m/z 500 $[MH]^+$ TR 3.01 min
235	 3-butil-8-cloro-1-[3-(3-{[4(trifluorometil)fenilimetil}-1,2,4-oxadiazol-5-il)propil]-3,7-dihidro-1H-purina-2,6-diona	37.7	m/z 511 $[MH]^+$ TR 3.65 min
236	 3-butil-8-cloro-1-{3-[3-(2-naftalenilmetil)-1,2,4-oxadiazol-5-il]propil}-3,7-dihidro-1H-purina-2,6-diona	47.5	m/z 493 $[MH]^+$ TR 3.69 min

EJEMPLO 237

3-Butil-8-cloro-1-(3-{3-[(2-oxo-2,3-dihidro-1*H*-benzimidazol-5-il)metil]-1,2,4-oxadiazol-5-il}propil)-3,7-dihidro-1*H*-purina-2,6-diona



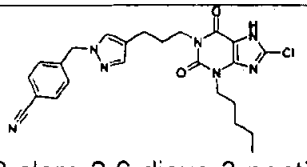
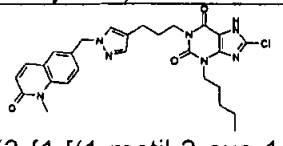
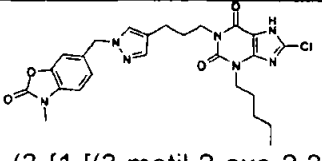
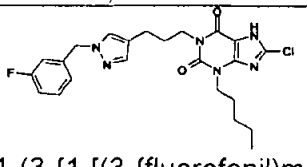
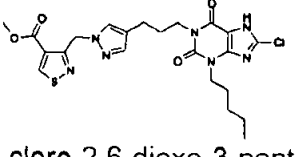
Sintetizado por un método análogo al del ejemplo 126 con la excepción de que se usaron 2 equivalentes adicionales de 21% de etóxido de sodio (0.11 ml), el tiempo de calentamiento extra fue de 20 min y el producto se aisló por filtración seguido por trituración con MeOH caliente. Rendimiento 14.5 mg.

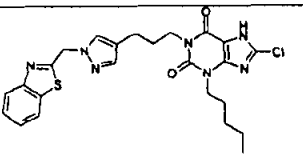
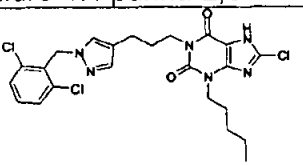
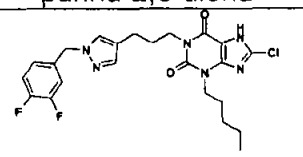
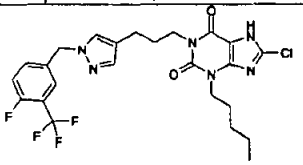
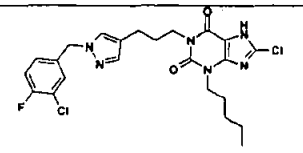
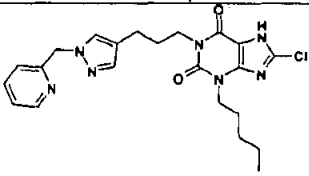
CL/EM: m/z 499 $[MH]^+$, TR 2.78 min.

Los siguientes compuestos (cuadro 14) se prepararon por un método análogo al del ejemplo 18 [con la excepción de que los ejemplos 238-243 todos se sintetizaron en una escala empezando a partir de 50 mg de 8-cloro-3-pentil-7-(2-propen-1-il)-1-[3-(1*H*-pirazol-4-il)propil]-3,7-dihidro-1*H*-purina-2,6-diona; los ejemplos 241, 243, 245, 246 y 247 se purificaron adicionalmente por MDAP seguido por SPE de aminopropilo; el ejemplo 242 se purificó adicionalmente por recristalización a partir de MeOH seguido por SPE de aminopropilo; para el ejemplo 248, se usaron 128 mg (1.2 mmoles) de carbonato de sodio; durante el tratamiento, la fase acuosa se ajustó a pH 6 antes de la extracción; y el producto se purificó por MDAP, después además por CLAR; para el ejemplo 241 los sólidos que se precipitaron durante el

tratamiento, se combinaron con los extractos de EtOAc antes de SPE].

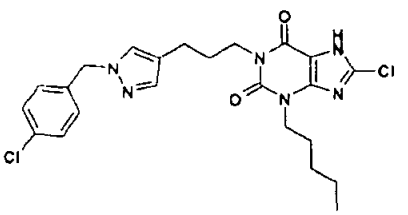
CUADRO 14

Ejemplo	Estructura	Rend. (mg)	CL/EM:
238	 4-([4-[3-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)propil]-1H-pirazol-1-il}metil)bezonitrilo	36.0	m/z 480 $[MH]^+$ TR 3.24 min
239	 8-cloro-1-(3-{1-[(1-metil-2-oxo-1,2-dihidro-6-quinolinil)metil]-1H-pirazol-4-il]propil)-3-pentil-3,7-dihidro-1H-purina-2,6-diona	7.6	m/z 536 $[MH]^+$ TR 3.03 min
240	 8-cloro-1-(3-{1-[(3-metil-2-oxo-2,3-dihidro-1,3-benzoxazol-6-il)metil]-1H-pirazol-4-il}propil)-3-pentil-3,7-dihidro-1H-purina-2,6-diona	34.0	m/z 526 $[MH]^+$ TR 3.11 min
241	 8-cloro-1-(3-{1-[(3-{fluorofenil)metil]-1H-pirazol-4-il}propil)-3-pentil-3,7-dihidro-1H-purina-2,6-diona	26.2	m/z 473 $[MH]^+$ TR 3.38 min
242	 3-({4-[3-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)propil]-1H-pirazol-1-il}metil}-4-isotiazolcarboxilato de metilo	16.2	m/z 520 $[MH]^+$ TR 3.12 min

243	 1-{3-[1-(1,3-benzotiazol-2-ilmetil)-1H-pirazol-4-il]propil}-8-cloro-3-pentil-3,7-dihidro-1H-purina-2,6-diona	21.0	m/z 512 $[MH]^+$ TR 3.36 min
244	 8-cloro-1-(3-{1-[(2,6-diclorofenil)metil]-1H-pirazol-4-il}propil)-3-pentil-3,7-dihidro-1H-purina-2,6-diona	65.0	m/z 523, 525 [isótopos Cl $MH]^+$ TR 3.77 min
245	 8-cloro-1-(3-{1-[(3,4-difluorofenil)metil]-1H-pirazol-4-il}propil)-3-pentil-3,7-dihidro-1H-purina-2,6-diona	35.0	m/z 491 $[MH]^+$ TR 3.61 min
246	 8-cloro-1-[3-(1-{[4-fiuoro-3-(trifluorometil)fenil]metil}1H-pirazol-4-il)propil]-3-pentil-3,7-dihidro-1H-purina-2,6-diona	17.0	m/z 541 $[MH]^+$ TR 3.76 min
247	 8-cloro-1-(3-{1-[(3-cloro-4-fluorofenil)metil]-1H-pirazol-4-il}propil)-3-pentil-3,7-dihidro-1H-purina-2,6-diona	27.0	m/z 507 $[MH]^+$ TR 3.73 min
248	 8-cloro-3-pentil-1-{3-[1-(2-piridinilmetil}-1H-pirazol-4-il]propil}-3,7-dihidro-1H-purina-2,6-diona	11.4	m/z 456 $[MH]^+$ TR 3.13 min

EJEMPLO 249

8-Cloro-1-(3-{1-[(4-clorofenil)metil]-1*H*-pirazol-4-il}propil)-3-pentil-3,7-dihidro-1*H*-purina-2,6-diona



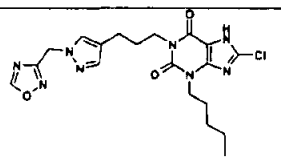
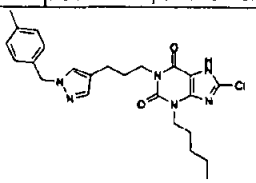
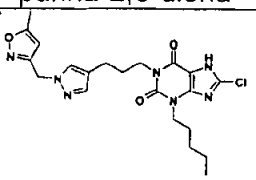
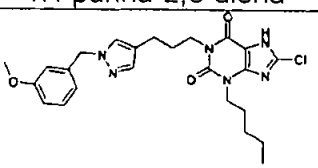
8-Cloro-3-pentil-7-(2-propen-1-il)-1-[3-(1*H*-pirazol-4-il)propil]-3,7-dihidro-1*H*-purina-2,6-diona (50 mg, 0.123 mmoles) en DMF seco (1.5 ml) se agitó con carbonato de sodio (75 mg, 0.708 mmoles) y 4-clorobromuro de bencilo (150 mg, 0.73 mmoles) a 40°C durante 18 hr. La mezcla se dividió entre EtOAc y agua, la fase orgánica se lavó con salmuera, se secó y se evaporó. El producto se purificó por cromatografía de fase normal sobre sílice (Companion System, gradiente de EtOAc-ciclohexano) dando un aceite (44 mg). Este se agitó en DMF seco, desgasificado (1 ml) con tetrakis-(trifenilfosfin)paladio(0) (19 mg) y morfolina (0.072 ml) bajo nitrógeno durante 6 hr. La mezcla se dividió entre EtOAc y HCl 2M y la fase orgánica se evaporó y se purificó por el procedimiento de SPE de aminopropilo usual. Rendimiento 21.0 mg.

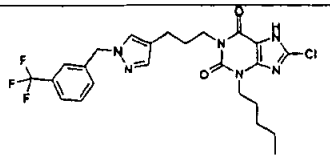
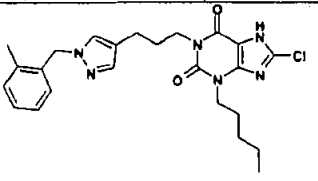
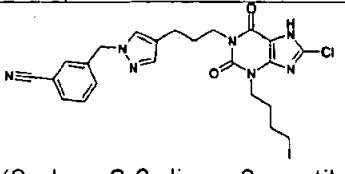
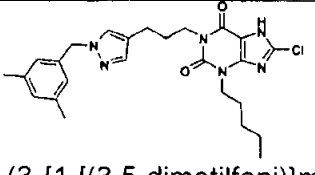
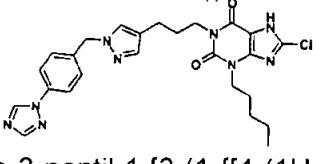
CL/EM: m/z 489 [MH^+], TR 3.59 min.

Los siguientes compuestos (cuadro 15) se prepararon por un método análogo al del ejemplo 23 [con la excepción que para el ejemplo 250 se añadió una segunda porción de $Pd(PPh_3)_4$ después de 5 hr, la agitación se

continuó durante la noche, y la purificación final se logró por CLAR; para el ejemplo 252 se requirió purificación adicional por MDAP; el ejemplo 257 requirió purificación adicional por recristalización a partir de MeOH; el ejemplo 258 requirió purificación adicional por trituración con MeOH].

CUADRO 15

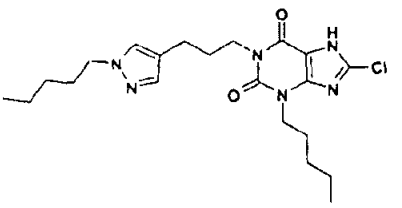
Ejemplo	Estructura	Rend. (mg)	CL/EM:
250	 8-cloro-1-{3-[1-(1,2,4-oxadiazol-3-ilmetil)-1H-pirazol-4-il]propil}-3-pentil-3,7-dihidro-1H-purina-2,6-diona	7.3	m/z 447 $[MH]^+$ TR 3.06 min
251	 8-cloro-1-(3-{1-[(4-metilfenil)metil]-1H-pirazol-4-il}propil)-3-pentil-3,7-dihidro-1H-purina-2,6-diona	23.7	m/z 469 $[MH]^+$ TR 3.49 min
252	 8-cloro-1-(3-{1-[(5-metil-3-isoxazolil)metil]-1H-pirazol-4il}propil)-3-pentil-3,7-dihidro-1H-purina-2,6-diona	29.0	m/z 460 $[MH]^+$ TR 3.10 min
253	 8-cloro-1-[3-(1-{[3-(metiloxi)fenil]metil}-1H-pirazol-4-il)propil]-3-pentil-3,7-dihidro-1H-purina-2,6-diona	56.0	m/z 485 $[MH]^+$ TR 3.41 min

254	 8-cloro-3-pentil-1-[3-(1-{[3-(trifluorometil)fenil]metil}-1H-pirazol-4-il)propil]-3,7-dihidro-1H-purina-2,6-diona	47.0	m/z 523 $[MH]^+$ TR 3.61 min
255	 8-cloro-1-(3-{1-[(2-metilfenil)metil]-1H-pirazol-4-il}propil)-3-pentil-3,7-dihidro-1H-purina-2,6-diona	44.0	m/z 469 $[MH]^+$ TR 3.54 min
256	 3-({4-[3-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)propil]-1H-pirazol-1-il)metil)benzonitrilo	51.0	m/z 480 $MH]^+$ TR 3.32 min
257	 8-cloro-1-(3-{1-[(3,5-dimetilfeni)}metil]-1H-pirazol-4-il}propil)-3-pentil-3,7-dihidro-1H-purina-2,6-diona	36.7	m/z 483 $[MH]^+$ TR 3.66 min
258	 8-cloro-3-pentil-1-[3-(1-{[4-(1H-1,2,4-triazol-1-il)fenil]metil}-1H-pirazol-4-il)propil]-3,7-dihidro-1H-purina-2,6-diona	21.2	m/z 522 $[MH]^+$ TR 3.09 min

EJEMPLO 259

510

8-Cloro-3-pentil-1-[3-(1-pentil-1*H*-pirazol-4-il)propil]-3,7-dihidro-1*H*-purina-2,6-diona



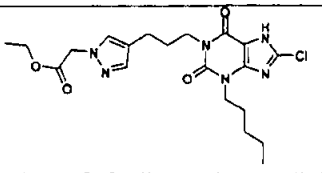
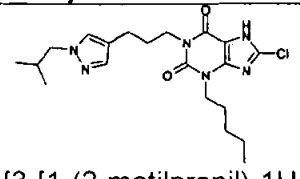
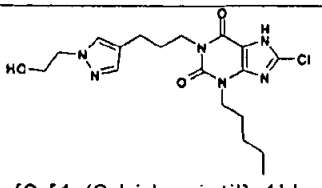
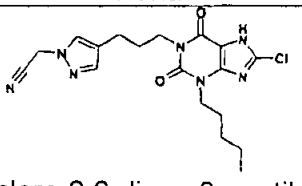
8-Cloro-3-pentil-7-(2-propen-1-il)-1-[3-(1*H*-pirazol-4-il)propil]-3,7-dihidro-1*H*-purina-2,6-diona (61 mg, 0.15 mmoles) y carbonato de sodio (32 mg, 0.3 mmoles) en DMF seco (1.5 ml) se calentó con 1-yodopentano (238 mg, 1.2 mmoles) en el reactor de microondas a 120°C durante 25 min. Después de enfriarse, la mezcla se desgasificó y se agitó con tetrakis(trifenilfosfin)paladio(0) (40 mg, 0.0346 mmoles) y morfolina (0.2 ml) durante 7 hr. 20 mg adicionales de $Pd(PPh_3)_4$ se añadieron después y la agitación se continuó durante la noche. La mezcla se agitó con EtOAc y HCl 2M durante 1 hr y la fase orgánica se separó y se evaporó. El producto se purificó por SPE de aminopropilo (5g) lavando con MeOH-THF (1:1), después MeOH, y eluyendo el producto con DCM-MeOH (1:1) que contenía 5% de AcOH añadido para dar el compuesto del título (25 mg).

CL/EM: m/z 435 $[MH]^+$, TR 3.65 min.

Los siguientes compuestos (cuadro 16) se prepararon por un método análogo al del ejemplo 259 [con la excepción de que los compuestos se purificaron por MDAP y para el ejemplo 261 el tiempo de calentamiento

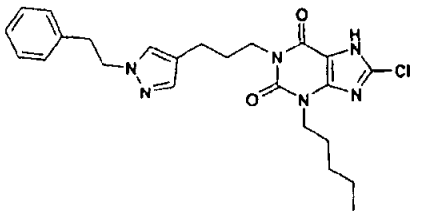
total en el reactor de microondas fue de 50 min].

CUADRO 16

Ejemplo	Estructura	Rend. (mg)	CL/EM:
260	 {4-[3-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)propil]-1H-pirazol-1-il}acetato de etilo	15.1	m/z 451 $[MH]^+$ TR 3.21 min
261	 8-cloro-1-{3-[1-(2-metilpropil)-1H-pirazol-4-il]propil}-3-pentil-3,7-dihidro-1H-purina-2,6-diona	1.34	m/z 421 $[MH]^+$ TR 3.48 min
262	 8-cloro-1-{3-[1-(2-hidroxietil}-1H-pirazol-4-il]propil}-3-pentil-3,7-dihidro-1H-purina-2,6-diona	0.32	m/z 409 $[MH]^+$ TR 2.79 min
263	 {4-[3-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)propil]-1H-pirazol-1-il}acetonitrilo	9.6	m/z 404 $[MH]^+$ TR 3.12 min

EJEMPLO 264

8-Cloro-3-pentil-1-{3-[1-(2-feniletil)-1*H*-pirazol-4-il]propil}-3,7-dihidro-1*H*-purina-2,6-diona

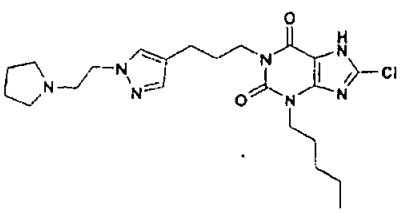


8-Cloro-3-pentil-7-(2-propen-1-il)-1-[3-(1*H*-pirazol-4-il)propil]-3,7-dihidro-1*H*-purina-2,6-diona (81 mg, 0.2 mmoles), carbonato de sodio (42 mg, 0.4 mmoles) y (2-yodoetil)benceno (0.174 ml, 1.2 mmoles) se calentaron juntos en DMF seco (1 ml) bajo irradiación de microondas a 120°C durante 25 min. Tetrakis(trifenilfosfin)paladio(0) (46 mg, 0.04 mmoles) y morfolina (0.174 ml) se añadieron y la mezcla se agitó durante 6 hr. Se añadieron cantidades adicionales (46 mg y 0.174 ml) de estos reactivos y la agitación continuó durante 60 hr adicionales. El tratamiento y purificación, como para los ejemplos en el cuadro 16, dio el compuesto del título (15.5 mg).

CL/EM: m/z 469 $[MH]^+$, TR 3.60 min.

EJEMPLO 265

8-Cloro-3-pentil-1-(3-{1-[2-(1-pirrolidinil)etil]-1*H*-pirazol-4-il}propil-3,7-dihidro-1*H*-purina-2,6-diona



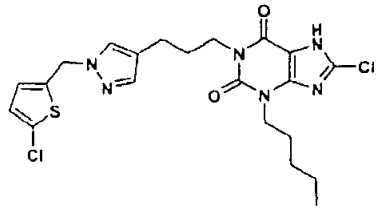
8-Cloro-3-pentil-7-(2-propen-1-il)-1-[3-(1*H*-pirazol-4-il)propil]-3,7-dihidro-1*H*-purina-2,6-diona (61 mg, 0.15 mmoles), carbonato de sodio (159 mg, 1.5 mmoles) y clorhidrato de 1-(2-cloroetil)pirrolidina (127 mg, 0.75 mmoles) se calentaron juntos en DMF seco (2 ml) a 80°C durante 65 hr. Yoduro de tetrabutilamonio (55 mg, 0.15 mmoles) se añadió y el calentamiento continuó durante otras 18 hr. Una cantidad adicional de clorhidrato de 1-(2-cloroetil)pirrolidina (127 mg, 0.75 mmoles) se añadió y la mezcla se calentó por microondas a 120°C, después se añadió una 3a. alícuota de clorhidrato de 1-(2-cloroetil)pirrolidina (100 mg), con 25 min adicionales a 120°C en el microondas. La mezcla se dividió entre agua y EtOAc, la fase orgánica se separó, se lavó con salmuera y se evaporó. Este material se dividió entre EtOAc y HCl 2M. La fase acuosa se separó, se basificó a pH 9, se saturó con NaCl y se extrajo con EtOAc (x2). Los extractos se evaporaron y el residuo (28 mg) se agitó en DMF desgasificado seco (1.5 ml) con tetrakis(trifenilfosfin)paladio(0) (50 mg) y morfolina (0.2 ml) durante 6 hr. La mezcla se dividió entre EtOAc y HCl 2M, la fase acuosa se filtró, se

extrajo dos veces con EtOAc y se evaporó a sequedad. El residuo se purificó por el procedimiento de SPE de aminopropilo, seguido por MDAP para dar el compuesto del título (1.9 mg).

CL/EM: m/z 462 $[MH]^+$, TR 2.46 min.

EJEMPLO 266

8-Cloro-1-(3-{1-[(5-cloro-2-tienil)metil]-1*H*-pirazol-4-il}propil)-3-3,7-dihidro-1*H*-purina-2,6-diona



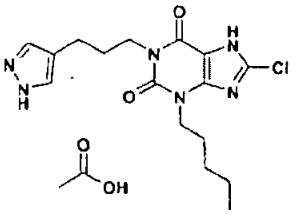
A 8-cloro-3-pentil-7-(2-propen-1-il)-1-[3-(1*H*-pirazol-4-il)propil]-3,7-dihidro-1*H*-purina-2,6-diona (61 mg, 0.15 mmoles) en THF seco (1 ml) a -78°C, bajo nitrógeno, se añadió t-butóxido de potasio (1M en THF, 0.15 ml), seguido por 2-cloro-5-(clorometil)tiofeno (25 mg, 0.15 mmoles). La agitación se continuó a –78°C durante 15 min, después a temperatura ambiente durante 1 hr y finalmente a 60°C durante 18 hr. La solución se desgasificó y se añadieron morfolina (0.13 ml) y tetrakis(trifenilfosfin)paladio(0) (35 mg) y la agitación continuó durante 6 hr. Cantidades adicionales (0.2 ml de morfolina, 50 mg de $Pd(PPh_3)_4$) se añadieron y la agitación se continuó durante la noche. Se trató dividiendo entre EtOAc y HCl 2M, la fase orgánica se evaporó y se purificó por el procedimiento de SPE de aminopropilo estándar seguido por

MDAP dando el compuesto del título como un sólido blanco (5.1 mg).

CL/EM: m/z 495 $[MH]^+$, TR 3.68 min.

EJEMPLO 267

Acetato de 8-cloro-3-pentil-1-[3-(1*H*-pirazol-4-il)propil]-3,7-dihidro-1*H*-purina-2,6-diona



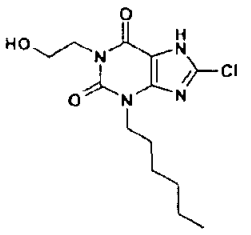
8-Cloro-3-pentil-7-(2-propen-1-il)-1-[3-(1*H*-pirazol-4-il)propil]-3,7-dihidro-1*H*-purina-2,6-diona (50 mg, 0.124 mmoles) en en THF desgasificado seco (1.5 ml) se agitó con tetrakis(trifenilfosfin)paladio(0) (29 mg, 0.025 mmoles) y morfolina (0.108 ml) bajo nitrógeno durante 5 hr. La mezcla se dividió entre EtOAc y ácido cítrico 0.5M y la fase orgánica se separó. Dos extracciones con EtOAc adicionales se realizaron y los compuestos orgánicos combinados se evaporaron y el producto se purificó por SPE de aminopropilo (2 g), cargando y lavando con THF-MeOH (1:1), después lavando con MeOH y eluyendo con DCM-MeOH (1:1) que contenía 5% de AcOH. Rendimiento 28.3 mg.

CL/EM: m/z 365 $[MH]^+$, TR 2.89 min.

EJEMPLO 268

8-Cloro-3-hexil-1-(2-hidroxietil)-3,7-dihidro-1*H*-purina-2,6-diona

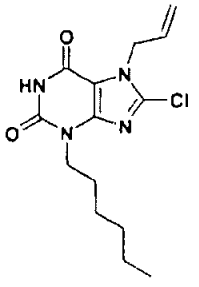
a) 8-Cloro-3-hexil-1-(2-hidroxietil)-3,7-dihidro-1*H*-purina-2,6-diona



8-Cloro-3-hexil-7-(2-propen-1-il)-3,7-dihidro-1*H*-purina-2,6-diona (100 mg, 0.322 mmoles), carbonato de cesio (126 mg, 0.387 mmoles) y 2-cloroetanol (29.8 mg, 0.37 mmoles) en DMF seco (3 ml) se calentaron juntos bajo nitrógeno a 55°C durante 42 hr. La mezcla enfriada se desgasificó completamente y se agitó con tetrakis(trifenilfosfin)paladio(0) (74 mg) y morfolina (0.28 ml) durante 5 hr. La reacción se trató dividiendo entre EtOAc y HCl 2M, la fase orgánica se separó y se evaporó. El residuo se cargó en un cartucho de SPE de aminopropilo (5g) en THF-MeOH (1:1), se lavó con el mismo solvente, después con MeOH neto, y el producto se eluyó con DCM-MeOH (1:1) que contenía AcOH (2.5% elevándose a 5%). El producto así obtenido se purificó además por MDAP para dar el compuesto del título (38 mg).

CL/EM: m/z 315 $[MH]^+$, TR 2.79 min.

b) 8-Cloro-3-hexil-7-(2-propen-1-il)-3,7-dihidro-1*H*-purina-2,6-diona

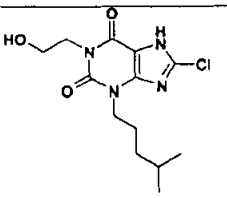
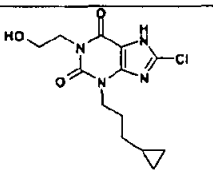


A 8-cloro-7-(2-propen-1-il)-3,7-dihidro-1*H*-purina-2,6-diona (226 mg, 1 mmoles) y carbonato de sodio (117 mg, 1.1 mmoles) en DMF seco (7 ml) se añadió 1-yodohexano (223 mg, 1.05 mmoles). La mezcla se agitó y se calentó a 50°C durante 2 días. Después de enfriarse, la mezcla se dividió entre EtOAc y agua, la fase orgánica se lavó con salmuera, se secó sobre Na_2SO_4 y se evaporó. El producto crudo se recristalizó a partir de EtOAc-ciclohexano (1:2). Rendimiento 146 mg.

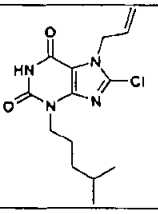
CL/EM: m/z 311 $[MH]^+$, TR 3.12 min.

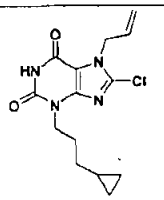
Los siguientes compuestos (cuadro 17) se prepararon por un método análogo al del ejemplo 268, excepto para el ejemplo 270 la escala se redujo a 75 mg (0.243 mmoles) del precursor 8-cloro-3-(3-ciclopropilpropil)-7-(2-propen-1-il)-3,7-dihidro-1*H*-purina- 2,6-diona.

CUADRO 17

Ejemplo	Estructura	Precursor	Rend. (mg)	CL/EM
269	 8-cloro-1-(2-hidroxietil)-3-(4-metilpentil)-3,7-dihidro-1H-purina-2,6-dona	8-cloro-3-(4-metilpentil)-7-(2-propen-1-il)-3,7-dihidro-1H-purina-2,6-diona	37	m/z 315 $[MH]^+$ TR 2.74 min
270	 8-cloro-3-(3-ciclopropilpropil)-1-(2-hidroxietil)-3,7-dihidro-1H-purina-2,6-dona	8-cloro-3-(3-ciclopropilpropil)-7-(2-propen-1-il)-3,7-dihidro-1H-purina-2,6-diona	26	m/z 313 $[MH]^+$ TR 2.58 min

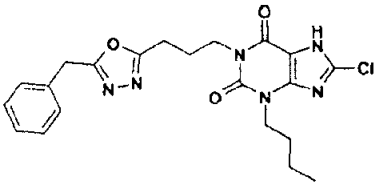
Los intermediarios se prepararon de conformidad con el método del ejemplo 268b, excepto que 8-cloro-3-(3-ciclopropilpropil)-7-(2-propen-1-il)-3,7-dihidro-1*H*-purina-2,6-diona se purificó por SPE de sílice (5 g) eluyendo con EtOAc-ciclohexano (2:3).

Intermediario	Nombre	Escala (mmoles)	Agente alquilante	Rend. (mg)	CL/EM
	8-cloro-3-(4-metilpentil)-7-(2-propen-1-il)-3,7-dihidro-1H-purina-2,6-diona	1	1-bromo-4-metilpentano (173 mg)	210	m/z 311 $[MH]^+$ TR 3.08 min

	8-cloro-3-(3-ciclopropilpropil)-7-(2-propen-1-il)-3,7-dihidro-1H-purina-2,6-diona	0.662	3-ciclopropil-propil 4-metil-bencensulfonato (170 mg)	125	m/z 309 $[MH]^+$ TR 2.93 min

EJEMPLO 271

3-Butil-8-cloro-1-{3-[5-(fenilmetil)-1,3,4-oxadiazol-2-il]propil}-3,7-dihidro-1*H*-purina-2,6-diona



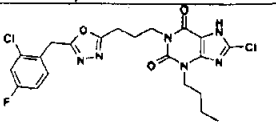
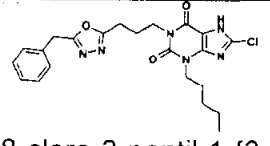
A 3-butil-8-cloro-7-(2-propen-1-il)-3,7-dihidro-1*H*-purina-2,6-diona (99 mg, 0.35 mmoles) en DMF seco (2 ml) se añadió carbonato de cesio (137 mg, 0.42 mmoles) seguido por una solución en DMF seco (1 ml) de 2-(3-cloropropil)-5-(fenilmetil)-1,3,4-oxadiazol (99 mg, 0.42 mmoles). La mezcla se agitó bajo nitrógeno y se calentó a 55°C durante 2.5 hr, después se agitó a temperatura ambiente durante la noche. La mezcla se desgasificó mediante evacuación repetida y admitiendo nitrógeno y después tetrakis(trifenilfosfin)paladio(0) (81 mg, 0.07 mmoles) y morfolina (0.305 ml, 3.5 mmoles) se añadieron y la agitación se continuó durante 5 hr. Se añadieron EtOAc y HCl 2M y la mezcla se agitó durante 20 min, después se filtró. La fase orgánica se separó y se evaporó, y el producto se purificó por SPE de aminopropilo (5g) lavando con THF-MeOH (1:1) después con MeOH y

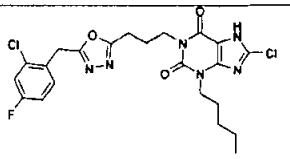
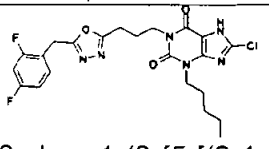
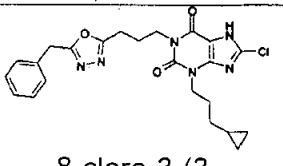
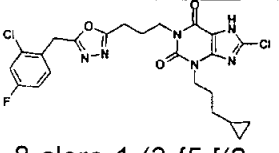
eluyendo el producto ácido con DCM-MeOH (1:1) que contenía 5% de AcOH añadido. El producto así obtenido se purificó de manera adicional por MDAP para dar el compuesto del título (92 mg).

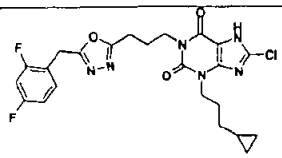
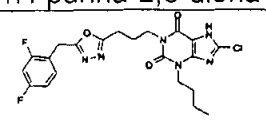
CL/EM: m/z 443 $[MH]^+$, TR 3.18 min.

Los siguientes compuestos (cuadro 18) se prepararon por un método análogo al del ejemplo 271, con la excepción de que el ejemplo 279 además se purificó por CLAR.

CUADRO 18

Ejemplo	Estructura de producto	Precursor de xantina	Agente alquilante	Rend. (mg)	CL/EM
272	 3-butil-8-cloro-1-(3-{5-[(2-cloro-4-fluoropentil)metil]-1,3,4-oxadiazol-2-il}propil)-3,7-dihidro-1H-purina-2,6-diona	3-butil-8-cloro-7-(2-propen-1-il)-3,7-dihidro-1H-purina,2,6-diona (99 mg)	2-[(2-cloro-4-fluorofenil)metil]-5-(3-cloropropil)-1,3,4-oxadiazol (121 mg)	90	m/z 495 $[MH]^+$ TR 3.34 min
273	 8-cloro-3-pentil-1-{3-[5-(fenilmetil)-1,3,4-oxadiazol-2-il]propil}-3,7-dihidro-1H-purina-2,6-diona	8-cloro-3-pentil-7-(2-propen-1-il)-3,7-dihidro-1H-purina,2,6-diona (104 mg)	2-(3-cloropropil)-5-(fenilmetil)-1,3,4-oxdiazol (99 mg)	98	m/z 457 $[MH]^+$ TR 3.35 min

274	 8-cloro-1-(3-{5-[(2-cloro-4-fluorofenil)metil]-1,3,4-oxadiazol-2-il}propil)-3-pentil-3,7-dihidro-1H-purina-2,6-diona	8-cloro-3-pentil-7-(2-propen-1-il)-3,7-dihidro-1H-purina,2,6-diona (104 mg)	2-[(2-cloro-4-fluorofenil)metil]-5-(3-cloropropil)-1,3,4-oxadiazol (121 mg)	98	m/z 509 $[MH]^+$ TR 3.52 min
275	 8-cloro-1-(3-{5-[(2,4-difluorofenil)metil]-1,3,4-oxadiazol-2-il}propil)-3-pentil-3,7-dihidro-1H-purina-2,6-diona	8-cloro-3-pentil-7-(2-propen-1-il)-3,7-dihidro-1H-purina,2,6-diona (104 mg)	2-(3-cloropropil)-5-[(2,4-difluorofenil)metil]-1,3,4-oxadiazol (111 mg)	43	m/z 493 $[MH]^+$ TR 3.40 min
276	 8-cloro-3-(3-ciclopropil)-1-{3-[5-(fenilmetil)-1,3,4-oxadiazol-2-il]propil}-3,7-dihidro-1H-purina-2,6-diona	8-cloro-3-(3-ciclopropilpropil)-7-(2-propen-1-il)-3,7-dihidro-1H-purina,2,6-diona (108 mg)	2-(3-cloropropil)-5-(fenilmetil)-1,3,4-oxadizol (99 mg)	95	m/z 469 $[MH]^+$ TR 3.34 min
277	 8-cloro-1-(3-{5-[(2-cloro-4-fluorofenil)metil]-1,3,4-oxadiazol-2-il}propil)-3-(3-ciclopropilpropil)-3,7-dihidro-1H-purina-2,6-diona	8-cloro-3-(3-ciclopropilpropil)-7-(2-propen-1-il)-3,7-dihidro-1H-purina,2,6-diona (108 mg)	2-[(2-cloro-4-fluorofenil)metil]-5-(3-cloropropil)-1,3,4-oxadiazol (121 mg)	99	m/z 521 $[MH]^+$ TR 3.51 min

278	 8-cloro-3-(3-ciclopropilpropil)-1-(3-{5-[(2,4-difluorofenil)metil]-1,3,4-oxadiazol-2-il}propil)-3,7-dihidro-1H-purina-2,6-diona	8-cloro-3-(3-ciclopropilpropil)-7-(2-propen-1-il)-3,7-dihidro-1H-purina,2,6-diona (108 mg)	2-(3-cloropropil)-5-[(2,4-difluorofenil)metil]-1,3,4-oxadiazol (111 mg)	49	m/z 505 $[MH]^+$ TR 3.40 min
279	 3-butil-8-cloro-1-(3-{5-[(2,4-difluorofenil)metil]-1,3,4-oxadiazol-2-il}propil)-3,7-dihidro-1H-purina-2,6-diona	3-butil-8-cloro-7-(2-propen-1-il)-3,7-dihidro-1H-purina,2,6-diona (99 mg)	2-(3-cloropropil)-5-[(2,4-difluorofenil)-metil]-1,3,4-oxadiazol (111 mg)	38.9	m/z 479 $[MH]^+$ TR 3.31 min

Síntesis de intermediaries de cloropropil 1,3,4-oxadiazol del cuadro 18:

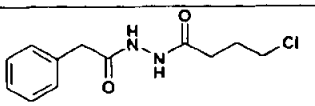
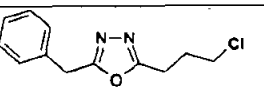
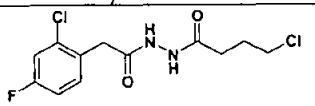
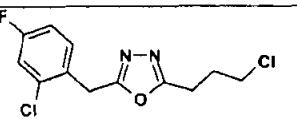
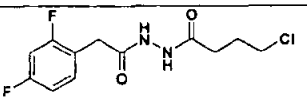
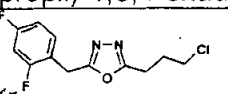
2-[(2-cloro-4-fluorofenil)metil]-5-(3-cloropropil)-1,3,4-oxadiazol

2-(3-cloropropil)-5-[(2,4-difluorofenil)metil]-1,3,4-oxadiazol

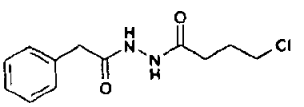
2-(3-cloropropil)-5-(fenilmetil)-1,3,4-oxadiazol

Diacilhidrazinas (500 mg, síntesis más adelante) se agitaron en tolueno seco (4 ml) y se añadió oxicloruro de fósforo (4 ml). Las mezclas se calentaron a 90°C durante 2 hr, después se dejaron enfriar y los solventes se evaporaron. Los residuos se disolvieron en tolueno seco, se evaporaron y después se dividieron entre EtOAc y $NaHCO_3$ acuoso. Las fases orgánicas se lavaron con salmuera, se secaron sobre Na_2SO_4 y se evaporaron para dar los oxadiazoles requeridos como aceites incoloros. Estos no se purificaron de

manera adicional, pero se hicieron reaccionar directamente con las xantinas como antes.

Diacil hidrazina	Producto de oxadiazol	Rend. (mg)	CL/EM
 4-cloro-*N*'-(fenilacetil)butanohidrazina	 2-(3-cloropropil)-5-(fenilmetil)-1,3,4-oxadiazol	446	m/z 237 $[MH]^+$ TR 2.94 min
 4-cloro-*N*'-[(2-cloro-4-fluorofenil)acetilbutano-hidrazina	 2-[(2-cloro-4-fluorofenil)metil]-5-(3-cloropropil)-1,3,4-oxadizol	405	m/z 289 $[MH]^+$ TR 3.17 min
 4-cloro-*N*'-[(2,4-difluorofenil)acetil]butano-hidrazina	 2-(3-cloropropil)-5-[(2,4-difluorofenil)metil]-1,3,4-oxadiazol	333	m/z 273 $[MH]^+$ TR 3.03 min

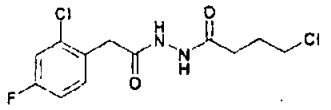
Preparación de 4-cloro-N'-(fenilacetil)butanohidrazida



A cloruro de 4-clorobutirilo (1.12 ml, 10 mmoles) en DCM seco (10 ml) se añadió, gota a gota, durante 40 min, una mezcla de fenilacético hidrazida (1.5 g, 10 mmoles) y DIPEA (1.77 ml, 10.2 mmoles) en DCM seco (40 ml) a temperatura ambiente. Se formó un precipitado blanco denso. Después de 20 min adicionales, se añadió HCl 2M (30 ml) y el compuesto del título (sólido blanco) se filtró, se lavó con agua y se secó (2.24 g).

CL/EM: m/z 255 $[MH]^+$, TR 2.20 min.

Preparación de 4-cloro-N'-[(2-cloro-4-fluorofenil)acetil] butanohidrazida



(i) Una solución de cloruro de 2-cloro-4-fluorofenilacetilo (10 mmoles) en DCM seco (15 ml) se añadió durante 20 min a una mezcla de carbazato de t-butilo (1.32 g, 10 mmoles) y DIPEA (1.77 ml, 10.2 mmoles) en DCM seco (20 ml). Después de agitar durante 2 hr adicionales, la mezcla se lavó con HCl 1M, después con $NaHCO_3$ acuoso. Un sólido blanco se precipitó en este punto, que se filtró, se lavó con agua y DCM después se secó para dar 2-[(2-cloro-4-fluorofenil)acetil]hidrazincarboxilato de 1,1-dimetiletilo (1.94 g).

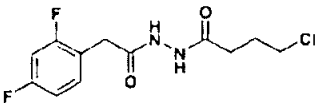
(ii) Este compuesto (1.92 g, 6.34 mmoles) se suspendió en dioxano (2 ml) y se añadió HCl 4M en dioxano (5 ml). Se formó un precipitado blanco denso. Después de 1 hr, la mezcla se dividió entre EtOAc y $NaHCO_3$ acuoso saturado y la fase orgánica se lavó con salmuera, se secó (Na_2SO_4) y se evaporó dando 2-(2-cloro-4-fluorofenil)acetohidrazida como un sólido blanco (1.07 g).

(iii) Una mezcla de 2-(2-cloro-4-fluorofenil)acetohidrazida (909 mg, 4.5 mmoles) y DIPEA (0.817 ml, 4.7 mmoles) en DCM seco (65 ml) se añadió durante 20 min a cloruro de 4-clorobutirilo (0.505 ml, 4.5 mmoles) en DCM seco (5 ml). Después de 1.5 hr, se añadió HCl 2M y la 4-cloro-*N*-[(2-cloro-4-fluorofenil)acetil]butanohidrazida precipitada se filtró, se lavó con agua

y se secó (1.24 g).

CL/EM: m/z 307 $[MH]^+$, TR 2.61 min.

Preparación de 2-(3-cloropropil)-5-[(2,4-difluorofenil)metil]-1,3,4-oxadiazol



(i) Una solución de cloruro e 2,4-difluorofenilacetilo (10 mmoles) en DCM seco (15 ml) se añadió durante 10 min a una mezcla de carbazato de t-butilo (1.32 g, 10 mmoles) y DIPEA (1.77 ml, 10.2 mmoles) en DCM seco (20 ml). Después de agitar durante 1.5 hr, la mezcla se lavó con HCl 1M, después con $NaHCO_3$ acuoso. La fase orgánica se evaporó para dar 1,1-2-[(2,4-difluorofenil)acetil]hidrazincarboxilato de dimetiletilo como un sólido blanco.

(ii) 1,1-2-[(2,4-difluorofenil)acetil]hidrazincarboxilato de dimetiletilo (10 mmoles) en dioxano (5 ml) se agitó con HCl 4M en dioxano (8 ml) durante 1.5 hr. La mezcla se dividió entre EtOAc y $NaHCO_3$ acuoso saturado y la fase orgánica se lavó con salmuera, se secó (Na_2SO_4) y se evaporó. La reacción no se completó por lo que el residuo se agitó nuevamente con HCl 4M en dioxano (10 ml) durante 2.5 hr. El tratamiento como antes dio 2-(2,4-difluorofenil)acetohidrazida como un sólido (570 mg).

(iii) Una mezcla de 2-(2,4-difluorofenil)acetohidrazida (570 mg, 3.06 mmoles) y DIPEA (0.553 ml, 3.2 mmoles) en DCM seco (30 ml) se añadió a cloruro de 4-clorobutirilo (0.343 ml, 3.06 mmoles) en DCM seco (5

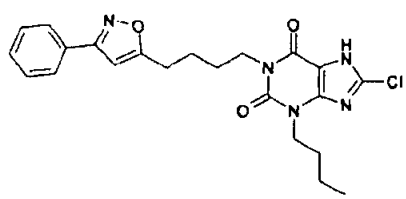
ml) durante 15 min. Se formó inmediatamente un precipitado blanco. Después de agitar durante 1 hr, se añadió HCl 2M (20 ml) y el sólido 2-(3-cloropropil)-5-[(2,4-difluorofenil)metil]-1,3,4-oxadiazol se filtró, se lavó con agua y se secó (726 mg).

CL/EM: m/z 291 $[MH]^+$, TR 2.45 min.

EJEMPLO 280

3-Butil-8-cloro-1-[4-(3-fenil-5-isoxazolil)butil]-3,7-dihidro-1*H*-purina-2,6-diona

a) 3-Butil-8-cloro-1-[4-(3-fenil-5-isoxazolil)butil]-3,7-dihidro-1*H*-purina-2,6-diona

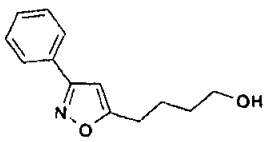


3-Butil-8-cloro-7-(2-propen-1-il)-3,7-dihidro-1*H*-purina-2,6-diona (100 mg, 0.354 mmoles) y 4-(3-fenil-5-isoxazolil)-1-butanol (77 mg, 0.355 mmoles) se disolvieron en THF seco (4 ml) bajo nitrógeno. Se añadió una solución de azodicarboxilato de dibencilo (94%, 224 mg, 0.708 mmoles) en THF seco (2 ml). La mezcla se enfrió a 0°C y una solución de trifenilfosfina (185 mg, 0.708 mmoles) en THF seco (1 ml) se añadió. La mezcla se agitó durante 20 min a 0°C, después a temperatura ambiente durante la noche. La

mezcla se desgasificó, después se agitó con morfolina (0.308 ml) y tetrakis(trifenilfosfin)paladio(0) (82 mg) durante 4.5 hr. Se añadieron 60 mg de tetrakis(trifenilfosfin)paladio(0) adicionales y la agitación se continuó durante la noche. La reacción se trató dividiendo entre EtOAc y HCl 2M, la fase orgánica se evaporó y se purificó por SPE de aminopropilo (5 g) lavando con THF-MeOH (1:1), MeOH y eluyendo con DCM-MeOH (1:1) que contenía 5% de AcOH. La purificación adicional por MDAP dio el compuesto del título (56 mg).

CL/EM: m/z 442 $[MH]^+$, TR 3.59 min.

b) 4-(3-Fenil-5-isoxazolil)-1-butanol



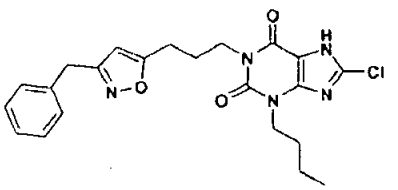
A Cloruro de N-hidroxibencencarboximidoilo (622 mg, 4 mmoles) en DCM seco (6 ml) se añadió 5-hexin-1-ol (431 mg, 4.4 mmoles). La mezcla se enfrió a 0°C bajo nitrógeno, como trietilamina (0.612 ml, 4.4 mmoles) se añadió gota a gota durante 10 min. Se agitó durante 20 min adicionales a 0°C, después a temperatura ambiente durante la noche. La mezcla se lavó con agua y la fase orgánica se evaporó. El producto se purificó por SPE de sílice (20 g) eluyendo con EtOAc-ciclohexano (1:2, después 3:1) para dar un sólido ceroso blanco (443 mg).

CL/EM: m/z 218 $[MH]^+$, TR 2.74 min.

EJEMPLO 281

3-Butil-8-cloro-1-{3-[3-(fenilmetil)-5-isoxazolil]propil)-3,7-dihidro-1*H*-purina-2,6-diona

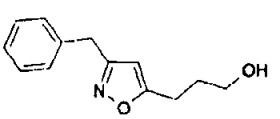
a) 3-Butil-8-cloro-1-{3-[3-(fenilmetil)-5-isoxazolil]propil}-3,7-dihidro-1*H*-purina- 2,6-diona



Preparado de manera análoga a 3-butil-8-cloro-1-[4-(3-fenil-5-isoxazolil)butil]-3,7-dihidro-1*H*-purina-2,6-diona (ejemplo 280) usando la mitad de las cantidades molares, empezando de 3-butil-8-cloro-7-(2-propen-1-il)-3,7-dihidro-1*H*-purina-2,6-diona (50 mg, 0.177 mmoles) y 3-[3-(fenilmetil)-5-isoxazolil]-1-propanol (38.4 mg, 0.177 mmoles). Rendimiento 24.2 mg,

CL/EM: m/z 442 $[MH]^+$, TR 3.43 min.

b) 3-[3-(Fenilmetil)-5-isoxazolil]-1-propanol



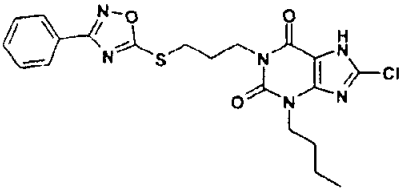
Sintetizado como con 4-(3-fenil-5-isoxazolil)-1-butanol, usando cloruro de N-hidroxi-2-feniletanimidoilo (253 mg, 1.5 mmoles) y 4-pentin-1-ol (139 mg, 1.65 mmoles). Rendimiento 61 mg de aceite amarillo pálido.

CL/EM: m/z 218 $[MH]^+$, TR 2.62 min.

EJEMPLO 282

3-Butil-8-cloro-1-{3-[(3-fenil-1,2,4-oxadiazol-5-il)tio]propil}-3,7-dihidro-1*H*-purina-2,6-diona

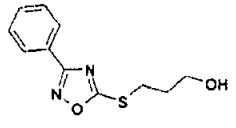
a) 3-Butil-8-cloro-1-{3-[(3-fenil-1,2,4-oxadiazol-5-il)tio]propil}-3,7-dihidro-1*H*-purina-2,6-diona



Se preparó por el método de 3-butil-8-cloro-1-[4-(3-fenil-5-isoxazolil)butil]-3,7-dihidro-1*H*-purina-2,6-diona empezando por 3-butil-8-cloro-7-(2-propen-1-il)-3,7-dihidro-1*H*-purina-2,6-diona (100 mg, 0.354 mmoles) y 3-[(3-fenil-1,2,4-oxadiazol-5-il)tio]-1-propanol (83.5 mg, 0.354 mmoles) excepto que una 2a. alícuota de 250 mg de tetrakis(trifenilfosfin)paladio(0) se añadió durante el paso de desprotección. Rendimiento 19.6 mg

CL/EM: m/z 461 $[MH]^+$, TR 3.75 min.

b) 3-[(3-fenil-1,2,4-oxadiazol-5-il)tio]-1-propanol



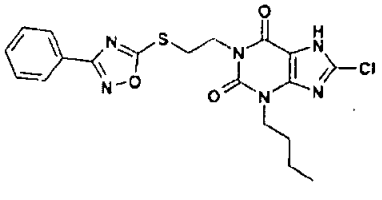
A 3-fenil-1,2,4-oxadiazol-5(2*H*)-tiona (178 mg, 1 mmoles) en THF seco (3 ml) se añadió DIPEA (0.174 ml, 1 mmol) y 3-bromo-1-propanol (139 mg, 1 mmoles). La agitación se continuó durante 65 hr, después la mezcla se dividió entre EtOAc y agua. La fase orgánica se lavó con salmuera, se secó (Na_2SO_4) y se evaporó para dar el compuesto del título como un aceite (235 mg).

CL/EM: m/z 237 $[MH]^+$, TR 2.94 min.

EJEMPLO 283

3-Butil-8-cloro-1-[2-[(3-fenil-1,2,4-oxadiazol-5-il)tio]etil)-3,7-dihidro-1*H*-purina-2,6-diona

a) 3-Butil-8-cloro-1-{2-[(3-fenil-1,2,4-oxadiazol-5-il)tio]etil}-3,7-dihidro-1*H*-purina-2,6-diona

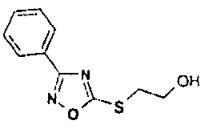


Se preparó por un método análogo al usado para el ejemplo 270

(3-butil-8-cloro-1-[4-(3-fenil-5-isoxazolil)butil]-3,7-dihidro-1*H*-purina-2,6-diona) empezando a partir de 3-butil-8-cloro-7-(2-propen-1-il)-3,7-dihidro-1*H*-purina-2,6-diona (141 mg, 0.5 mmoles) y 2-[(3-fenil-1,2,4-oxadiazol-5-il)tio]etanol (111 mg, 0.5 mmoles). Una porción individual de tetrakis(trifenilfosfin)paladio(0) (232mg) se usó en el paso de desprotección, sin embargo, la agitación se continuó durante 6 hr. La purificación por SPE de aminopropilo seguido por MDAP dio el compuesto del título como un sólido blanco (33.1 mg).

CL/EM: m/z 447 $[MH]^+$, TR 3.67 min.

b) 2-[(3-fenil-1,2,4-oxadiazol-5-il)tio]etanol



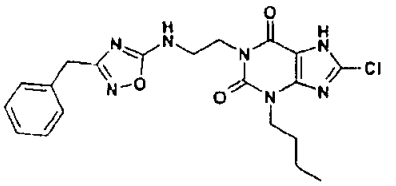
El compuesto del título se obtuvo de una manera similar a 3-[(3-fenil-1,2,4-oxadiazol-5-il)tio]-1-propanol, a partir de 2-bromoetanol, después de un tiempo de reacción de 24 hr y purificación por SPE de sílice (acetato de etilo-ciclohexano 1:1). Rendimiento 176 mg.

CL/EM: m/z 223 $[MH]^+$, TR 2.98 min.

EJEMPLO 284

3-Butil-8-cloro-1-(2-{[3-(fenilmetil)-1,2,4-oxadiazol-5-il]amino}etil)-3,7-dihidro-1*H*-purina-2,6-diona

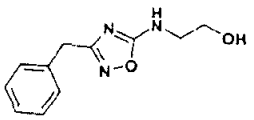
a) 3-Butil-8-cloro-1-(2-{[3-(fenilmetil)-1,2,4-oxadiazol-5-il]amino}-etil)-3,7-dihidro-1*H*-purina-2,6-diona



3-Butil-8-cloro-7-(2-propen-1-il)-3,7-dihidro-1*H*-purina-2,6-diona (64.4 mg, 0.228 moles), 2-{[3-(fenilmetil)-1,2,4-oxadiazol-5-il]amino}etanol (50 mg, 0.228 mmoles) y azodicarboxilato de dibencilo (136 mg, 0.456 mmoles) se agitaron en THF seco (3 ml) a 0°C, como trifenilfosfina (119 mg, 0.456 mmoles) en THF seco (1 ml) se añadió gota a gota. La mezcla se agitó a 0°C durante 10 min, después a temperatura ambiente durante 2 periodos de noche entera. Esta fue completamente desgasificada y se agitó con morfolina (0.2 ml) y tetrakis(trifenilfosfin)paladio(0) (53 mg, 0.046 mmoles) durante 5 hr. De manera adicional, 53 mg del catalizador se añadieron después y la agitación se continuó durante la noche. La reacción se trató dividiendo entre EtOAc y HCl 2M, la fase orgánica se evaporó y se purificó por SPE de aminopropilo (5g) lavando con THF-MeOH (1:1), MeOH y eluyendo con DCM-MeOH (1:1) que contenía 5% de AcOH. La purificación adicional por MDAP dio el compuesto del título (11.8 mg).

CL/EM: m/z 444 $[MH]^+$, TR 3.12 min.

b) 2-{[3-(Fenilmetil)-1,2,4-oxadiazol-5-il]amino}etanol



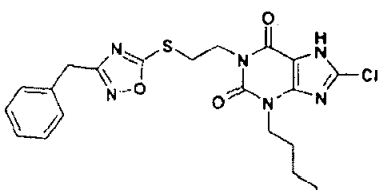
3-(Fenilmetil)-5-(triclorometil)-1,2,4-oxadiazol (140 mg, 0.505 mmoles) en DMF seco (2 ml) se agitó con etanolamina (0.25 ml) durante 1.5 hr. La mezcla se dividió entre EtOAc y agua, la fase orgánica se lavó con agua, salmuera, se secó (Na_2SO_4) y se evaporó para dar un sólido ceroso blanco (87 mg).

CL/EM: m/z 220 $[MH]^+$, TR 2.22 min.

EJEMPLO 285

3-Butil-8-cloro-1-(2-{[3-(fenilmetil)-1,2,4-oxadiazol-5-il]tio}etil)-3,7-dihidro-1*H*-purina-2,6-diona

a) 3-Butil-8-cloro-1-(2-{[3-(fenilmetil)-1,2,4-oxadiazol-5-il]tio}etil)-3,7-dihidro-1*H*-purina-2,6-diona

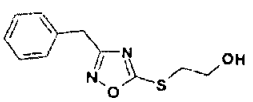


3-Butil-8-cloro-7-(2-propen-1-il)-3,7-dihidro-1*H*-purina-2,6-diona

(150 mg, 0.531 mmoles) y 2-{[3-(fenilmetil)-1,2,4-oxadiazol-5-il]tio}etanol (125 mg, 0.530 mmoles) en THF seco (4 ml) se enfriaron a 0°C y se añadió azodicarboxilato de dibencilo (94%, 336 mg, 1.06 mmoles) en THF seco (2 ml) seguido por trifenilfosfina (278 mg, 1.06 mmoles). La mezcla se agitó a 0°C durante 15 min, después a temperatura ambiente durante 2 periodos de noche. Morfolina (1 g) y tetrakis(trifenilfosfin)paladio(0) (250 mg, 0.216 mmoles) se añadieron a la solución desgasificada, y después de 5 hr adicionales, 100 mg de $Pd(PPh_3)_4$ se añadieron y la agitación continuó durante 3 periodos de noche. La reacción se trató dividiendo entre EtOAc y HCl 2M, la fase orgánica se evaporó y se purificó por SPE de aminopropilo (5g) lavando con THF-MeOH (1:1), MeOH y eluyendo con DCM-MeOH (1:1) que contenía 5% de AcOH. La purificación adicional por MDAP dio el compuesto del título (26 mg).

CL/EM: m/z 461 $[MH]^+$, TR 3.47 min.

b) 2-{[3-(Fenilmetil)-1,2,4-oxadiazol-5-il]tio}etanol



A 3-(fenilmetil)-1,2,4-oxadiazol-5(2*H*)-tiona (384 mg, 2 mmoles) en THF seco (5 ml) se añadió DIPEA (0.348 ml, 2 mmoles) y 2-bromoetanol (250 mg, 2 mmoles). La mezcla se agitó a temperatura ambiente durante la noche y después se dividió entre EtOAc y HCl 1M. La fase orgánica se lavó con salmuera, se secó, se evaporó y se purificó por SPE de sílice (10g)

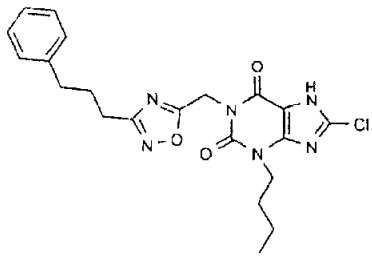
eluyendo con EtOAc-ciclohexano (1:2) para dar el compuesto del título (315 mg) como un aceite incoloro.

CL/EM: m/z 237 $[MH]^+$, TR 2.74 min.

EJEMPLO 286

3-Butil-8-cloro-1-{[3-(3-fenilpropil)-1,2,4-oxadiazol-5-il]metil}-3,7-dihidro-1*H*-purina-2,6-diona

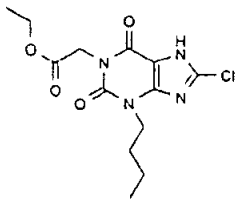
a) 3-Butil-8-cloro-1-{[3-(3-fenilpropil)-1,2,4-oxadiazol-5-il]metil}-3,7-dihidro-1*H*-purina-2,6-diona



(3-Butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1H-purin-1-il)acetato de etilo (66 mg, 0.2 mmoles) y (1*Z*)-*N*-hidroxi-4-fenilbutanimidamida (39 mg, 0.22 mmoles) se agitaron en etanol seco (1 ml) con etóxido de sodio etanólico (solución al 21% en peso, 0.111 ml, 0.3 mmoles) y se calentaron bajo irradiación de microondas a 140°C durante 10 min. La mezcla enfriada se dividió entre acetato de etilo y ácido clorhídrico 2M, la fase orgánica se separó y se evaporó. El producto se purificó por MDAP para dar el compuesto del título como un sólido (31.5 mg).

CL/EM: m/z 443 $[MH]^+$, TR 3.56 min.

b) (3-Butil-8-cloro-2,6-dioxo-2,3,6l7-tetrahidro-1H-purin-1-il)acetato de etilo

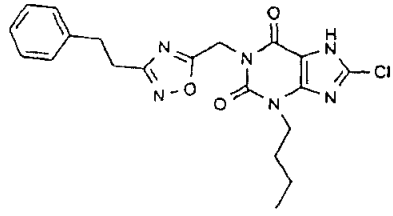


3-Butil-8-cloro-7-(2-propen-1-il)-3,7-dihidro-1*H*-purina-2,6-diona (1.5 g, 5.31 mmoles) y carbonato de cesio (1.903 g, 5.84 mmoles) se agitaron juntos en DMF seco (25 ml). Bromoacetato de etilo (0.648 ml, 5.84 mmoles) se añadió y la mezcla se agitó a 55°C durante la noche. La mezcla enfriada se desgasificó usando nitrógeno y se agitó con tetrakis(trifenilfosfin)paladio(0) (1g) y morfolina (3.73 ml) durante 4.5 hr. La mezcla se dividió entre acetato de etilo (80 ml) y HCl 2M (50 ml). La fase orgánica se lavó con 3 x 80 ml de salmuera, se filtró, se secó sobre Na_2SO_4 y se evaporó. El producto se purificó por SPE de aminopropilo (20 g), lavando con THF-MeOH (1:1), después MeOH neto y eluyendo el producto con DCM-MeOH (1:1) que contenía ácido acético (2.5% elevado a 5%), que dio el compuesto del título puro (1.16 g).

CL/EM: m/z 329 $[MH]^+$, TR 2.87 min.

EJEMPLO 287

3-Butil-8-cloro-1-{[3-(2-feniletil)-1,2,4-oxadiazol-5-il]metil}-3,7-dihidro-1*H*-purina-2,6-diona

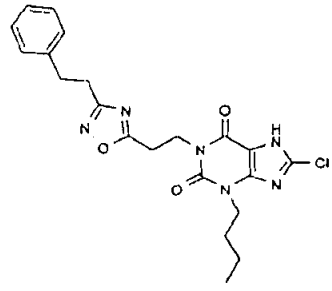


Se sintetizó por un método análogo al del ejemplo 286, empezando a partir de (1*Z*)-*N*-hidroxi-3-fenilpropanimidamida. Rendimiento 22.6 mg.

CL/EM: m/z 429 [MH]+, TR 3.43 min.

EJEMPLO 288

3-Butil-8-cloro-1-{2-[3-(2-feniletil)-1,2,4-oxadiazol-5-il]etil}-3,7-dihidro-1*H*-purina-2,6-diona



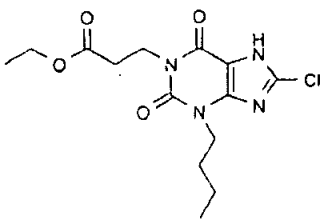
Se sintetizó por un método análogo al del ejemplo 286, empezando a partir de (1*Z*)-*N*-hidroxi-3-fenilpropanimidamida y 3-(3-butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1*H*-purin-1-il)propanoato de etilo.

Rendimiento 23.3 mg.

CL/EM: m/z 443 $[MH]^+$, TR 3.40 min.

EJEMPLO 289

3-(3-butil-8-cloro-2,6-dioxo-2,3.6,7-tetrahidro-1*H*-purin-1-il)propanoato de etilo



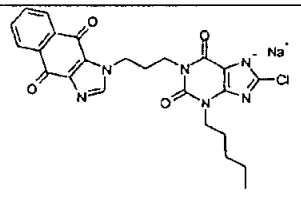
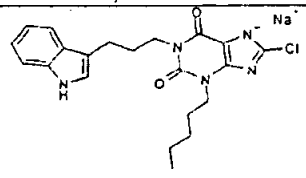
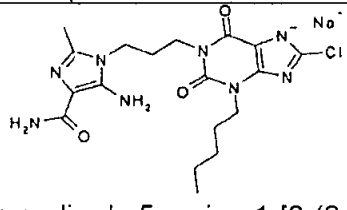
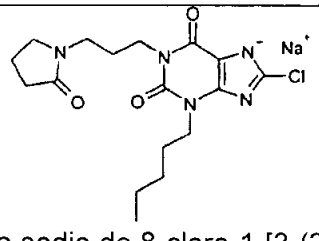
Se sintetizó como para (3-butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1*H*-purin-1-il)acetato de etilo empezando a partir de 3-bromopropanoato de etilo (0.749 ml, 5.84 mmoles), excepto que, después del periodo de calentamiento inicial durante la noche, se añadió 3-bromopropanoato de etilo adicional (1.5 ml), el calentamiento se reanudó por 4 hr adicionales, después una porción adicional de carbonato de cesio (1.903 g), seguido 2 hr después por una tercera porción de 3-bromopropanoato de etilo (1.5 ml) se añadieron. El calentamiento a 55°C después se continuó por un segundo periodo de noche antes de tratamiento y desprotección como antes. Rendimiento 0.404 g.

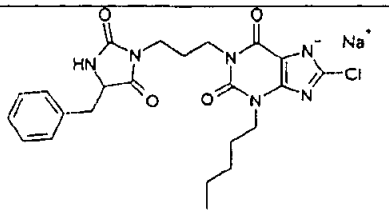
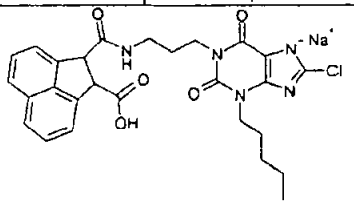
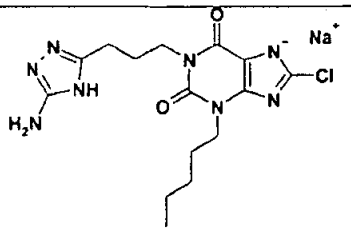
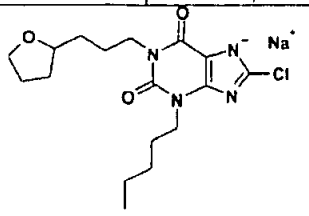
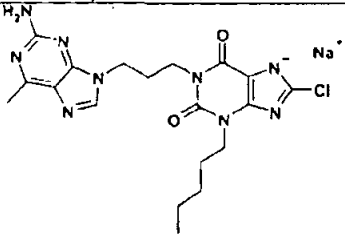
CL/EM: m/z 343 [MH]+, TR 2.90 min.

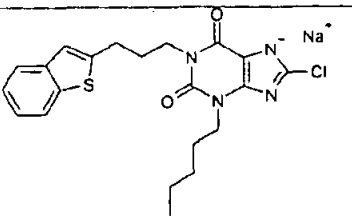
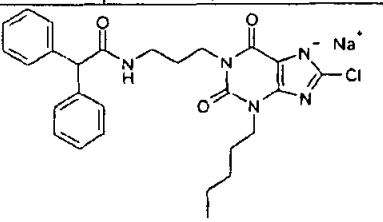
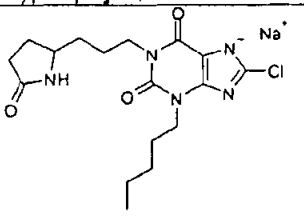
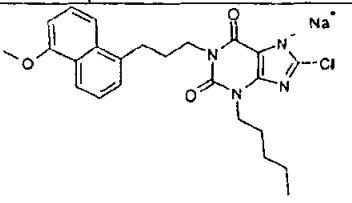
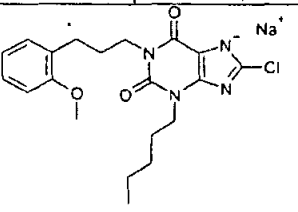
Los siguientes compuestos (cuadro 19) se prepararon por un método análogo al del ejemplo 3, con cualquier modificación mencionada en

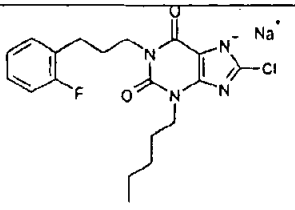
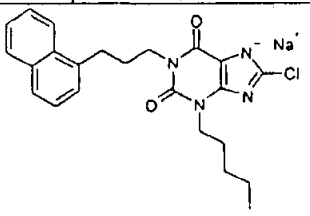
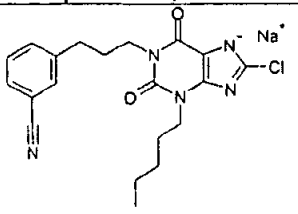
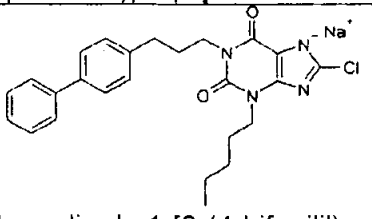
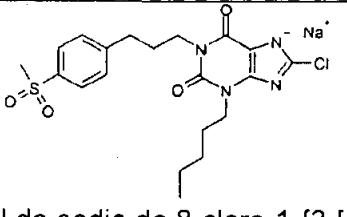
el método A-F.

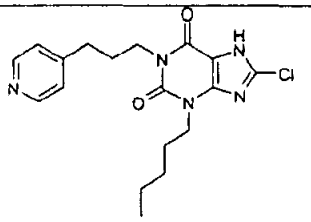
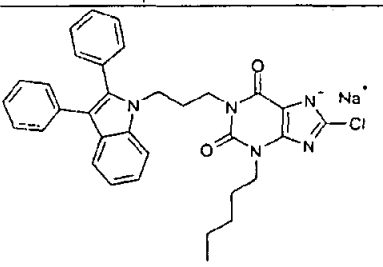
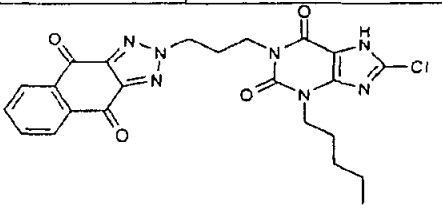
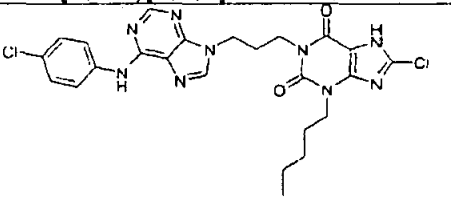
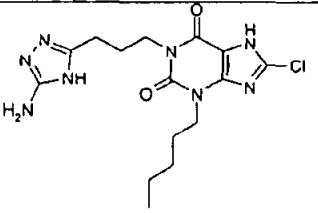
CUADRO 19

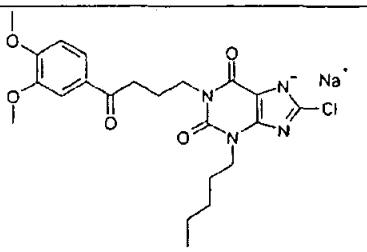
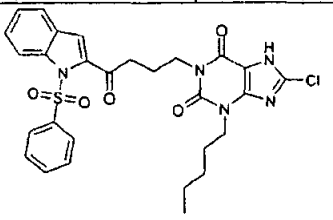
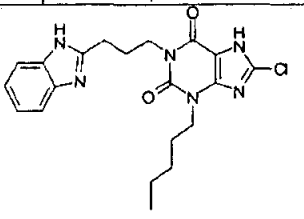
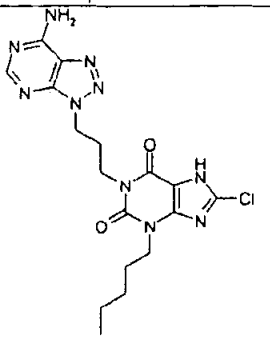
Ejemplo	Estructura	Rend. (mg)	CL/EM	Método
290	 Sal de sodio de 1-[3-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-il)propil]-1H-nafto[2,3-d]imidazol-4,9-diona	10	m/z 495 $[MH]^+$ TR 3.30 min	A
291	 Sal de sodio de 8-cloro-1-[3-(1H-indol-3-il)propil]-3-pentil-3,7-dihidro-1H-purino-2,6-diona	24	m/z 414 $[MH]^+$ TR 3.72 min	A
292	 Sal de sodio de 5-amino-1-[3-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)propil]-2-metil-1H-imidazol-4-carboxamida	27	m/z 437 $[MH]^+$ TR 2.41 min	A
293	 Sal de sodio de 8-cloro-1-[3-(2-oxo-pirrolidinil)propil]-3-pentil-3,7-dihidro-1H-purino-2,6-diona	21	m/z 382 $[MH]^+$ TR 2.86 min	A

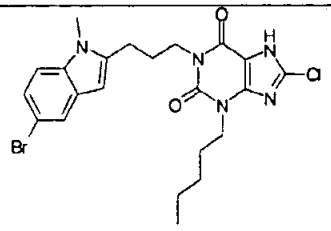
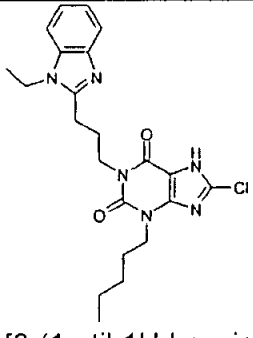
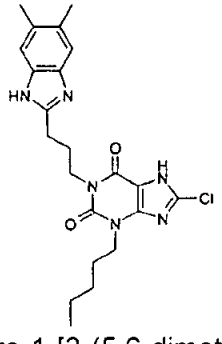
294	 Sal de sodio de 8-cloro-1-{3-[2,5-dioxo-4-(fenilmetil)-1-imidazolidinil]propil}3-pentil-3,7-dihidro-1H-purino-2,6-diona	9	m/z 487 $[MH]^+$ TR 3.15 min	A
295	 Sal de sodio de ácido 2-({[3-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-il)propil]amino}carbonil)-1,2-dihidro-1-acenaftilencarboxílico	39	m/z 538 $[MH]^+$ TR 3.46 min	A
296	 Sal de sodio de 1-[3-(3-amino-1H-1,2,4-triazol-5-il)propil]-8-cloro-3-pentil-3,7-dihidro-1H-purino-2,6-diona	18	m/z 381 $[MH]^+$ TR 2.33 min	A
297	 Sal de sodio de 8-cloro-3-pentil-1-[3-(tetrahidro-2-furanil)propil]-3,7-dihidro-1H-purino-2,6-diona	22	m/z 369 $[MH]^+$ TR 3.2 min	A
298	 Sal de sodio de 1-[3-(2-amino-6-rnetil-9H-purin-9-il)propil]-8-cloro-3-pentil-3,7-dihidro-1H-purino-2,6-diona	8	m/z 446 $[MH]^+$ TR 2.55 min	A

299	 Sal de sodio de 1-[3-(1-benzotien-2-il)propil)-8-cloro-3-pentil-3,7-dihidro-1H-purino-2,6-diona	21	m/z 431 $[MH]^+$ TR 3.9 min	A
300	 Sal de sodio de N-[3-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)propil]-2,2-difenilacetarnida	31	m/z 508 $[MH]^+$ TR 3.56 min	A
301	 Sal de sodio de 8-cloro-1-[3-(5-oxo-2-pirrolidinil)propil]-3-pentil-3,7dihidro-1H-purino-2,6-diona	22	m/z 382 $[MH]^+$ TR 2.76 min	A
302	 Sal de sodio de 8-cloro-1-{3-[5-(metiloxi)-1-naftalenil]propil}-3-pentil-3,7-dihidro-1H-purino-2,6-diona	33	m/z 455 $[MH]^+$ TR 4.01 min	A
303	 Sal de sodio de 8-cloro-1-(3-[2-(metiloxi)fenil]propil}-3-pentil-3,7-dihidro-1H-purino-2,6-diona	5	m/z 405 $[MH]^+$ TR 3.71 min	A

304	 Sal de sodio de 8-cloro-1-[3-(2-fluorofenil)propil]-3-pentil-3,7-dihidro-1H-purino-2,6-diona	15	m/z 393 $[MH]^+$ TR 3.7 min	A
305	 Sal de sodio 8-cloro-1-[3-(1-naftalenil)propil]-3-pentil-3,7-dihidro-1H-purino-2,6-diona	15	m/z 425 $[MH]^+$ TR 4.04 min	A
306	 Sal de sodio de 3-[3-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)propil]benzonitrilo	13	m/z 400 $[MH]^+$ TR 3.51 min	A
307	 Sal de sodio de 1-[3-(4-bifenilil)propil]-8-cloro-3-pentil-3,7-dihidro-1H-purino-2,6-diona	19	m/z 451 $[MH]^+$ TR 4.06 min	A
308	 Sal de sodio de 8-cloro-1-{3-[4-(metilsulfonil)fenil]propil}-3-pentil-3,7-dihidro-1H-purino-2,6-diona	30	m/z 453 $[MH]^+$ TR 3.2 min	A

309	 Sal de sodio 8-cloro-3-pentil-1-[3-(4-piridinil)propil]-3,7-dihidro-1H-purino-2,6-diona	2	m/z 376 $[MH]^+$ TR 2.41 min	A
310	 Sal de sodio de 8-cloro-1-[3-(2,3-difenil-1H-indol-1-il)propil]-3-pentil-3,7-dihidro-1H-purino-2,6-diona	46	m/z 566 $[MH]^+$ TR 4.23 min	A
311	 2-[3-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)propil]-2H-nafto[2,3-d)[1,2,3]triazol-4,9-diona	1	m/z 513 $[MH]^+$ TR 3.38 min	B
312	 8-cloro-1-(3-{6-[(4-clorofenil)amino]-9H-purin-il}propil)-3-pentil-3,7-dihidro-1H-purino-2,6-diona	21	m/z 542 $[MH]^+$ TR 3.62 min	B
313	 1-[3-(3-amino-1H-1,2,4-triazol-5-il)propil]-8-cloro-3-pentil-3,7-dihidro-1H-purino-2,6-diona	7	m/z 381 $[MH]^+$ TR 2.33 min	B

314	 Sal de sodio de 1-{4-[3,4-bis(metiloxi)fenil]-4-oxobutil)-8-cloro-3-pentil-3,7-dihidro-1H-purino-2,6-diona	17	m/z 463 $[MH]^+$ TR 3.24 min	B
315	 8-cloro-1-{4-oxo-4-[1-(fenilsulfonil)-1H-indol-2-il]butil)-3-pentil-3,7-dihidro-1H-purino-2,6-diona	2	m/z 582 $[MH]^+$ TR 3.79 min	B
316	 1-[3-(1H-benzimidazol-2-il)propil]-8-cloro-3-pentil-3,7-dihidro-1H-purino-2,6-diona	14	m/z 415 $[MH]^+$ TR 2.45 min	B
317	 1-[3-(7-amino-3H-[1,2,3]triazolo[4,5-d]pirimidin-3-il)propil]-8-cloro-3-pentil-3,7-dihidro-1H-purino-2,6-diona	5	m/z 433 $[MH]^+$ TR 2.69 min	C

318	 1-(3-(5-bromo-1-metil-1H-indol-2-il)propil]-8-cloro-3-pentil-3,7-dihidro-1H-purino-2,6-diona	2	m/z 508 $[MH]^+$ TR 4.11 min	D
319	 8-cloro-1-[3-(1-etil-1H-benzimidazol-2-il)propil]-3-pentil-3,7-dihidro-1H-purino-2,6-diona	17	m/z 443 $[MH]^+$ TR 2.59 min	E
320	 8-cloro-1-[3-(5,6-dimetil-1H-benzimidazol-2-il)propil]-3-pentil-3,7-dihidro-1H-purino-2,6-diona	25	m/z 443 $[MH]^+$ TR 2.61 min	F

Método A: Análogo al del ejemplo 3

Método B: Similar al método A, excepto que el material se purificó usando CLAR autopreparativa después de purificación por SPE de aminopropilo.

Método C: Similar al método A, excepto que el material se

purificó lavando con agua después de purificación por SPE de aminopropilo.

Método D: Similar al método A, excepto que el material se purificó por MDAP después de purificación por SPE de aminopropilo.

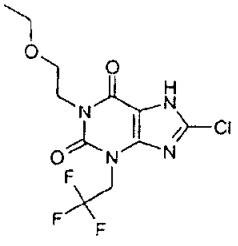
Método E: Similar al método A, excepto que el material se purificó por SCX SPE después de purificación inicial usando SPE de aminopropilo.

Método F: Similar al método A, excepto que el material se purificó usando CLAR preparativa usando una columa Zorbax Fenilo.

EJEMPLO 321

8-Cloro-1-[3-(etiloxi)etil]-3-(2,2,2-trifluoroetil)-3,7-dihidro- 1*H*-purina-2,6-diona

a) 8-Cloro-1-[3-(etiloxi)etil]-3-(2,2,2-trifluoroetil)-3,7-dihidro-1*H*-purina-2,6-diona



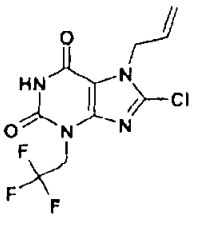
A un tubo de invernadero equipado con un agitador se añadió carbonato de cesio (85 mg, 0.26 mmoles), seguido por una solución de 8-cloro-7-(2-propen-1-il)-3-(2,2,2-trifluoroetil)-3,7-dihidro-1*H*-purina-2,6-diona (69 mg, 0.22 mmoles) en DMF seco (1 ml) y después una solución de 1-bromo-3-

(etiloxi)etano (60 mg, 0.39 mmoles) en DMF seco (1 ml). La mezcla se calentó a 80°C durante 5 hr bajo nitrógeno, después se dejó enfriar hasta temperatura ambiente durante 16 hr. La mezcla de reacción se concentró usando una centrífuga de vacío. THF (2.5 ml) se añadió a la mezcla, seguido por $Pd(PPh_3)_4$ (30 mg, 0.026 mmoles) y morfolina (190 ul, 2.2 mmoles) y la mezcla se agitó a t.a. bajo nitrógeno durante 72 hr. La mezcla se dividió entre HCl 2N (2 ml) y cloroformo (4 ml), la capa orgánica se separó usando una frita hidrofóbica, y la capa acuosa se extrajo con cloroformo (2x4 ml). Las capas orgánicas combinadas se concentraron bajo presión reducida, después se cargaron en 1:1 de DCM/MeOH en una SPE de aminopropilo (5 g), lavando con 1:1 de DCM/MeOH y eluyendo con 20% a 80% de ácido acético en 1:1 de DCM/MeOH. El solvente se removió bajo presión reducida para dar el compuesto del título como un sólido (70 mg, 93%).

^{1}H RMN (MeOD) δ: 1.11 (t, 3H, J = 7Hz), 3.51 (q, 2H, J = 7Hz), 3.64 (t, 2H, J = 6Hz), 4.18 (t, 2H, J = 6Hz), 4.73 (q, 2H, J = 9Hz).

CL/EM: m/z 341 $[MH]^+$, TR 2.72 min.

b) 8-Cloro-7-(2-propen-1-il)-3-(2,2,2-trifluoroetil)-3,7-dihidro-1*H*-purina-2,6-diona



8-Cloro-7-(2-propen-1-il)-3,7-dihidro-1*H*-purina-2,6-diona (1.5 g, 6.62 mmoles) en DMF seco (50 ml) se agitó con carbonato de sodio (980 mg, 9.25 mmoles) y 1,1,1-trifluoro-2-yodoetano (1.2 g, 5.71 mmoles) a temperatura ambiente durante 18 hr bajo nitrógeno. La mezcla se calentó a 50°C durante 6 hr después se enfrió a t.a. y se agitó durante 10 hr adicionales. La mezcla se calentó a 120°C durante 4 hr, además se añadió 1,1,1-trifluoro-2-yodoetano (426 mg, 2.03 mmoles) y la mezcla de reacción se calentó a 120°C durante 3 hr adicionales. La mezcla de reacción se concentró bajo presión reducida.

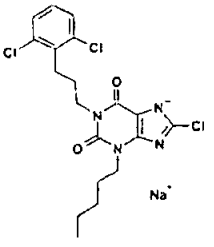
Una cantidad adicional de 8-cloro-7-(2-propen-1-il)-3,7-dihidro-1*H*-purina-2,6-diona (3.8 g, 16.8 mmoles) en DMF seco (125 ml) se agitó con carbonato de sodio (2.5 g, 23.1 mmoles) y 1,1,1-trifluoro-2-yodoetano (4.1 g, 19.5 mmoles) y la mezcla de reacción se calentó a 120°C durante 16 hr bajo nitrógeno. Esta mezcla de reacción se combinó con el material crudo anterior y se concentró bajo presión reducida. El residuo se trituró con DCM, la mezcla se filtró, y el filtrado se concentró bajo presión reducida, después se disolvió en DCM (20 ml). 10 ml de este material se purificaron por cromatografía de sílice usando una columna de sílice 100g, eluyendo el compuesto del título con un gradiente adecuado de acetato de etilo/ciclohexano. Los 10 ml restantes se purificaron usando un cartucho de Sílice RediSep (130g) en Companion, eluyendo el compuesto del título con un gradiente adecuado de acetato de etilo/ciclohexano. Las fracciones que contenía el compuesto del título a partir de ambos modos de purificación se combinaron y se concentraron bajo presión reducida para dar el compuesto del título como un

sólido blanco (1.6 g, 22% rendimiento total).

CL/EM: m/z 309 $[MH]^+$, TR 2.59 min.

EJEMPLO 322

Sal de sodio de 8-cloro-1-[3-(2,6-diclorofenil)propin]-3-pentil-3,7-dihidro-1*H*-purina-2,6-diona



A una solución de 8-cloro-3-pentil-7-(2-propen-1-il)-3,7-dihidro-1*H*-purina-2,6-diona (40 mg, 0.14 mmoles) en DMF seco (0.25 ml) se añadió carbonato de cesio (49 mg, 0.15 mmoles) seguido por una solución de 2-(3-bromopropil)-1,3-diclorobenceno (54 mg, 0.20 mmoles) en DMF seco (0.25 ml). La mezclas se agitaron a 60°C durante 16 hr, después se añadió $Pd(PPh_3)_4$ (16 mg, 0.014 mmoles), seguido por morfolina (118 ul, 1.4 mmoles) y las mezclas se agitaron durante 16 hr adicionales. El solvente se removió usando una centrífuga de vacío y la muestra se disolvió en DMSO (0.25 ml), después se cargó en un SPE de C18 (5g). Se añadió NaOH 2N (0.5 ml) y un gradiente adecuado de amoniaco/agua/MeCN se usó para eluir el producto. El compuesto del título se aisló como un sólido (52 mg, 83%).

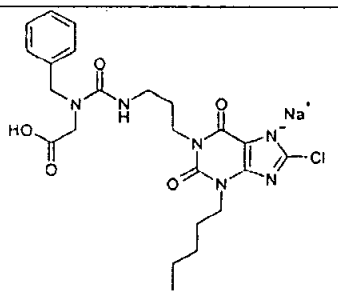
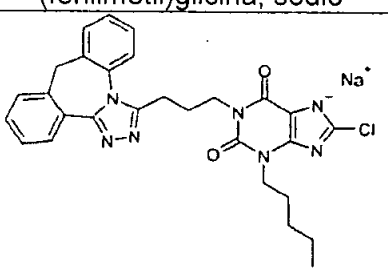
^{1}H RMN (DMSO-d_6) δ: 0.84 (t, 3H, J = 7Hz), 1.18-1.36 (m, 4H), 1.55-1.69 (m, 2H), 1.69-1.85 (m, 2H), 2.78-2.89 (m, 2H), 3.85 (t, 2H, J = 7Hz),

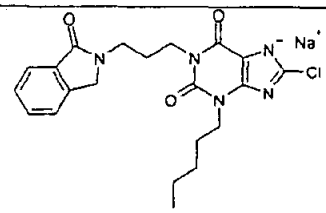
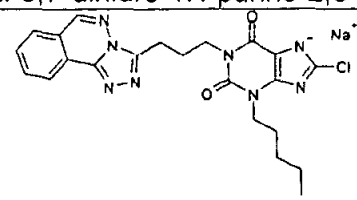
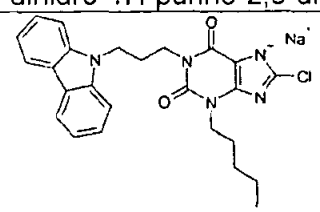
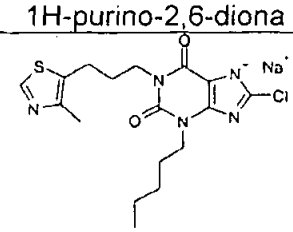
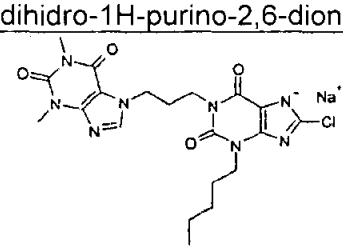
3.95 (t, 2H, J = 7Hz), 7.23 (dd, 1H, J = 9 y 7Hz), 7.41 (d, 2H, J = 7Hz).

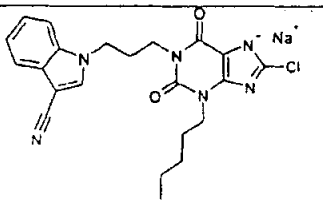
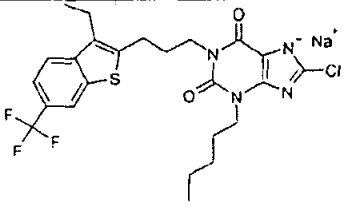
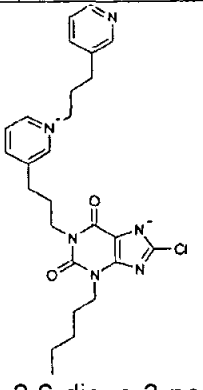
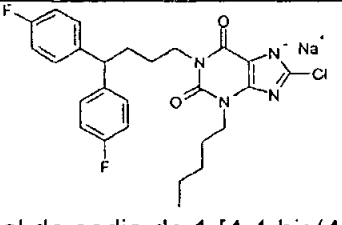
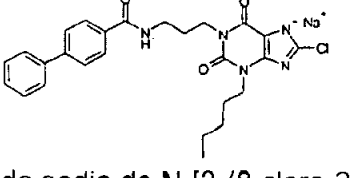
CL/EM: m/z 445 $[MH]^+$, TR 4.05 min.

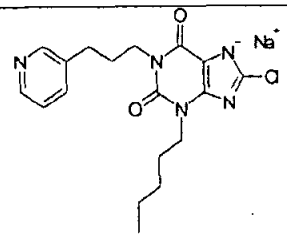
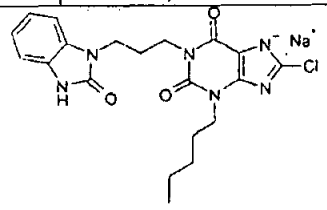
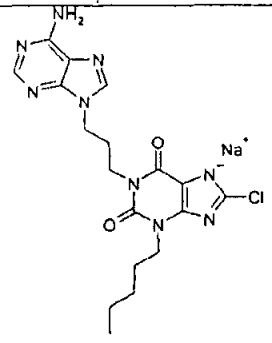
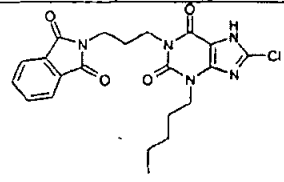
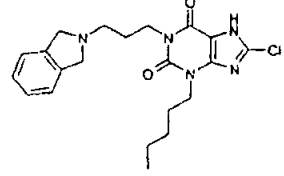
Los siguientes compuestos (cuadro 20) se prepararon usando un método análogo al del ejemplo 322, a partir de los halogenuros de alquilo correspondientes:

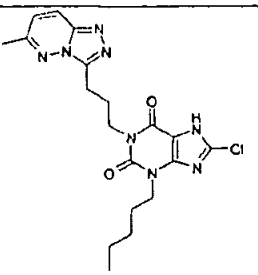
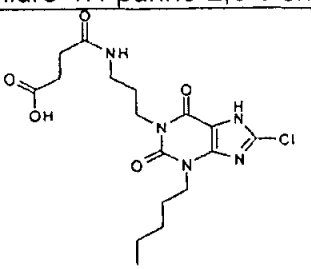
CUADRO 20

Ejemplo	Estructura	Rend. (mg)	CL/EM	Método
323	 N-({[3-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-il)propil]amino}carbonil)-N-(fenilmetil)glicina, sodio	57	m/z 505 $[MH]^+$ TR 3.14 min	A
324	 8-cloro-1-[3-(9H-dibenzo[c,f][1,2,4]triazolo[4,3-a]azepin-3-il)propil]-3-pentil-3,7-dihidro-1H-purino-2,6-diona, sodio	16	m/z 530 $[MH]^+$ TR 3.36 min	A

325	 Sal de sodio de 8-cloro-1-[3-(1-oxo-1,3-dihidro-2H-isoindol-2-il)propil]-3-pentil-3,7-dihidro-1H-purino-2,6-diona	18	m/z 430 $[MH]^+$ TR 3.12 min	A
326	 Sal de sodio de 8-cloro-3-pentil-1-(3-[1,2,4]triazolo[3,4-a]ftalazin-3-ilpropil)-3,7-dihidro-1H-purino-2,6-diona	18	m/z 467 $[MH]^+$ TR 2.99 min	A
327	 Sal de sodio de 1-(3-(9H-carbazol-9-il)propil]-8-cloro-3-pentil-3,7-dihidro-1H-purino-2,6-diona	30	m/z 464 $[MH]^+$ TR 4.03 min	A
328	 Sal de sodio de 8-cloro-1-[3-(4-metil-1,3-tiazol-5-il)propil]-3-pentil-3,7-dihidro-1H-purino-2,6-diona	42	m/z 396 $[MH]^+$ TR 3.17 min	A
329	 Sal de sodio de 7-[3-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)propil]-1,3-dimetil-3,7-dihidro-1H-purino-2,6-diona	31	m/z 477 $[MH]^+$ TR 2.83 min	A

330	 Sal de sodio de 1-[3-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)propil]-1H-indol-3-carbonitrilo	50	m/z 439 $[MH]^+$ TR 3.56 min	A
331	 8-cloro-1-{3-[3-etil-6-(trifluorometil)-1-benzotien-2-il]propil}-3-pentil-3,7-dihidro-1H-purino-2,6-diona, sodio	10	m/z 527 $[MH]^+$ TR 4.3 min	A
332	 3-[3-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)propil]-1-(3-(3-piridinil)propil]piridinio	5	m/z 495 $[MH]^+$ TR 2.21 min	A
333	 Sal de sodio de 1-[4,4-bis(4-fluorofenii)butill-8-cloro-3-pentil-3,7-dihidro-1H-purino-2,6-diona	45	m/z 501 $[MH]^+$ TR 4.01 min	A
334	 Sal de sodio de N-[3-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-	33	m/z 494 $[MH]^+$ TR 3.69 min	A

335	 Sal de sodio de 8-cloro-3-pentil-1-[3-(3-piridinil)propil}-3,7-dihidro-1H-purino-2,6-diona	18	m/z 376 $[MH]^+$ TR 2.5 min	A
336	 Sal de sodio de 8-cloro-1-[3-(2-oxo-2,3-dihidro-1H-benzimidazol-1-il)propil]-3-pentil-3,7-dihidro-1H-purino-2,6-diona	39	m/z 431 $[MH]^+$ TR 3.13 min	A
337	 Sal de sodio de 1-[3-(6-amino-9H-purin-9-il)propil)-8-cloro-3-pentil-3,7-dihidro-1H-purino-2,6-diona	4	m/z 432 $[MH]^+$ TR 2.53 min	B
338	 8-cloro-1-[3-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)propil]-3-pentil-3,7-dihidro-1H-purino-2,6-diona	1	m/z 444 $[MH]^+$ TR 3.39 min	C
339	 8-cloro-1-[3-(1,3-dihidro-2H-isoindol-2-il)propil]-3-pentil-3,7-dihidro-1H-purino-2,6-diona	3	m/z 416 $[MH]^+$ TR 2.87 min	C

340	 8-cloro-1-[3-(6-metil[1,2,4]triazolo[4,3-b]piridazin-3-il)propil]-3-pentil-3,7-dihidro-1H-purino-2,6-diona	8	m/z 431 $[MH]^+$ TR 2.83 min	D
341	 8-cloro-1-[3-(6-metil[1,2,4]triazolo[4,3-b]piridazin-3-il)propil]-3-pentil-3,7-dihidro-1H-purino-2,6-diona	3	m/z 414 $[MH]^+$ TR 2.64 min	E

Método A: Análogo al del ejemplo 3

Método B: Similar al método A, excepto que después de concentración por centrífuga de vacío, el material se dividió entre HCl 2M y DCM, la capa acuosa se aisló, después se purificó usando SPE de C18 de la manera descrita en el Método A.

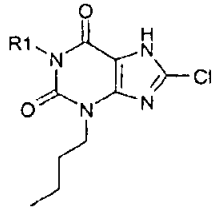
Método C: Similar al método A, excepto que después de concentración por centrífuga de vacío, el material se dividió entre HCl 2M y DCM, y el producto se aisló de la capa orgánica después de CLAR autopreparativa.

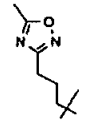
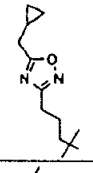
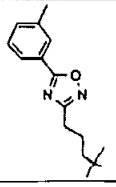
Método D: Similar al método A, excepto que el producto se aisló usando SPE de aminopropilo.

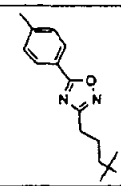
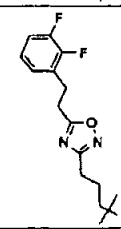
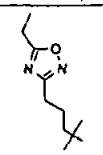
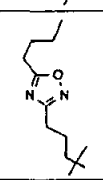
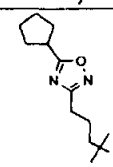
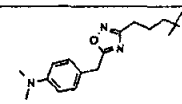
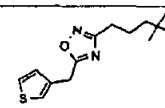
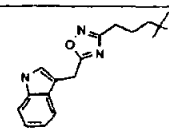
Método E: Similar al método A, excepto que el material además se purificó sobre una CLAR de fenilo usando un gradiente adecuado de agua/MeOH/MeCN/TFA, después CLAR autopreparativa, usando un gradiente adecuado de agua/acetonitrilo.

Los siguientes compuestos (cuadro 21) se prepararon usando un método análogo al del ejemplo 142, a partir de los ácidos correspondientes y (1*Z*)-4-(3-butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1*H*-purin-1-il)-*N*-hidroxi-butanimidamida.

CUADRO 21

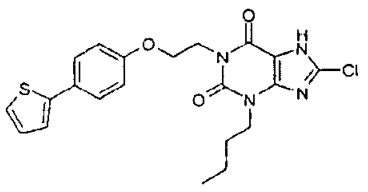


Ejemplo	Nombre	Compuesto: R1 =	CL/EM
342	3-butil-8-cloro-1-[3-(5-metil-1,2,4-oxadiazol-3-il)propil]-3,7-dihidro-1H-purino-2,6-diona		m/z 367 $[MH]^+$ TR 2.7 min
343	3-butil-8-cloro-1-{3-[5-(ciclopropilmetil)-1,2,4-oxadiazol-3-il]propil}-3,7-dihidro-1H-purino-2,6-diona		m/z 407 $[MH]^+$ TR 3.11 min
344	3-butil-8-cloro-1-{3-[5-(3-metilfenil)-1,2,4-oxadiazol-3-il]propil}-3,7-dihidro-1H-purino-2,6-diona		m/z 443 $[MH]^+$ TR 3.47 min

345	3-butil-8-cloro-1-{3-(5-(4-metilfenil)-1,2,4-oxadiazol-3-il]propil}-3,7-dihidro-1H-purino-2,6-diona		m/z 443 $[MH]^+$ TR 3.34 min
346	3-butil-8-cloro-1-(3-[5-[2-(2,3-difluorofenil)etil]-1,2,4-oxadiazol-3-il}propil)-3,7-dihidro-1H-purino-2,6-diona		m/z 493 $[MH]^+$ TR 3.47 min
347	3-butil-8-cloro-1-[3-(5-etil-1,2,4-oxadiazol-3-il)propil]-3,7-dihidro-1H-purino-2,6-diona		m/z 381 $[MH]^+$ TR 2.9 min
348	3-butil-1-[3-(5-butil-1,2,4-oxadiazol-3-il)propil]-8-cloro-3,7-dihidro-1H-purino-2,6-diona		m/z 409 $[MH]^+$ TR 3.27 min
349	3-butil-8-cloro-1-(3-(5-ciclopentil-1,2,4-oxadiazol-3-il)propil]-3,7-dihidro-1H-purino-2,6-diona		m/z 421 $[MH]^+$ TR 3.29 min
350	3-butil-8-cloro-1-[3-(5-{[4-(dimetilamino)fenil]metil}-1,2,4-oxadiazol-3-il)propil]-3,7-dihidro-1H-purino-2,6-diona		m/z 486 $[MH]^+$ TR 3.24 min
351	3-butil-8-cloro-1-{3-[5-(3-tienilmetil)-1,2,4-oxadiazol-3-il)propil}-3,7-dihidro-1H-purino-2,6-diona		m/z 449 $[MH]^+$ TR 3.24 min
352	3-butil-8-cloro-1-{3-[5-(1H-indol-3-ilmetil)-1,2,4-oxadiazol-3-il]propil)-3,7-dihidro-1H-purino-2,6-diona		m/z 482 $[MH]^+$ TR 3.29 min

EJEMPLO 353

3-Butil-8-cloro-1-(2-{[4-(2-tienil)fenil]oxi}etil)-3,7-dihidro-1*H*-purina-2,6-diona

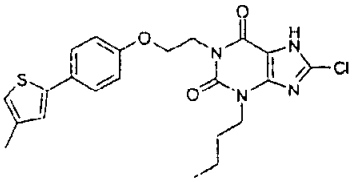


Un vial de microondas que contenía una barra de agitación magnética se cargó con ácido 2-tienilborónico (16 mg, 0.125 mmoles), 1-{2-[(4-bromofenil)oxi]etil}-3-butil-8-cloro-3,7-dihidro-1*H*-purina-2,6-diona (50 mg, 0.113 mmoles), carbonato de sodio acuoso (1 ml, solución 1M) y dimetoxietano (1 ml). Esta mezcla se desgasificó con nitrógeno y después se añadió $Pd(PPh_3)_2Cl_2$ (4 mg, 5.6x10-6 moles). La mezcla de reacción se tapó y se calentó a 140°C en un microondas durante 15 min (la presión alcanzó 7bar). La mezcla de reacción cruda se acidificó con HCl (2M, 1.5 ml), se lavó con cloroformo (2x1 ml) y las fases se separaron. Los compuestos orgánicos combinados se evaporaron y el producto crudo se purificó por MDAP para dar el compuesto del título (10 mg).

CL/EM: m/z 445 $[MH]^+$, TR 3.76 min

EJEMPLO 354

3-Butil-8-cloro-1-(2-{[4-(4-metil-2-tienil)fenil]oxi}etil)-3,7-dihidro-1*H*-purina-2,6-diona



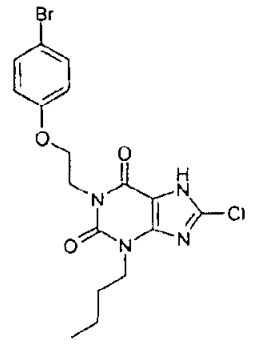
Un vial de microondas que contenía una barra de agitación magnética se cargó con ácido (4-metil-2-tienil)borónico (18 mg, 0.125 mmoles), 1-{2-[(4-bromofenil)oxi]etil}-3-butil-8- cloro-3,7-dihidro-1*H*-purina-2,6-diona (50 mg, 0.1 13 mmoles), carbonato de sodio acuoso (1 ml, solución 1M) y dimetoxietano (1 ml). Esta mezcla se desgasificó con nitrógeno y después se añadió $Pd(PPh_3)_2Cl_2$ (4 mg, 0.0056 mmoles). La mezcla de reacción se tapó y se calentó a 140°C en un microondas durante 15 min (la presión alcanzó 7bar). La mezcla de reacción cruda se acidificó con HCl (2M, 1.5 ml), se lavó con cloroformo (2x1 ml) y las fases se separaron. Los compuestos orgánicos combinados se evaporaron y el producto crudo se purificó por MDAP para dar el compuesto del título (17 mg).

CL/EM: m/z 459 $[MH]^+$, TR 3.9 min

EJEMPLO 355

1-{2-[(4-Bromofenil)oxi]etil}-3-butil-8-cloro-3,7-dihidro-1*H*-purina-2,6-diona

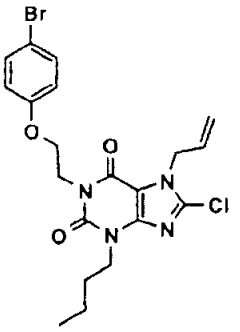
a) 1-{2-[(4-Bromofenil)oxi]etil}-3-butil-8-cloro-3,7-dihidro-1*H*-purina-2,6-diona



1-{2-[(4-Bromofenil)oxi]etil}-3-butil-8-cloro-7-(2-propen-1-il)-3,7-dihidro-1*H*-purina-2,6-diona (2.3 g, 4.8 mmoles) se agitó en una mezcla de DCM desgasificado con nitrógeno (40 ml) y AcOH (4 ml). Tetrakis(trifenilfosfin)paladio (1.1 g, 0.896 mmoles) y fenilsilano (5.9 ml, 48 mmoles) se añadieron y la mezcla se agitó a t.a. durante 2 hr. Esta después se evaporó y el residuo se trituró con una mezcla de éter dietílico:ciclohexano (1:2) para dar el compuesto del título (1.02 g, 49%) como un sólido blanco.

CL/EM: m/z 441/443 $[MH]^+$, TR 3.6 min.

b) 1-{2-[(4-bromofenil)oxi]etil}-3-butil-8-cloro-7-(2-propen-1-il)-3,7-dihidro-1*H*-purina-2,6-diona



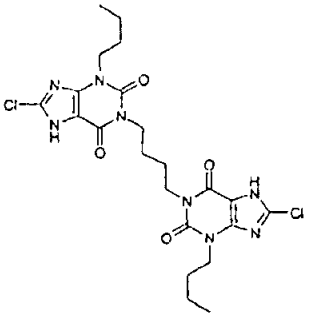
A 3-Butil-8-cloro-7-(2-propen-1-il)-3,7-dihidro-1*H*-purina-2,6-diona (2.8 g, 9.8 mmoles) en DMF seco (50 ml) se añadió Cs_2CO_3 (6.4 g, 19.6 mmoles) seguido por éter 2-bromoetil-4-bromofenílico (3.6 g, 13 mmoles). La mezcla se calentó a 80°C durante 17 hr y después se dejó enfriar. La mezcla de reacción se evaporó y el producto crudo se dividió entre EtOAc y HCl (2N). La fase orgánica se separó y se lavó con salmuera, se secó ($MgSO_4$) y se evaporó para dar el producto crudo. Este se purificó por SPE de sílice (50g), eluyendo con ciclohexano:acetato de etilo (10:1 a 1:1) para dar el compuesto del título como un sólido color crema (2.9 g, 62%).

CL/EM: m/z 381/483 $[MH]^+$, TR 3.87 min.

EJEMPLO 356

1,1'-(1,-Butanodiil)bis(3-butil-8-cloro-3,7-dihidro-1*H*-urina-2,6-diona)

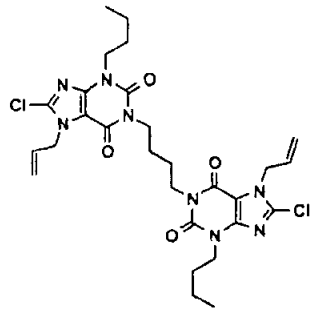
a) 1,1'-(1,4-butanodiil)bis(3-butil-8-cloro-3,7-dihidro-1*H*-purina-2,6-diona)



1,1'-(1,4-Butanodiil)bis[3-butil-8-cloro-7-(2-propen-1-il)-3,7-dihidro-1*H*-purina-2,6-diona] (24 mg, 0.039 mmoles) se agitó en una mezcla de DCM desgasificado con nitrógeno (2 ml) y AcOH (0.2 ml). Tetrakis(trifenilfosfin)paladio (38 mg, 0.033 mmoles) y fenilsilano (42 ul, 0.39 mmoles) se añadieron y la mezcla se agitó a t.a. durante 2 hr. Esta después se evaporó y el producto crudo se purificó por cromatografía de fase inversa (gradiente 5-95%, H_2O: CH_3CN) para dar el compuesto del título (2 mg).

CL/EM: m/z 539 $[MH]^+$, TR 3.33min

b) 1,1'-(1,4-Butanodiil)bis[3-butil-8-cloro-7-(2-propen-1-il)-3,7-dihidro-1*H*-purina-2,6- diona]

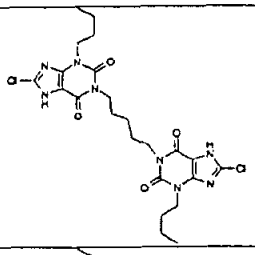
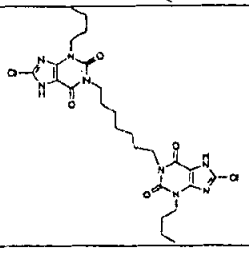


A 3-Butil-8-cloro-7-(2-propen-1-il)-3,7-dihidro-1*H*-purina-2,6-diona (60 mg, 0.212 mmoles) en DMF seco (1 ml) se añadió Cs_2CO_3 (207 mg, 0.636 moles) seguido por 1,4-diyodobutano (16 ul, 0.106 mmoles). La mezcla se calentó a 80°C durante 17 hr y después se dejó enfriar. La mezcla de reacción se dividió entre DCM y HCl (2M). La fase orgánica se separó y se lavó con salmuera, se secó ($MgSO_4$) y se evaporó para dar el producto crudo. Este se purificó por MDAP para dar el compuesto del título como un sólido color crema (24 mg).

CL/EM: m/z 619 $[MH]^+$, TR 3.95 min.

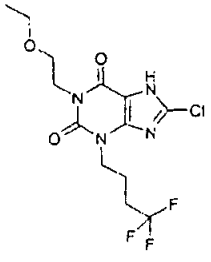
Los siguientes compuestos (cuadro 22) se prepararon usando un método análogo al del ejemplo 356.

CUADRO 22

Ejemplo	Nombre	Estructura	Rend. (mg)	CL/EM
357	3-butil-1-[5-(3-butil-8-cloro-2,6-dioxo-2,3,6,9-tetrahidro-1H-purin-1-il)pentil]-8-cloro-3,7-dihidro-1H-purino-2,6-diona		2.4 mg	m/z 553 $[MH]^+$ TR 3.43 min
358	3-butil-1-[7-(3-butil-8-cloro-2,6-dioxo-2,3,6,9-tetrahidro-1H-purin-1-il)heptil]-8-cloro-3,7-dihidro-1H-purino-2,6-diona		3.6 mg	m/z 581 $[MH]^+$ TR 3.72 min

EJEMPLO 359

8-Cloro-1-[2-(etiloxi)etil}-3-(4,4,4-trifluorobutil)-3,7-dihidro-1*H*-purina-2,6-diona



Una solución de 8-cloro-7-(2-propen-1-il)-3-(4,4,4-trifluorobutil)-3,7-dihidro-1H-purina-2,6-diona (84 mg, 0.25 mmoles) en DMF (1 ml) se trató con carbonato de cesio (163 mg, 0.5 mmoles) y 1-bromo-2-(etiloxi)etano (42 mg, 0.275 mmoles). La mezcla se calentó a 80°C durante 4 hr y después se enfrió.

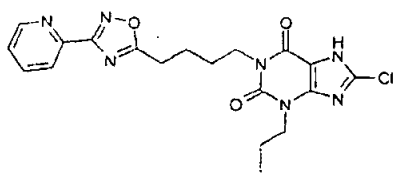
La mezcla de reacción se desgasificó con nitrógeno y después se trató con morfolina (220 ul) y tetrakis(trifenilfosfin)paladio (29 mg, 0.025 mmoles) y se agitó durante 4 hr. La mezcla de reacción se dividió entre cloroformo y HCl (2M). La fase orgánica se separó y se evaporó. El producto crudo se cargó en un SPE de aminopropilo. Las impurezas no ácidas se eluyeron con una mezcla de DCM y MeOH y el producto deseado se eluyó con 10% de AcOH en DCM. La evaporación dio el compuesto del título (77 mg).

CL/EM: m/z 369 $[MH]^+$, TR 1.96 min.

EJEMPLO 360

8-Cloro-3-propil-1-{4-[3-(2-piridinil)-1,2,4-oxadiazol-5-il]butil}-3,7-dihidro-1*H*-purina-2,6-diona

a) 8-Cloro-3-propil-1-{4-[3-(2-piridinil)-1,2,4-oxadiazol-5-il]butil}-3,7-dihidro-1*H*-purina-2,6-diona

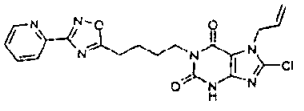


Una solución de 8-cloro-7-(2-propen-1-il)-1-{4-[3-(2-piridinil)-1,2,4-oxadiazol-5-il]butil}-3,7-dihidro-1H-purina-2,6-diona (40 mg, 0.09 mmoles) en DMF (3 ml) se trató con carbonato de potasio (15 mg, 0.11 mmoles) y 1-yodopropano (19 mg, 0.11 mmoles). La mezcla se calentó a 40°C

durante 3 hr, después a 70°C durante 3 hr adicionales. La mezcla se enfrió y se desgasificó mediante la aplicación sucesiva de vacío y nitrógeno gaseoso. La mezcla después se trató con una solución de tetrakis(trifenilfosfin)-paladio(0) (10 mg, 0.009 mmoles) y morfolina (0.1 ml, 1.2 mmoles) y después se agitó durante la noche. La mezcla se evaporó y se dividió entre cloroformo (2 ml) y agua (2 ml). La fase acuosa se extrajo con cloroformo de manera adicional (2 ml) y los compuestos orgánicos combinados se evaporaron y el residuo se disolvió en metanol (2 ml). La solución se aplicó a un SPE de aminopropilo 1g y se eluyó con metanol y después con 5% de ácido acético en metanol. Las fracciones que contenían producto se pusieron en acervo y se evaporaron y el producto se purificó adicionalmente por MDAP para revelar 8-cloro-3-propil-1-{4-[3-(2-piridinil)-1,2,4-oxadiazol-5-il]butil}-3,7-dihidro-1*H*-purina-2,6-diona (1.4 mg) como un sólido blanco.

CL/EM: m/z 430 $[MH]^+$, TR 2.84 min.

b) 8-Cloro-7-(2-propen-1-il)-1-{4-[3-(2-piridinil)-1,2,4-oxadiazol-5-il]butil}-3,7-dihidro-1*H*-purina-2,6-diona



Una suspensión de N-hidroxi-2-piridinacarboximidamida (1.15 g, 8.4 mmoles) en THF anhidro (20 ml) se trató con metóxido de sodio (0.38 g, 7.0 mmoles) y la mezcla se agitó durante 5 min. La mezcla se trató con 5-[8-

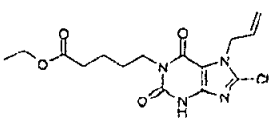
cloro-2,6-dioxo-7-(2-propen- 1-il)-2,3,6,7-tetrahidro-1H-purin-1-il]pentanoato de etilo (2 g, 5.6 mmoles) y se agitó durante aproximadamente 5 min hasta que todo el material se había disuelto. La mezcla se selló después y se calentó en un microondas a 120°C durante 15 min, después se enfrió y se dividió entre acetato de etilo (100 ml) y bicarbonato de sodio acuoso saturado (50 ml). La fase acuosa se extrajo de manera adicional con acetato de etilo (50 ml) y los compuestos orgánicos combinados se secaron ($MgSO_4$), se filtraron y se evaporaron. El producto se purificó por cromatografía instantánea usando un gradiente de elución de 1:9 de acetato de etilo/ciclohexano a acetato de etilo para revelar 8-cloro-7-(2-propen-1-il)-1-{4-[3-(2-piridinil)-1,2,4-oxadiazol-5-il]butil}-3,7-dihidro-1*H*-purina-2,6-diona (1.49 g) como un sólido blanco.

CL/EM: m/z 428 $[MH]^+$, TR 2.70 min.

De manera similar, se preparó 8-cloro-1-(3-{3-[(2,4-difluorofenil)metil]-1,2,4-oxadiazol-5-il}propil)-7-(2-propen-1-il)-3,7-dihidro-1*H*-purina-2,6-diona usando 4-[8-cloro-2,6-dioxo-7-(2-propen-1-il)-2,3,6,7-tetrahidro-1*H*-purin-1-il]butanoato de etilo.

CL/EM: m/z 463 $[MH]^+$, TR 3.09 min.

c) 5-[8-Cloro-2,6-dioxo-7-(2-propen-1-il)-2,3,6,7-tetrahidro-1*H*-purin-1-il]pentanoato de etilo



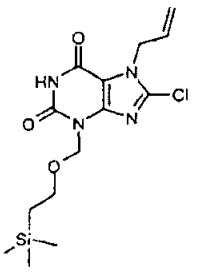
Una solución de 8-cloro-7-(2-propen-1-il)-3-({[2-(trimetilsilil)etil]oxi}metil)-3,7-dihidro-1*H*-purina-2,6-diona (10 g, 28 mmoles) en DMF (10 ml) se trató con carbonato de potasio (4.8 g, 35 mmoles) y 5-bromopentanoato de etilo (6.5 g, 31 mmoles) y después se calentó a 70°C durante 3 hr, se enfrió y se evaporó. El residuo se dividió entre acetato de etilo (100 ml) y agua (50 ml). La fase orgánica se secó ($MgSO_4$), se filtró y se evaporó y el intermediario crudo se disolvió en diclorometano (90 ml), se trató con ácido trifluoroacético (17 ml) y la mezcla se agitó a temperatura ambiente durante la noche. Se añadió tolueno (50 ml) y la mezcla se evaporó a sequedad. El producto se purificó por cromatografía instantánea usando un gradiente de elución de ciclohexano a acetato de etilo para revelar 8.65 g de 5-[8-cloro-2,6-dioxo-7-(2-propen-1-il)-2,3,6,7-tetrahidro-1*H*-purin-1-il]pentanoato de etilo como un sólido blanco.

CL/EM: m/z 355 $[MH]^+$, TR 2.75 min.

De manera similar, se preparó 4-[8-cloro-2,6-dioxo-7-(2-propen-1-il)-2,3,6,7-tetrahidro- 1H-purin-1-il]butanoato de etilo.

CL/EM: m/z 341 $[MH]^+$, TR 2.61 min.

d) 8-Cloro-7-(2-propen-1-il)-3-({[2-(trimetilsilil)etil]oxi}metil)-3,7-dihidro-1*H*-purina-2,6-diona

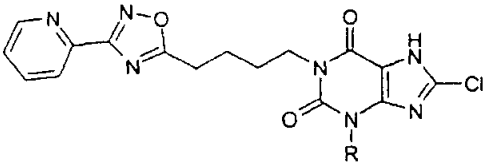


A una solución de 8-cloro-7-(2-propen-1-il)-3,7-dihidro-1*H*-purina-2,6-diona (5 g, 22.1 mmoles) en DMF (80 ml) se añadió cloruro de 2-2-(trimetilsilil)etoximetílico (4.3 ml, 24.2 mmoles) y carbonato de sodio (2.6 g, 24.2 mmoles). Depués de agitarse a temperatura ambiente durante la noche cloruro de 2-2-(trimetilsilil)etoximetílico adicional (4.3 ml, 24.2 mmoles) y carbonato de sodio (1.3 g, 12.1 mmoles) se añadieron y la agitación continuó durante 2 hr. La mezcla de reacción después se dividió entre LiCl ac. al 5% y acetato de etilo. El extracto orgánico se separó, se lavó con salmuera, se secó ($MgSO_4$) y se concentró. La purificación por cromatografía de Biotage™ usando un cartucho de sílice, eluyendo a 1:4-1:2 de acetato de etilo/ciclohexano dio el compuesto del título (3.14 g, 40%).

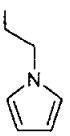
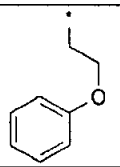
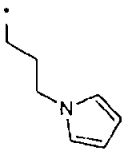
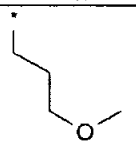
m/z 374 [MNH_4^+]

Los siguientes compuestos (cuadro 23) se prepararon por un método análogo al del ejemplo 360, a partir de 8-cloro-7-(2-propen-1-il)-1-{4-[3-(2-piridinil)-1,2,4-oxadiazol-5-il]butil}-3,7-dihidro-1*H*-purina-2,6-diona y el agente alquilante apropiado.

CUADRO 23

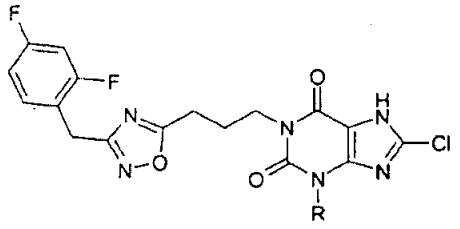


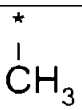
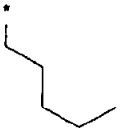
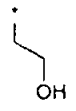
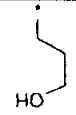
Ejemplo	R=	Nombre	Rend. (mg)	m/z	TR (min)
361		8-cloro-1-{4-[3-(2-piridinil)-1,2,4-oxadiazol-5-il]butil}-3,7-dihidro-1H-purino-2,6-diona	25	388	2.37
362		8-cloro-3-metil-1-{4-[3-(2-piridinil)-1,2,4-oxadiazol-5-il]butyl}-3,7-dihidro-1H-purino-2,6-diona	1.7	402	2.53
363		8-cloro-3-etil-1-{4-[3-(2-piridinil)-1,2,4-oxadiazol-5-il]butyl}-3,7-dihidro-1H-purino-2,6-diona	1.4	416	2.66
364		8-cloro-3-(fenilmetil)-3-(fenilmetil)-1-{4-[3-(2-piridinil)-1,2,4-oxadiazol-5-il]butil}-3,7-dihidro-1H-purino-2,6-diona	1.3	478	3.09
365		8-cloro-3-(2-metilpropil)-1-{4-[3-(2-piridinil)-1,2,4-oxadiazol-5-il]butil}-3,7-dihidro-1H-purino-2,6-diona	2.0	444	2.99
366		8-cloro-3-(3-metilbutil)-1-{4-[3-(2-piridinil)-1,2,4-oxadiazol-5-il]butil}-3,7-dihidro-1H-purino-2,6-diona	1.6	458	3.21
367		8-cloro-3-(2-feniletil)-1-{4-[3-(2-piridinil)-1,2,4-oxadiazol-5-il]butil}-3,7-dihidro-1H-purino-2,6-diona	2.1	492	3.18
368		8-cloro-1-{4-[3-(2-piridinil)-1,2,4-oxadiazol-5-il]butil}-3-(4,4,4-trifluorobutil)-3,7-dihidro-1H-purino-2,6-diona	2.1	498	3.07

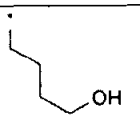
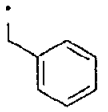
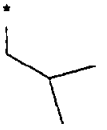
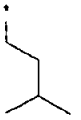
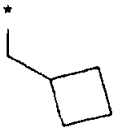
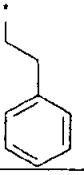
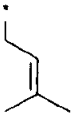
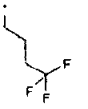
369		8-cloro-1-{4-[3-(2-piridinil)-1,2,4-oxadiazol-5-il]buti})-3-[2-(1H-pirrol-1-il)etil]-3,7-dihidro-1H-purino-2,6-diona	2.7	481	2.89
370		8-cloro-3-[2-(feniloxi)etil]-1-(4-[3-(2-piridinil)-1,2,4-oxadiazol-5-il]butil]-3,7-dihidro-1H-purino-2,6-diona	1.7	508	3.11
371		8-cloro-1-{4-[3-(2-piridinil)-1,2,4-oxadiazol-5-il]butyl}-3-[3-(1H-pirrol-1-il)propil]-3,7-dihidro-1H-purino-2,6-diona	2.1	495	3.01
372		8-cloro-3-(2-propen-1-il)-1-{4-[3-(2-piridinil)-1,2,4-oxadiazol-5-il]butil}-3,7-dihidro-1H-purino-2,6-diona	1.3	428	2.73
373		8-cloro-3-[3-(metiloxi)propil]-1-{4-[3-(2-piridinil)-1,2,4-oxadiazol-5-il]butil}-3,7-dihidro-1H-purino-2,6-diona	1.0	460	2.65

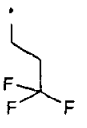
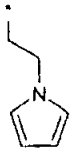
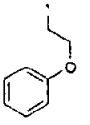
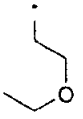
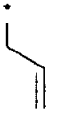
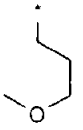
Los siguientes compuestos (cuadro 24) se prepararon por un método análogo al del ejemplo 360, a partir de 8-cloro-1-(3-{3-[(2,4-difluorofenil)metil]-1,2,4-oxadiazol-5-il}propil)-7-(2-propen-1-il)-3,7-dihidro-1*H*-purina-2,6-diona y el agente alquilante apropiado.

CUADRO 24



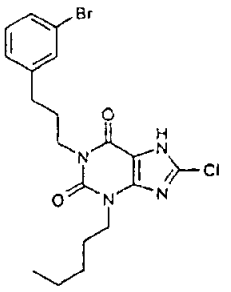
Ejemplo	R=	Nombre	Rend. (mg)	m/z	TR (min)
374		8-cloro-1-(3-{3-[(2,4-difluorofenil)-(metil)-1,2,4-oxadiazol-5-il}propil)-3,7-dihidro-1H-purino-2,6-diona	2.5	423	2.71
375		8-cloro-1-(3-{3-[(2,4-difluorofenil)metil]-1,2,4-oxadiazol-5-il}propil)-3-metil-3,7dihidro-1H-purino-2,6-diona	1.7	437	2.92
376		8-cloro-1-(3-{3-[(2,4-difluorofenil)metil]-1,2,4-oxadiazol-5-il}propil)-3metil-3,7-dihidro-1H-purino-2,6-diona	1.4	451	3.06
377		8-cloro-1-(3-{3-[(2,4-difluorofenil)metil]-1,2,4-oxadiazol-5-il}propil)-3-propil-3,7-dihidro-1H-purino-2,6-diona	2.2	465	3.22
378		8-cloro-1-(3-{3-[(2,4-difluorofenil)metil]-1,2,4-oxadiazol-5-il}propil)-3-pentil-3,7-dihidro-1H-purino-2,6-diona	2.6	493	3.54
379		8-cloro-1-(3-{3-[(2,4-difluorofenil)metil]-1,2,4-oxadiazol-5-il}propil)-3-(2-hidroxietil)-3,7-dihidro-1H-purino-2,6-diona	2.7	467	2.72
380		8-cloro-1-(3-{3-[(2,4-difluorofenil)metil]-1,2,4-oxadiazol-5-il}propil)-3-(3-hidroxipropil)-3,7-dihidro-1H-purino-2,6-diona	2.0	481	2.77

381		8-cloro-1-(3-{3-[(2,4-difluorofenil)metil]-1,2,4-oxadiazol-5-il}propil)-3-(4-hidroxibutil)-3,7-dihidro-1H-purino-2,6-diona	1.4	495	2.80
382		8-cloro-1-(3-{3-[(2,4-difluorofenil)metil]-1,2,4-oxadiazol-5-il}propil)-3-(fenilmetil)-3,7-dihidro-1H-purino-2,6-diona	1.6	513	3.43
383		8-cloro-3-(ciclopropilmetil)-1-(3-{3-[(2,4-difluorofenil)metil]-1,2,4-oxadiazol-5-il}propil)-3,7-dihidro-1H-purino-2,6-diona	1.8	477	3.30
384		8-cloro-1-(3-{3-[(2,4-difluorofenil)metil]-1,2,4-oxadiazol-5-il}propil)-3-(2-metilpropil)-3,7-dihidro-1H-purino-2,6-diona	3.5	479	3.36
385		8-cloro-1-(3-{3-[(2,4-difluorofenil)metil]-1,2,4-oxadiazol-5-il}propil)-3-(3-metilbutil)-3,7-dihidro-1H-purino-2,6-diona	3.1	493	3.53
386		8-cloro-3-(ciclobutilmetil)-1-(3-{3-[(2,4-difluorofenil)metil]-1,2,4-oxadiazol-5-il}propil)-3,7-dihidro-1H-purino-2,6-diona	2.2	491	3.45
387		8-cloro-1-(3-{3-[(2,4-difluorofenil)metil]-1,2,4-oxadiazol-5-il}propil)-3-(2-feniletil)-3,7-dihidro-1H-purino-2,6-diona	2.4	527	3.50
388		8-cloro-1-(3-{3-[(2,4-difluorofenil)metil]-1,2,4-oxadiazol-5-il}propil)-3-(3-metil-2-buten-1-il)-3,7-dihidro-1H-purino-2,6-diona	3.1	491	3.46
389		8-cloro-1-(3-{3-[(2,4-difluorofenil)metil]-1,2,4-oxadiazol-5-il}propil)-3-(4,4,4-trifluorobutil)-3,7-dihidro-1H-purino-2,6-diona	3.0	533	3.39

390		8-cloro-1-(3-{3-[(2,4-difluorofenil)metil]-1,2,4-oxadiazol-5-il}propil)-3-(3,3,3-trifluoropropil)-3,7-dihidro-1H-purino-2,6-diona	2.7	519	3.34
391		8-cloro-1-(3-{3-[(2,4-difluorofenil)metil]-1,2,4-oxadiazol-5-il}propil)-3-[2-(1H-pirrol-1-il}propil)-3-[2-1H-pirrol-1-il)etil]-3,7-dihidro-1H-purino-2,6-diona	2.0	516	3.27
392		8-cloro-1-(3-{3-[(2,4-difluorofenil)metil]-1,2,4-oxadiazol-5-il}propil)-3-[2-(feniloxi)etil]-3,7-dihidro-1H-purino-2,6-diona	1.6	543	3.44
393		8-cloro-1-(3-{3-[(2,4-difluorofenil)metil]-1,2,4-oxadiazol-5-il}propil)-3-[2-(etiloxi)etil]-3,7-dihidro-1H-purino-2,6-diona	2.8	495	3.11
394		8-cloro-1-(3-{3-[(2,4-difluorofenil)metil)-1,2,4-oxadiazol-5-il}propil)-3-[2-(metiloxi)etil]-3,7-dihidro-1H-purino-2,6-diona	2.6	481	2.98
395		8-cloro-1-(3-{3-[(2,4-difluorofenil)metil]-1,2,4-oxadiazol-5-il}propil)-3-(2-propen-1-il)-3,7-dihidro-1H-purino-2,6-diona	3.1	463	3.17
396		8-cloro-1-(3-{3-[(2,4-difluorofenil)metil]-1,2,4-oxadiazol-5-il}propil)-3-[3-(metiloxi)propil]-3,7-dihidro-1H-purino-2,6-diona	2.1	495	3.04
397		8-cloro-3-ciclopentil-1-(3-{3-[(2,4-difluorofenil)metil]-1,2,4-oxadiazol-5-il}propil)-3,7-dihidro-1H-purino-2,6-diona	2.5	491	3.52

EJEMPLO 398

1-[3-(3-Bromofenil)propil]-8-cloro-3-pentil-3,7-dihidro-1*H*-purina-2,6-diona



Una solución de 3-(3-bromofenil)-propan-1-ol (1.627 g, 7.56 mmoles) en THF (65 ml) se trató con 8-cloro-3-pentil-7-(2-propen-1-il)-3,7-dihidro-1*H*-purina-2,6-diona (2.04 g, 6.87 mmoles) bajo nitrógeno. PPh_3 (2.164 g, 8.25 mmoles) se añadió a la mezcla agitada después de 2 min y después de 6 min adicionales, DBAD (1.9 g, 8.25 mmoles) se añadió en una porción. La mezcla se agitó durante 2.5 hr y después se dejó reaccionar durante 16 hr. La mezcla se desgasificó aplicando un vacío y después se introdujo nitrógeno. $Pd(PPh_3)_4$ (794 mg, 0.69 mmoles) se añadió y la mezcla se desgasificó una vez más. Se añadió morfolina (6 ml, 68.8 mmoles) y la mezcla se agitó bajo nitrógeno durante 6 hr. La mezcla se dividió entre HCl 2M (ac.) y EtOAc. La capa orgánica se separó, se lavó con salmuera, se secó ($MgSO_4$) y se concentró. El residuo se recogió en MeOH y se purificó haciendo pasar un SPE de aminopropilo, el producto se eluyó con 2-5% de AcOH/MeOH. El compuesto del título se obtuvo como un sólido blanquecino (2.48 g, 79%).

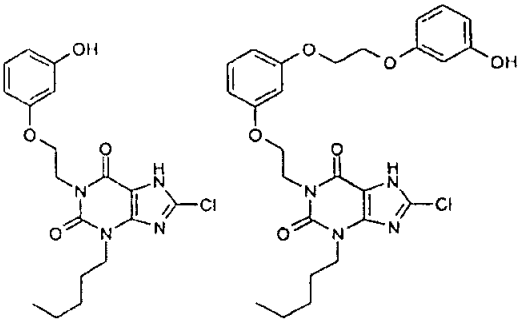
CL/EM: m/z 455, 453 $[MH]^+$, TR 3.85 min.

EJEMPLO 399

8-Cloro-1-{2-[(3-hidroxifenil)oxi]etil}-3-pentil-3,7-dihidro-1*H*-purina-2,6-diona y

EJEMPLO 400

8-cloro-1-(2-{[3-({2-[(3-hidroxifenil)oxi]etil}oxi)fenil]oxi}etil)-3-pentil-3,7-dihidro-1*H*-purina- 2,6-diona



Una solución de 2-(2-hidroxietil)-resorcinol (1.156 g, 7.5 mmoles) en THF (60 ml) se trató con 8-cloro-3-pentil-7-(2-propen-1-il)-3,7-dihidro-1*H*-purina-2,6-diona (2.016 g, 6.79 mmoles) bajo nitrógeno. PPh_3 (2.138 g, 8.15 mmoles) se añadió a la mezcla agitada después de 4 min y, después de 8 min adicionales, DBAD (1.88 g, 8.16 mmoles) se añadió en una porción. La mezcla se agitó durante 1 hr 50 minutos y después se dejó reaccionar durante 16 hr. La mezcla se desgasificó aplicando un vacío y después se introdujo nitrógeno. Se añadió $Pd(PPh_3)_4$ (785 mg, 0.68 mmoles) y la mezcla se desgasificó una vez más. Se añadió morfolina (5.9 ml, 67.7 mmoles) y la mezcla se agitó bajo nitrógeno durante 4.5 hr. La mezcla se dividió entre HCl 2M (ac.) y EtOAc. La capa orgánica se separó, se lavó con salmuera, se secó ($MgSO_4$) y se concentró. El residuo se recogió en MeOH y se purificó

haciendo pasar un SPE de aminopropilo, el gradiente de elución de producto con 2-5% de AcOH/MeOH. Las fracciones que contenían producto se evaporaron para dar una espuma amarillo pálido (2.39 g) y una goma amarillo pálido (213 mg). La espuma se disolvió en diclorometano (50 ml) y se hizo pasar a través de una frita hidrofóbica. La solución se evaporó y se secó bajo vacío para dar 8-cloro-1-{2-[(3-hidroxifenil)oxi]etil}-3-pentil-3,7-dihidro-1*H*-purina-2,6-diona como un sólido blanco (1.919 g, que contenía 15% de 8-cloro-1-(2-{[3-({2-[(3-hidroxifenil)oxi]etil}oxi)fenil]oxi}etil)-3-pentil-3,7-dihidro-1*H*-purina-2,6- diona).

La goma se purificó por MDAP para dar 8-cloro-1-{2-[(3-hidroxifenil)oxi]etil}-3-pentil-3,7-dihidro-1*H*-purina-2,6-diona como un sólido blanco (126 mg).

CL/EM: m/z 393 $[MH]^+$, TR 3.23min

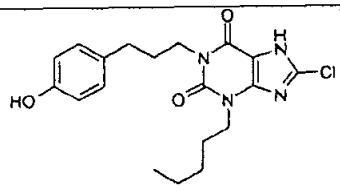
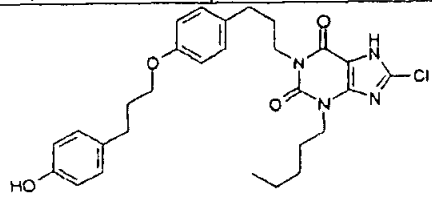
así como

8-cloro-1-(2-{[3-({2-[(3-hidroxifenil)oxi]etil}oxi)fenil]oxi}etil)-3-pentil-3,7-dihidro-1*H*-purina-2,6-diona como un sólido amarillo pálido (38 mg).

CL/EM: m/z 529 $[MH]^+$, TR 3.62 min.

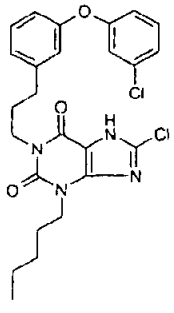
Los siguientes compuestos (cuadro 25) se prepararon usando un método análogo al de 8-cloro-1-{2-[(3-hidroxifenil)oxi]etil}-3-pentil-3,7-dihidro-1*H*-purina-2,6-diona anterior, a partir del alcohol correspondiente.

CUADRO 25

Ejemplo	Estructura	Rend. (mg)	CL/EM:
401	 8-cloro-1-[3-(4-hidroxifenil)propil]-3-pentil-3,7-dihidro-1H-purino-2,6-diona	58	m/z 391 $[MH]^+$ TR 3.38 min
402	 8-cloro-1-[3-(4-{[3-(4-hidroxifenil)propil]oxi}fenil)propil]-3-pentil-3,7-dihidro-1H-purino-2,6-diona	12	m/z 525 $[MH]^+$ TR 4.07 min

EJEMPLO 403

8-Cloro-1-(3-{3-[(3-clorofenil)oxi]fenil}propil)-3-pentil-3,7-dihidro-1*H*-purina-2,6-diona



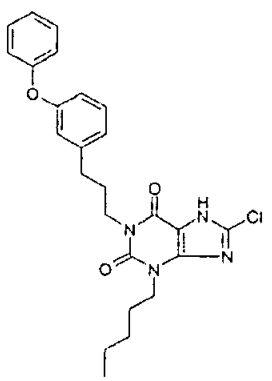
1-[3-(3-Bromofenil)propil]-8-cloro-3-pentil-3,7-dihidro-1*H*-purina-2,6-diona (100 mg, 0.22 mmoles) se disolvió en dioxano (0.75 ml). Yoduro de cobre (1) (9 mg, 0.05 mmoles), Clorhidrato de N,N-dimetilglicina (9 mg, 0.06

mmoles), carbonato de cesio (215 mg, 0.66 mmoles) y 3-clorofenol (52 mg, 0.4 mmoles) se añadieron a la solución. La mezcla se calentó bajo irradiación de microondas a 200°C durante 10 min, seguido por otros 10 min a 200°C después de lo cual la mezcla enfriada se filtró y el residuo se lavó con EtOAc y MeOH. El filtrado y lavados se combinaron y se evaporaron bajo presión reducida para dejar un sólido rojo/café. El sólido se dividió entre DCM y agua. Las fases se separaron by frita hidrofóbica y la fase orgánica se evaporó bajo presión reducida para dejar un sólido. El sólido se purificó por MDAP para dar el compuesto del título como un sólido/goma amarilla (27 mg, 24%).

CL/EM: m/z 501 $[MH]^+$, TR 4.25 min.

EJEMPLO 404

8-Cloro-3-pentil-1-{3-[3-(feniloxi)fenil]propil}-3,7-dihidro-1*H*-purina-2,6-diona



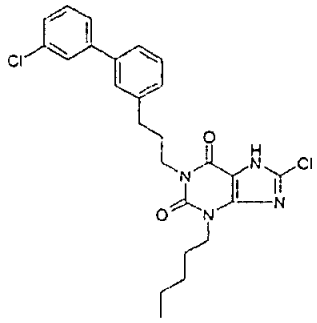
1-[3-(3-Bromofenil)propil]-8-cloro-3-pentil-3,7-dihidro-1*H*-purina-2,6-diona (100 mg, 0.22 mmoles), yoduro de cobre (1) (4 mg, 0.02 mmoles), clorhidrato de N,N-dimetilglicina (9 mg, 0.06 mmoles) carbonato de cesio (144

mg, 0.44 mmoles) y fenol (31 mg, 0.33 mmoles) se colocaron en dioxano (0.44 ml). Después la mezcla se calentó en el microondas a 150°C durante 3.3 min, después cantidades adicionales de carbonato de cesio (72 mg, 0.22 mmoles), yoduro de cobre (1) (6 mg, 0.03 mmoles) y dioxano (0.44 ml) se añadieron a la mezcla y se calentó en el microondas a 170°C durante 10 min, seguido por otros 10 min a 200°C. La mezcla enfriada se filtró y el residuo se lavó con EtOAc. El filtrado y los lavados se combinaron y se evaporaron bajo presión reducida para dejar una goma café oscuro. La goma se purificó por MDAP para dar el compuesto del título como un sólido color crema pálido (44 mg, 42%).

CL/EM: m/z 467 $[MH]^+$, TR 4.14 min.

EJEMPLO 405

8-Cloro-1-[3-(3'-cloro-3-bifenilil)propil]-3-pentil-3,7-dihidro-1*N*-purina-2,6-diona



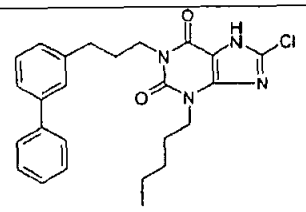
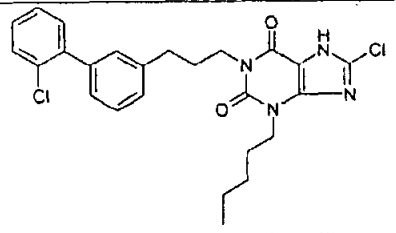
Una mezcla de 1-[3-(3-bromofenil)propil]-8-cloro-3-pentil-3,7-dihidro-1*H*-purina-2,6-diona (100 mg, 0.22 mmoles) y ácido 3-clorofeniborónico (35 mg, 0.22 mmoles) se agitó en isopropanol (0.35 ml). Una

solución de carbonato de sodio (70 mg, 0.66 mmoles) en agua (0.35 ml) se añadió a la mezcla seguido por 10% de paladio sobre carbón (6 mg, tipo Degussa E101 NE/W). La mezcla se calentó en el microondas a 160°C durante 10 min, después se filtró (filtro de fibra de vidrio) y los residuos se lavaron con IPA. El filtrado y los lavados se combinaron y se evaporaron bajo presión reducida para dejar una goma. La goma se dividió entre DCM y agua. La fase orgánica se separó y la fase acuosa se extrajo con EtOAc. Las fases orgánicas combinadas se secaron ($MgSO_4$) y se concentraron para dejar una espuma. La espuma se purificó por MDAP para dar el compuesto del título como una goma incolora (40 mg, 37%).

CL/EM: m/z 485 $[MH]^+$, TR 4.27 min.

Los siguientes compuestos (cuadro 26) se prepararon usando un método análogo al de 8-cloro-1-[3-(3'-cloro-3-bifenilil)propil]-3-pentil-3,7-dihidro-1*H*-purina-2,6-diona (ejemplo 405) anterior, a partir del ácido borónico correspondiente, excepto que el análogo de 2-clorofenilo se calentó en el microondas a 160°C durante 10 min dos veces, mientras que el tratamiento se usó ácido clorhídrico 1M en lugar de agua. También se omitió la extracción con EtOAc.

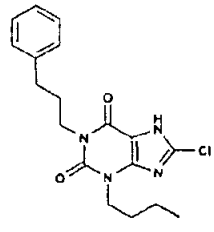
CUADRO 26

Ejemplo	Estructura	Rend. (mg)	CL/EM:
406	 1-[3-(3-bifenilil)propil]-8-cloro-3-pentil-3,7-dihidro-1H-purino-2,6-diona	51	m/z 451 $[MH]^+$ TR 4.02 min
407	 8-cloro-1-[3-(2'-cloro-3-bifenilil)propil]-3-pentil-3,7-dihidro-1H-purino-2,6-diona	56	m/z 485 $[MH]^+$ TR 4.15 min

EJEMPLO 408

3-Butil-8-cloro-1-(3-fenilpropil)-3,7-dihidro-1*H*-purina-2,6-diona

a) 3-Butil-8-cloro-1-(3-fenilpropil)-3,7-dihidro-1*H*-purina-2,6-diona



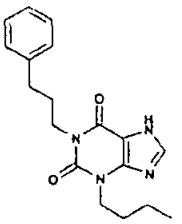
3-Butil-1-(3-fenilpropil)-3,7-dihidro-1*H*-purina-2,6-diona (100 mg, 0.31 mmoles) y NCS (41 mg, 0.31 mmoles) se suspendieron en MeCN (5 ml) y se calentaron a 120°C bajo irradiación de microondas durante 10 min. La

mezcla de reacción se concentró bajo presión reducida y el compuesto del título se aisló usando CLAR.

^{1}H RMN ($CDCl_3$) δ: 0.96 (3H, t), 1.37-1.43 (2H, m), 1.70-1.78 (2H, m), 2.00-2.09 (2H, m), 2.73 (2H, t), 4.08 (2H, t), 4.14 (2H, t), 7.13-7.26 (5H, m), 12.6 (1H, br.s).

CL/EM: m/z 361 $[MH]^+$.

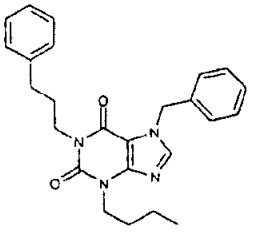
b) 3-Butil-1-(3-fenilpropil)-3,7-dihidro-1*H*-purina-2,6-diona



3-Butil-7-(fenilmetil)-1-(3-fenilpropil)-3,7-dihidro-1*H*-purina-2,6-diona (0.6 g, 1.44 mmoles) se disolvió en ácido acético (35 ml), se añadió 20% de hidróxido de paladio sobre carbón (0.366 g) y la mezcla se agitó bajo hidrógeno (a 3.51 kg/cm^2) durante la noche. El catalizador se removió por filtración a través de Celite® y se lavó con ácido acético. El filtrado se concentró bajo presión reducida y el compuesto del título se aisló usando CLAR (0.385 g, 82%).

CL/EM: m/z 327 $[MH]^+$.

c) 3-Butil-7-(fenilmetil)-1-(3-fenilpropil)-3,7-dihidro-1*H*-purina-2,6-diona

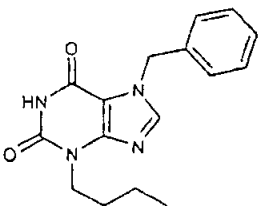


7-Bencil-3-butil-3,7-dihidro-1*H*-purina-2,6-diona (0.5 g, 1.68 mmoles) y carbonato de potasio (0.347 g, 2.5 mmoles) se suspendieron en DMF (20 ml), se añadió (3-bromopropil)benceno (390 mg, 1.96 mmoles). La mezcla de reacción se agitó a temperatura ambiente durante la noche. La mezcla de reacción se evaporó a sequedad y el residuo se dividió entre agua y acetato de etilo. La capa orgánica se lavó con agua, seguido por salmuera, se secó sobre sulfato de sodio anhidro y se concentró bajo presión reducida para dar el compuesto del título.

^{1}H RMN ($CDCl_3$) δ: 0.95 (3H, t), 1.34-1.43 (2H, m), 1.68-1.76 (2H, m), 1.98-2.07 (2H, m), 2.71 (2H, t), 4.05-4.10 (4H, m), 5.49 (2H, s), 7.19-7.24 (5H, m), 7.33-7.38 (5H, m), 7.52 (1H, s).

CL/EM: m/z 417 $[MH]^+$.

d) 7-Bencil-3-butil-3,7-dihidro-1*H*-purina-2,6-diona



7-Bencil-3,7-dihidro-1*H*-purina-2,6-diona (17.14 g, 70.8 mmoles) [Synthetic Communications, 20(16), 2459-2467, 1990] y carbonato de potasio (11.43 g, 82.8 mmoles) se suspendieron en DMF (400 ml) a 40°C. Después de agitar durante treinta minutos, yoduro de butilo (8.76 ml, 77.0 mmoles) se añadió, y la mezcla se agitó a 40°C durante la noche. Se añadió ácido acético acuoso al 50% (60 ml) y la solución se concentró bajo presión reducida. El residuo se suspendió en agua (500 ml), y el productos se extrajeron en cloroformo. Los compuestos orgánicos se recogieron, se concentraron y el producto se aisló usando cromatografía instantánea eluyendo con 1% de metanol en diclorometano (9.49 g, 45%).

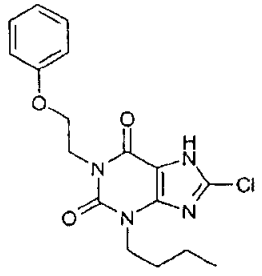
^{1}H RMN ($CDCl_3$) δ: 0.95 (3H, t), 1.34-1.41 (2H, m), 1.70-1.78 (2H, m), 4.05 (2H, t), 5.46 (2H, s), 7.31-7.40 (5H, m), 7.56 (1H, s), 8.21 (1H, br.s).

CL/EM: m/z 299 $[MH]^+$.

EJEMPLO 409

3-Butil-8-cloro-1-[2-(feniloxi)etil]-3,7-dihidro-1*H*-purina-2,6- diona

a) 3-Butil-8-cloro-1-[2-(feniloxi)etil]-3,7-dihidro-1*H*-purina-2,6-diona

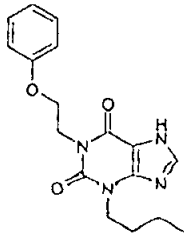


El compuesto del título se preparó usando el procedimiento para 3-butil-8-cloro-1-(3-fenilpropil)-3,7-dihidro-1*H*-purina-2,6-diona, a partir de 3-butil-1-[2-(feniloxi)etil]-3,7-dihidro-1*H*-purina-2,6-diona y NCS.

^{1}H RMN ($CDCl_3$) δ: 0.95 (3H, t), 1.36-1.45 (2H, m), 1.71-1.79 (2H, m), 4.11 (2H, t), 4.29 (2H, t), 4.54 (2H, t), 6.87-6.94 (3H, m), 7.21-7.27 (2H, m), 13.10 (1H, br.s).

CL/EM: m/z 363 $[MH]^+$.

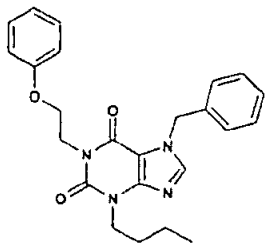
b) 3-Butil-1-[2-(feniloxi)etil]-3,7-dihidro-1*H*-purina-2,6-diona



El compuesto del título se preparó usando el procedimiento delineado para 3-butil-1-(3-fenilpropil)-3,7-dihidro-1*H*-purina-2,6-diona, a partir de 3-butil-7-(fenilmetil)-1-[2-(feniloxi)etil]-3,7-dihidro-1*H*-purina-2,6-diona.

CL/EM: m/z 329 $[MH]^+$.

c) 3-Butil-7-(fenilmetil)-1-[2-(feniloxi)etil]-3,7-dihidro-1*H*-purina-2,6-diona



El compuesto del título se preparó usando el procedimiento delineado para 3-butil-7-(fenilmetil)-i-(3-fenilpropil)-3,7-dihidro-1*H*-purina-2,6-diona, a partir de 7-bencil-3-butil-3,7-dihidro-1*H*-purina-2,6-diona y éter 2-bromoetilfenílico.

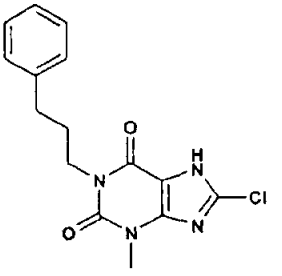
^1H RMN ($CDCl_3$) δ: 0.95 (3H, t), 1.35-1.44 (2H, m), 1.69-1.78 (2H, m), 4.07-4.11 (2H, m), 4.26 (2H, t), 4.434 (2H, t), 5.49 (2H, s), 6.87-7.38 (10H, m), 7.55 (1H, s).

CL/EM: m/z 419 $[MH]^+$.

EJEMPLO 410

8-Cloro-3-metil-1-(3-fenilpropil)-3,7-dihidro-1*H*-purina-2,6- diona

a) 8-Cloro-3-metil-1-(3-fenilpropil)-3,7-dihidro-1*H*-purina-2,6-diona

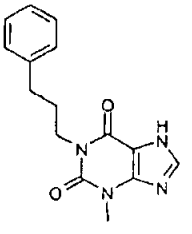


El compuesto del título se preparó usando el procedimiento delineado para 3-butil-8-cloro-1-(3-fenilpropil)-3,7-dihidro-1*H*-purina-2,6-diona, a partir de 3-metil-1-(3-fenilpropil)-3,7-dihidro-1*H*-purina-2,6-diona y NCS.

^{1}H RMN ($CDCl_3$) δ: 2.01-2.12 (2H, m), 2.74 (2H, t), 3.57 (3H, s), 4.14 (2H, t), 6.99-7.24 (5H, m), 12.5 (1H, br.s).

CL/EM: m/z 319 $[MH]^+$.

b) 3-Metil-1-(3-fenilpropil)-3,7-dihidro-1*H*-purina-2,6-diona

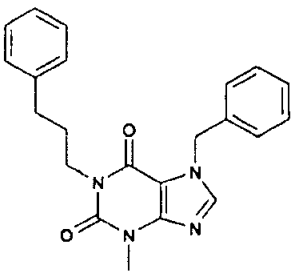


El compuesto del título se preparó usando el procedimiento

delineado para 3-butil-1-(3-fenilpropil)-3,7-dihidro-1*H*-purina-2,6-diona, a partir de 3-metil-7-(fenilmetil)-1-(3-fenilpropil)-3,7-dihidro-1*H*-purina-2,6-diona.

CL/EM: m/z 285 $[MH]^+$.

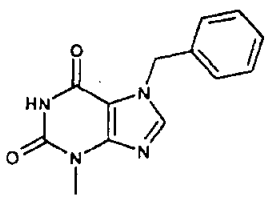
c) 3-Metil-7-(fenilmetil)-1-(3-fenilpropil)-3,7-dihidro-1*H*-purina-2,6-diona



El compuesto del título se preparó usando el procedimiento delineado para 3-butil-7-(fenilmetil)-1-(3-fenilpropil)-3,7-dihidro-1*H*-purina-2,6-diona, a partir de 3-metil-7-(fenilmetil)-3,7-dihidro-1*H*-purina-2,6-diona y (3-bromopropil)benceno.

CL/EM: m/z 375 $[MH]^+$.

d) 3-Metil-7-(fenilmetil)-3,7-dihidro-1*H*-purina-2,6-diona



El compuesto del título se preparó usando el procedimiento

descrito para 7-bencil-3-butil-3,7-dihidro-1*H*-purina-2,6-diona usando yoduro de metilo (0.28 ml, 4.46 mmoles). La purificación se logró por trituración. El producto se aisló como un sólido, insoluble en cloroformo y agua (0.334 g, 57%).

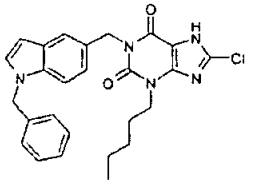
^{1}H RMN (DMSO-d_6) δ: 3.34 (3H, s), 5.44 (2H, s), 7.26-7.37 (5H, m), 8.21 (1H, s), 11.13 (1H, s).

CL/EM: m/z 257 $[MH]^+$.

EJEMPLO 411

8-Cloro-3-pentil-1-{[1-(fenilmetil)-1*H*-indol-5-il]metil}-3,7-dihidro-1*H*-purina-2,6-diona

a) 8-Cloro-3-pentil-1-{[1-(fenilmetil)-1*H*-indol-5-il]metil}-3,7-dihidro-1*H*-purina-2,6-diona



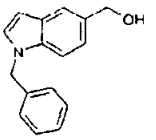
8-Cloro-3-pentil-3,7-dihidro-1*H*-purina-2,6-diona (156 mg, 0.5 mmoles) se disolvió en THF anhidro (5 ml) bajo nitrógeno y se añadió [1-(fenilmetil)-1*H*-indol-5-il]metanol (138 mg, 0.58 mmoles). Después de varios minutos, se añadió trifenilfosfina (168 mg, 0.63 mmoles) seguido 5-10 min más tarde por DBAD (155 mg, 0.67 mmoles) y la solución se agitó durante 18 hr. La mezcla se desgasificó aplicando un vacío y después se introdujo

590

nitrógeno. Se añadió $Pd(PPh_3)_4$ (63 mg, 0.054 mmoles) y la mezcla se desgasificó una vez más. Morfolina (0.461 ml, 5.3 mmoles) se añadió y la mezcla se agitó bajo nitrógeno durante 24 hr. Una cantidad adicional de $Pd(PPh_3)_4$ (58 mg, 0.05 mmoles) se añadió y la mezcla se agitó bajo nitrógeno durante 96 hr. La mezcla se diluyó con EtOAc y se lavó con HCl 2M (5 ml), después con salmuera (15 ml), se secó ($MgSO_4$) y se concentró. El material crudo se purificó por un SPE de aminopropilo (eluyente MeOH para lavar las impurezas, después con 3-4% de AcOH/MeOH). Las fracciones de producto se combinaron y se concentraron para dar el compuesto del título como un sólido blanco (43 mg, 17%).

CL/EM: m/z 476 $[MH]^+$, TR 3.78 min.

b) [1-(Fenilmetil)-1*H*-indol-5-il]metanol



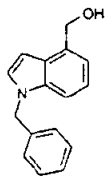
1-(Fenilmetil)-1*H*-indol-5-carboxilato de metilo (1.17 g, 4.4 mmoles) se disolvió en THF anhidro bajo nitrógeno y se enfrió a -5°C. Hidruro de litio-aluminio 1M en éter dietílico (4.0 ml) se añadió lentamente. El baño de enfriamiento se removió y la mezcla de reacción se dejó durante la noche a temperatura ambiente. La reacción se extinguió mediante la adición secuencial de agua (0.15 ml), NaOH al 15% (0.15 ml) seguido por agua (0.45 ml), después se añadieron acetato de etilo y sulfato de sodio y la mezcla se

agitó durante 0.5 hr. El material insoluble se filtró y se lavó bien con acetato de etilo. El filtrado se concentró bajo vacío para dar el compuesto del título como un sólido color crema que se oscureció en reposo (1.04 g, 100%).

CL/EM: m/z 238 $[MH]^+$, TR 3.03 min.

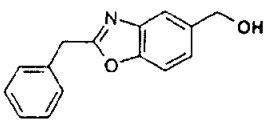
Los siguientes alcoholes se prepararon por reducción del éster metílico correspondiente de una manera similar:

[1-(Fenilmetil)-1*H*-indol-4-il]methanol



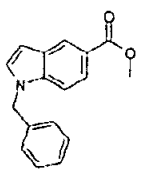
CL/EM: m/z 238 $[MH]^+$, TR 3.03 min.

[2-(Fenilmetil)-1,3-benzoxazol-4-il]metanol



CL/EM: m/z 240 $[MH]^+$, TR 2.02 min.

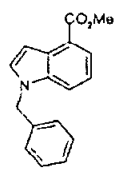
c) 1-(Fenilmetil)-1*H*-indol-5-carboxilato de metilo



1*H*-indol-5-carboxilato de metilo (1.0 g, 5.7 mmoles) se disolvió en DMF anhidro bajo nitrógeno y se enfrió a 2°C. Se añadió hidruro de sodio (0.25 g, 6.3 mmoles, 60% en parafina). Después de 0.5 hr, se añadió bromuro de bencilo (0.75 ml, 6.0 mmoles) y la mezcla de reacción se agitó durante 4 hr a temperatura ambiente, después se dejó durante la noche. La mezcla de reacción se vació en agua (50 ml) y acetato de etilo (10 ml). La fase acuosa se extrajo de manera adicional con acetato de etilo (50 ml). Las fases orgánicas combinadas se lavaron con amoniaco dil., después salmuera, se secó ($MgSO_4$) y se concentró bajo vacío. El producto crudo se purificó sobre un Si SPE 50g (gradiente de elución ciclohexano/acetato de etilo 8% a 16%). Las fracciones pertinentes se concentraron bajo vacío para dar el compuesto del título como un sólido blanco (1.17 g, 77%)

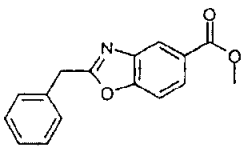
CL/EM: m/z 266 $[MH]^+$, TR 3.60 min.

1-(Fenilmetil)-1*H*-indol-4-carboxilato de metilo se preparó de una manera similar



CL/EM: m/z 266 $[MH]^+$, TR 3.58 min.

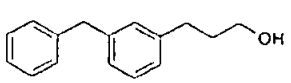
2-(Fenilmetil)-1,3-benzoxazol-5-carboxilato de metilo



Ortoformiato de trimetilbencilo (1.34 g, 6.8 mmoles) se disolvió en metanol (2 ml) y hidoxibenzoato de metil-3-amino (0.56 g, 3.35 mmoles) se añadió seguido por ácido clorhídrico concentrado (9.1 ml). La mezcla se agitó a reflujo durante 4.75 hr, se dejó enfriar y se evaporó bajo vacío. El residuo se dividió entre éter dietílico (10 ml) y solución de NaOH 2M (5 ml). La fase orgánica se lavó con agua (5 ml) y las fases acuosas combinadas se volvieron a extraer con éter (10 ml). Las fases orgánicas combinadas se secaron ($MgSO_4$) y se concentraron bajo vacío para dejar un aceite anaranjado (1.37 g). El producto crudo se purificó sobre sílice (40 g SPE, gradiente de elución ciclohexano/acetato de etilo 0-100%) para dar el compuesto del título como un sólido blanco (0.72 g, 80%).

CL/EM: m/z 268 $[MH]^+$, TR 3.27 min.

3-[3-(Fenilmetil)fenil]-1-propanol



Acido 3-[3-(fenilcarbonil)fenil]propanoico (491 mg, 1.96 mmoles) se disolvió en THF anhidro bajo nitrógeno y se enfrió a 0°C. $LiAlH_4$ 1M en éter (2.13 ml) se añadió lentamente y la mezcla de reacción se agitó a temperatura

ambiente durante 20 hr. La reacción se enfrió en hielo y se añadió tetrahidrofurano (5 ml) y solución de $LiAlH_4$ 1 M en éter (2.2 ml). La mezcla de reacción se calentó a reflujo durante 7 hr después se dejó a temperatura ambiente durante 3 días. La reacción se extinguió secuencialmente con agua (0.16 ml), NaOH al 15% (0.16 ml) y agua (0.47 ml), después se diluyó con acetato de etilo y se secó con sulfato de sodio. El material insoluble se filtró y se lavó completamente con acetato de etilo. El filtrado se concentró bajo vacío para dar 3-{3-[hidroxi(fenil)metil]fenil}-1-propanol como un aceite opaco blanco (0.42 g, 90%)

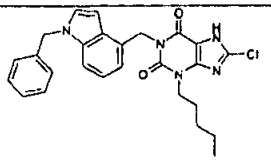
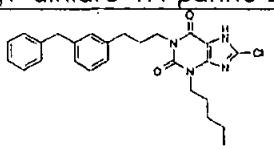
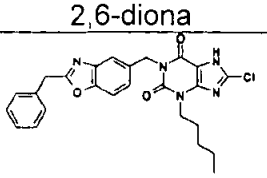
CL/EM: m/z 243 $[MH]^+$, TR 2.71 min.

El material anterior (200 mg, 0.82 mmoles) se disolvió en diclorometano anhidro (5 ml) y se añadió trietilsilano (0.53 ml, 3.2 mmoles) seguido por ácido trifluoroacético (0.36 ml, 4.1 mmoles). La mezcla de reacción se agitó durante 1 hr, después se lavó con solución de bicarbonato de sodio saturado. La fase orgánica se filtró a través de una frita hidrofóbica y se concentró bajo vacío. El producto crudo se purificó sobre sílice (4g SPE, gradiente de elución ciclohexano/acetato de etilo 0-30%) para dar el compuesto del titulo como un aceite incoloro (68 mg, 37%).

CL/EM: m/z 227 $[MH]^+$, TR 3.25 min.

Los siguientes compuestos (cuadro 27) se prepararon usando un método análogo al de 8-cloro-3-pentil-1-{[1-(fenilmetil)-1*H*-indol-5-il]metil}-3,7-dihidro-1*H*-purina-2,6-diona a partir de los alcoholes correspondientes como se describió antes.

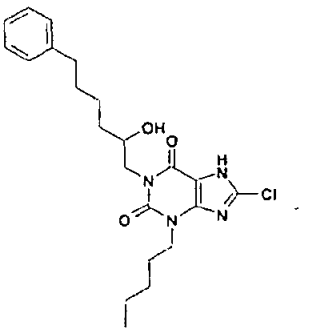
CUADRO 27

Ejemplo	Estructura	Rend. (mg)	CL/EM:
412	 8-cloro-3-pentil-1-{[1-(fenilmetil)-1H-indol-4-il]metil}-3,7-dihidro-1H-purino-2,6-diona	49	m/z 476 $[MH]^+$ TR 3.82 min
413	 8-cloro-3-pentil-1-{3-[3-(fenilmetil)fenil]propil}-3,7-dihidro-1H-purino-2,6-diona	70	m/z 465 $[MH]^+$ TR 4.01 min
414	 8-cloro-3-pentil-1-{[2-(fenilmetil)-1,3-benzoxazol-5-il]metil}-3,7-dihidro-1H-purino-2,6-diona	174	m/z 478 $[MH]^+$ TR 3.70 min

EJEMPLO 415

8-Cloro-1-(2-hidroxi-6-fenilhexil)-3-pentil-3,7-dihidro-1*H*-purina-2,6-diona

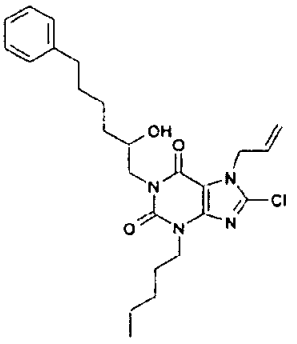
a) 8-Cloro-1-(2-hidroxi-6-fenilhexil)-3-pentil-3,7-dihidro-1*H*-purina-2,6-diona



Una solución de 8-cloro-1-(2-hidroxi-6-fenilhexil)-3-pentil-7-(2-propen-1-il)-3,7-dihidro-1*H*-purina-2,6-diona (0.084 g, 0.18 mmoles) y $Pd(PPh_3)_4$ (0.042 g, 0.035 mmoles) en THF (5 ml) se desgasificó (evacuación secuencial seguida por adición de nitrógeno x 3) después se añadió morfolina (0.25 ml, 2.8 mmoles) y la mezcla se agitó durante la noche. La solución se cargó en un SPE de aminopropilo (5g) y se eluyó con MeOH para remover subproductos, después con 5% de AcOH/MeOH para aislar el compuesto del título, después de concentración, como un aceite (0.022 g, 29%).

CL/EM: m/z 433 $[MH]^+$

b) 8-Cloro-1-(2-hidroxi-6-fenilhexil)-3-pentil-7-(2-propen-1-il)-3,7-dihidro-1*H*-purina-2,6-diona



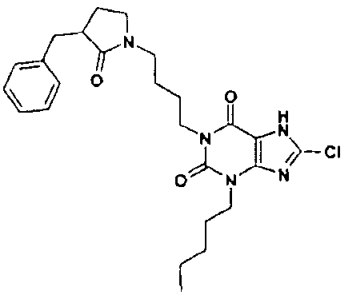
A una solución de 8-cloro-3-pentil-7-(2-propen-1-il)-3,7-dihidro-1*H*-purina-2,6-diona (0.107 g, 0.36 mmoles) y 1-cloro-6-fenil-2-hexanol (0.107 g, 0.5 mmoles) en DMF (5 ml) se añadió carbonato de cesio (0.24 g, 0.74 mmoles) y la mezcla se calentó a 60°C durante 3 hr, después de lo cual 80 mg de carbonato de cesio adicionales se añadieron y el calentamiento se continuó a 100°C durante 18 hr. La solución se dejó enfriar, se concentró y los residuos se purificaron por cromatografía sobre sílice (20 g de SPE, eluyendo primero con DCM, después con DCM/10% de éter) para dar el compuesto del título como un aceite amarillo (0.085 mg, 53%).

CL/EM: m/z 473 $[MH]^+$

EJEMPLO 416

8-Cloro-1-{4-[2-oxo-3-(fenilmetil)-1-pirrolidinil]butil}-3-pentil-3,7-dihidro-1*H*-purina-2,6-diona

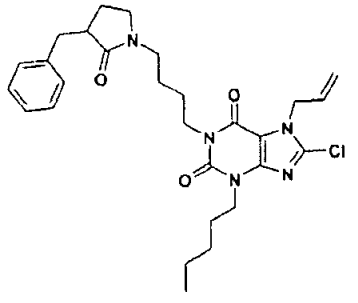
a) 8-Cloro-1-{4-[2-oxo-3-(fenilmetil)-1-pirrolidinil]butil}-3-pentil-3,7-dihidro-1*H*-purina-2,6-diona



Una solución de 8-cloro-1-{4-[2-oxo-3-(fenilmetil)-1-pirrolidinil]butil}-3-pentil-7-(2-propen-1-il)-3,7-dihidro-1*H*-purina-2,6-diona (0.35 g, 0.67 mmoles), $Pd(PPh_3)_4$ (0.082 g, 0.07 mmoles) y morfolina (0.6 ml, 6.7 mmoles) en THF (10 ml) se desgasificó (evacuación secuencial seguida por adición de nitrógeno x 3), después se agitó durante 4 hr. La solución se cargó en un SPE de aminopropilo (5g) y se eluyó primero con MeOH, después con 5% de AcOH/MeOH para proveer el compuesto del título que contenía una pequeña impureza. La purificación adicional sobre sílice (10 g de SPE, gradiente de elución éter/acetato de etilo 1:0 a 0:1) dio el compuesto del título como un aceite claro (0.10 g, 31%).

CL/EM: m/z 486 $[MH]^+$

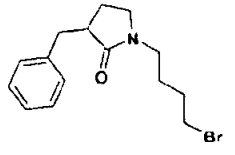
b) 8-Cloro-1-{4-[2-oxo-3-(fenilmetil)-1-pirrolidinil]butil}-3-pentil-7-(2-propen-1-il)-3,7-dihidro-1*H*-purina-2,6-diona



Se preparó como 8-cloro-1-(2-hidroxi-6-fenilhexil)-3-pentil-7-(2-propen-1-il)-3,7-dihidro-1*H*-purina-2,6-diona usando 1-(4-bromobutil)-3-(fenilmetil)-2-pirrolidinona como el agente alquilante, carbonato de potasio como la base y el calentamiento a 50°C durante 18 hr. Rendimiento 86%.

CL/EM: m/z 526 $[MH]^+$

c) 1-(4-bromobutil)-3-(fenilmetil)-2-pirrolidinona



A una solución de 3-(fenilmetil)-2-pirrolidinona (0.23 g, 1.3 mmoles) y 1,4- dibromobutano (0.57 g, 4.2 mmoles) en DMF (5 ml) se añadió t-butóxido de sodio (0.151 g, 1.6 mmoles) y la solución se agitó durante 18 hr. La solución se concentró y los residuos se sometieron a cromatografía sobre sílice (20 g de SPE, eluyendo primero con ciclohexano, después con DCM) para proveer el compuesto del título como un aceite incoloro que contenía una

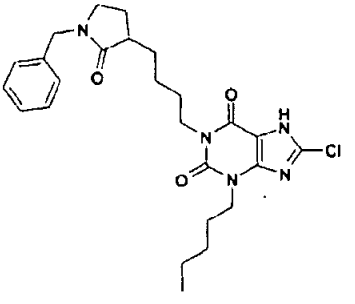
traza de DMF (0.25 g, 61%).

CL/EM: m/z 31 1 $[MH]^+$

EJEMPLO 417

8-Cloro-1-{4-[2-oxo-1-(fenilmetil)-3-pirrolidinil]butil}-3-pentil-3,7-dihidro-1*H*-purina-2,6-diona

a) 8-Cloro-1-{4-[2-oxo-1-(fenilmetil)-3-pirrolidinil]butil}-3-pentil-3,7-dihidro-1*H*-purina-2,6-diona

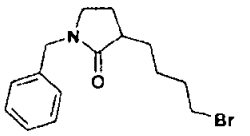


A una solución de 8-cloro-3-pentil-7-(2-propen-1-il)-3,7-dihidro-1*H*-purina-2,6-diona (0.086 g, 0.29 mmoles) y 3-(4-bromobutil)-1-(fenilmetil)-2-pirrolidinona (0.17 g, 0.55 mmoles, mezcla de 1:1 con 2-(fenilmetil)-2-azaspiro[4.4]nonan-1-ona) en THF (5 ml) se añadió carbonato de potasio (0.08 g, 0.58 mmoles) y la mezcla se calentó y se agitó a 50°C durante 18 hr. La solución se dejó enfriar, después se desgasificó (evacuación secuencial seguida por adición de nitrógeno x 3) y se añadió $Pd(PPh_3)_4$ (0.09 g, 0.077 mmoles) seguido por morfolina (0.2 ml, 2.2 mmoles) y la solución se agitó a temperatura ambiente durante 18 hr. La solución se separó entre acetato de

etilo y HCl dil. y los compuestos orgánicos se lavaron con salmuera, se secaron y se concentraron. La purificación de los residuos usando un SPE de aminopropilo (5 g) eluyendo primero con MeOH después con 5% de AcOH/MeOH dio el compuesto del título como un aceite amarillo que se cristalizó en reposo bajo éter (0.031 g, 22%).

CL/EM: m/z 486 $[MH]^+$

b) 3-(4-Bromobutil)-1-(fenilmetil)-2-pirrolidinona

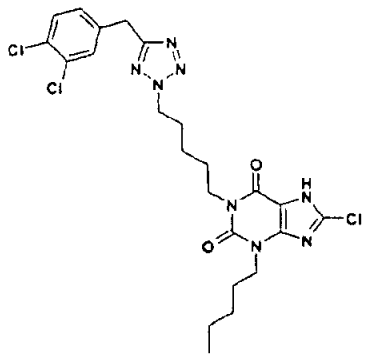


A una solución de 1-(fenilmetil)-2-pirrolidinona (0.47 g, 2.7 mmoles) en THF (10 ml) a -78°C se añadió hexametildisililazina de litio (2.8 ml, 2.7 mmoles, solución 1M) durante 5 min. Después de 15 min se añadió 1,4-dibromobutano (0.32 ml, 2.7 mmoles) y la solución se dejó para obtener temperatura ambiente durante 2 hr, después se agitó durante 18 hr adicionales. La solución se separó entre acetato de etilo y agua y los compuestos orgánicos se aislaron, se secaron y se concentraron. La cromatografía sobre sílice (20 g de SPE) eluyendo con ciclohexano después con DCM y finalmente con éter dio un aceite claro que fue una mezcla 1:1 del compuesto del título y 2-(fenilmetil)-2-azaspiro[4.4]nonan-1-ona (0.17 g). Esta se usó en el siguiente paso sin purificación adicional.

CL/EM: m/z 310, 312 $[MH]^+$

EJEMPLO 418

8-Cloro-1-(5-{5-[(3,4-diclorofenil)metil]-2*H*-tetrazol-2-il}pentil)-3-pentil-3,7-dihidro-1*H*-purina-2,6-diona

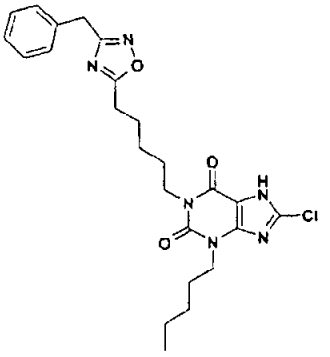


A una solución de 8-cloro-3-pentil-7-(2-propen-1-il)-3,7-dihidro-1*H*-purina-2,6-diona (0.18 g, 0.61 mmoles) en THF (5 ml) se añadió 5-{5-[(3,4-diclorofenil)metil]-2*H*-tetrazol-2-il}-1-pentanol (0.191 g, 0.61 mmoles; preparado de manera similar al ejemplo 35), trifenilfosfina (0.36 g, 1.3 mmoles) y finalmente dicarboxilato de dibencilo (0.40 g, 1.3 mmoles). La solución se agitó durante 18 hr, después de lo cual se añadió $Pd(PPh_3)_4$ (0.16 g, 0.137 mmoles) seguido por morfolina (0.75 ml, 8.3 mmoles) y la solución se agitó a temperatura ambiente durante 6 hr. La solución se cargó en un SPE de aminopropilo (5g) y se eluyó con MeOH después con 5% de AcOH/MeOH para dar el compuesto del titulo que contenía impurezas menores. Cromatografía adicional (SPE de sílice, 20g) eluyendo con éter dio el compuesto del título como un sólido blanco (0.061 g, 18%).

CL/EM: m/z 553 $[MH]^+$

EJEMPLO 419

8-Cloro-3-pentil-1-{5-[3-(fenilmetil)-1,2,4-oxadiazol-5-il]pentil}-3,7-dihidro-1*H*-purina-2,6-diona

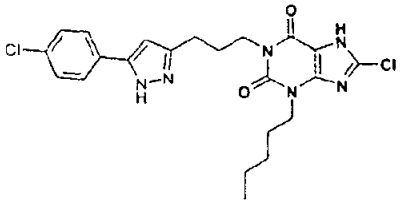


A una solución de 8-cloro-3-pentil-7-(2-propen-1-il)-3,7-dihidro-1*H*-purina-2,6-diona (0.093 g, 0.3 mmoles) en THF (5 ml) se añadió 5-[3-(fenilmetil)-1,2,4-oxadiazol-5-il]-1-pentanol (0.077 g, 0.3 mmoles; preparado de manera similar al ejemplo 87b), trifenilfosfina (0.17 g, 0.6 mmoles) y finalmente dicarboxilato de dibencilo (0.20 g, 0.6 mmoles). La solución se agitó durante 18 hr, se desgasificó, después de lo cual se añadió $Pd(PPh_3)_4$ (0.08 g, 0.07 mmoles) seguido por morfolina (0.35 ml, 3.9 mmoles) y la solución se agitó a temperatura ambiente durante 6 hr. La solución se cargó en un SPE de aminopropilo (5g) y se eluyó con MeOH después con 5% de AcOH/MeOH para dar el compuesto del título como un sólido color crema (0.051 g, 34%).

CL/EM: m/z 485 $[MH]^+$

EJEMPLO 420

8-Cloro-1-{3-[5-(4-clorofenil)-1*H*-pirazol-3-il]propil}-3-pentil-3,7-dihidro-1H-purina-2,6-diona

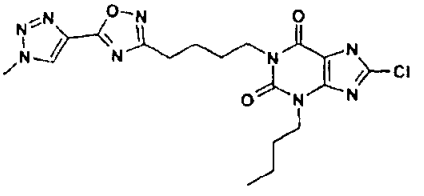


Se preparó como 8-cloro-1-(5-{5-[(3,4-diclorofenil)metil]-2*H*-tetrazol-2-il}pentil)-3-pentil-3,7-dihidro-1*H*-purina-2,6-diona usando 3-[5-(4-clorofenil)-1H-pirazol-3-il]-1-propanol. El material de producto final se lavó con éter para dar el compuesto del título como un sólido color crema (30%).

CL/EM: m/z 475 $[MH]^+$

EJEMPLO 421

3-Butil-8-cloro-1-{4-[5-(1-metil-1*H*-1,2,3-triazol-4-il)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1*H*-purina-2,6-diona



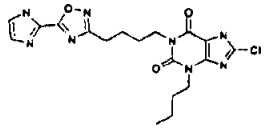
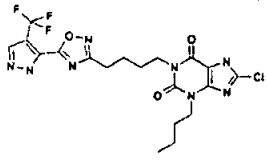
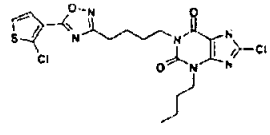
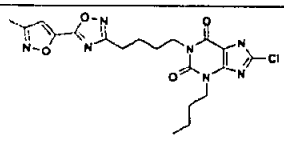
Una solución del ácido 1-metil-1*H*-1,2,3-triazol-4-carboxílico (18 mg, 0.14 mmoles) en DMF (0.5 ml) se trató con CDI (23 mg, 0.14 mmoles) a t.a. durante 1 hr. Una solución de (1Z)-5-(3-butil-8-cloro-2,6-dioxo-2,3,6,7-

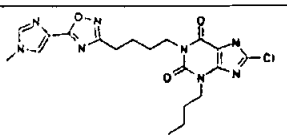
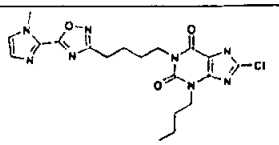
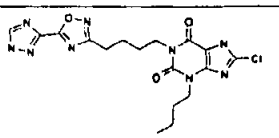
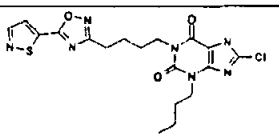
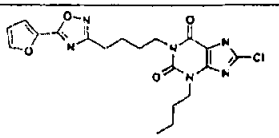
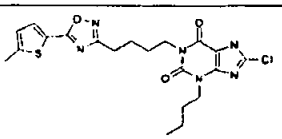
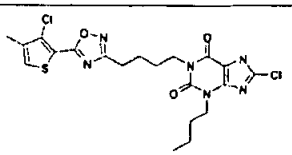
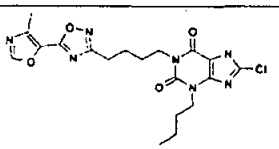
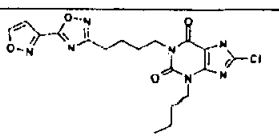
tetrahidro-1*H*-purin-il)-N-hidroxipentanimidamida (50 mg, 0.14 mmoles) en DMSO (0.4 ml) se añadió a la mezcla, después se calentó a 100°C durante 18 hr. La mezcla de reacción se purificó por MDAP para dar el compuesto del título como un sólido blanco (18 mg).

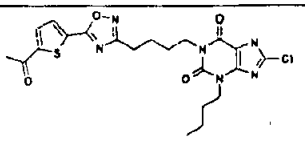
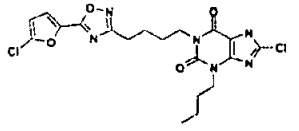
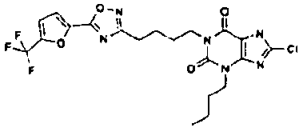
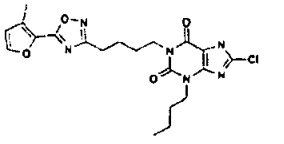
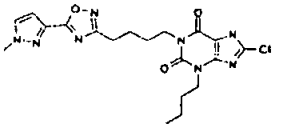
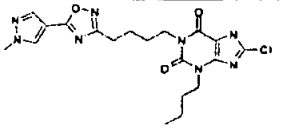
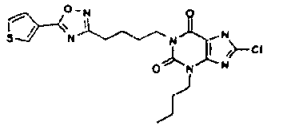
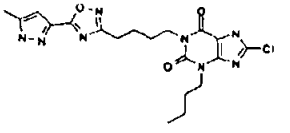
CL/EM: m/z 448 $[MH]^+$, TR 2.86 min.

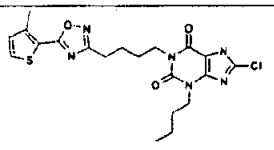
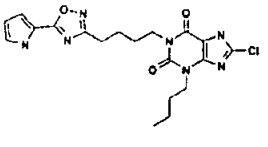
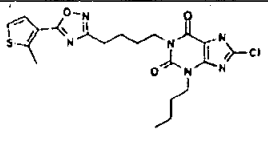
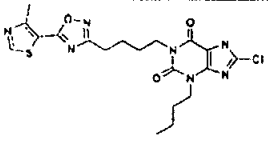
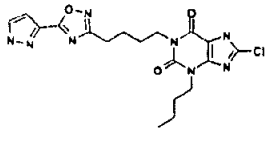
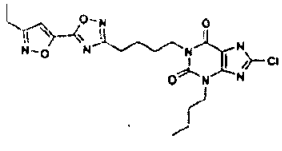
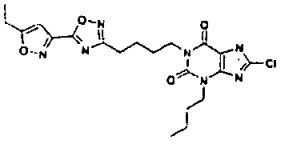
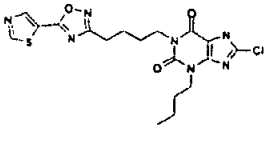
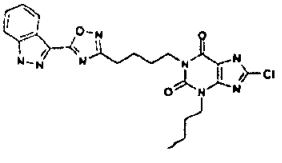
Los siguientes compuestos (cuadro 28) se prepararon usando un método análogo al del ejemplo 421, usando el ácido carboxílico apropiado.

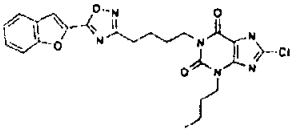
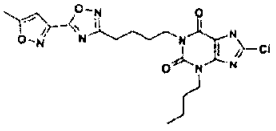
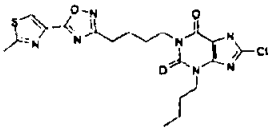
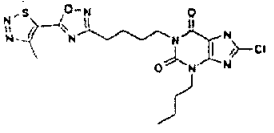
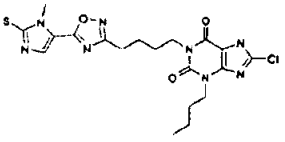
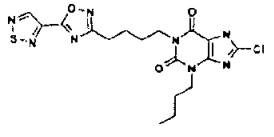
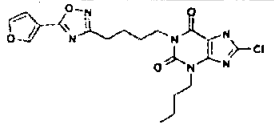
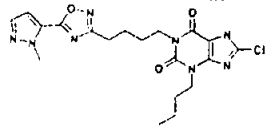
CUADRO 28

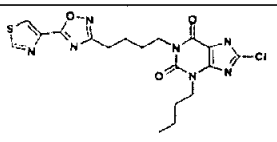
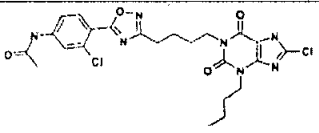
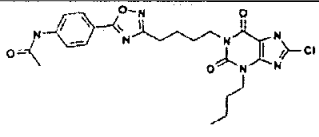
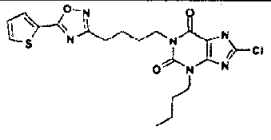
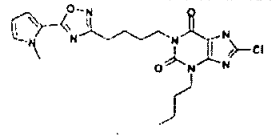
Ejemplo	Estructura	Nombre	Rend. (mg)	CL/EM:
422		3-butil-8-cloro-1-{-[5-(1H-imidazol-2-il)-1,2,4-oxadiazol-3-il]butil}3,7-dihidro-1H-purino-2,6-diona	16	m/z 433 $[MH]^+$ TR 2.79 min
423		3-butil-8-cloro-1-(4-{5-[4-(trifluorometil)-1H-pirazol-5-il]1,2,4-oxadiazol-3-il}butil)-3,7-dihidro-1H-purino-2,6-diona	19	m/z 501 $[MH]^+$ TR 3.28 min
424		3-butil-8-cloro-1-{4-[5-(2-cloro-3-tienil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purino-2,6-diona	26	m/z 483 $[MH]^+$ TR 3.59 min
425		3-butil-8-cloro-1-{4-[5-(3-metil-5-isoxazolil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purino-2,6-diona	25	m/z 448 $[MH]^+$ TR 3.21 min

426		3-butil-8-cloro-1-{4-[5-(1-metil-1H-imidazol-4-il)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purino-2,6-diona	16	m/z 447 $[MH]^+$ TR 2.74 min
427		3-butil-8-cloro-1-{4-[5-(1-metil--1H-imidazol-2-il)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purino-2,6-diona	9	m/z 447 $[MH]^+$ TR 2.91 min
428		3-butil-8-cloro-1-{4-[5-(1H-1,2,4-triazol-3-il)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purino-2,6-diona	10	m/z 434 $[MH]^+$ TR 2.73 min
429		3-butil-8-cloro-1-{4-[5-(5-isotiazolil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purino-2,6-diona	17	m/z 450 $[MH]^+$ TR 3.34 min
430		3-butil-8-cloro-1-{4-[5-(2-furanil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purino-2,6-diona	26	m/z 443 $[MH]^+$ TR 3.27 min
431		3-butil-8-cloro-1-{4-[5-(5-metil-2-tienil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purino-2,6-diona	29	m/z 463 $[MH]^+$ TR 3.61 min
432		3-butil-8-cloro-1-{4-[5-(3-cloro-4-metil-2-tienil)-1,2,4-oxadiazol-3-il]butil]-3,7-dihidro-1H-purino-2,6-diona	30	m/z 497 $[MH]^+$ TR 3.76 min
433		3-butil-8-cloro-1-{4-[5-.(4-metil-1,3-oxazol-5-il)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-.purino-2,6-diona	25	m/z 448 $[MH]^+$ TR 3.13 min
434		3-butil-8-cloro-1-{4-[5-(3-isoxazolil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purino-2,6-diona	23	m/z 434 $[MH]^+$ TR 3.20 min

435		1-{4-[5-(5-acetil-2-tienil)-1,2,4-oxadiazol-3-il]butil}-3-butil-8-cloro-3,7-dihidro-1H-purino-2,6-diona	28	m/z 491 [MH]$^+$ TR 3.43 min
436		3-butil-8-cloro-1-{4-[5-(5-cloro-2-furanil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purino-2,6-diona	27	m/z 467 [MH]$^+$ TR 3.51 min
437		3-butil-8-cloro-1-(4-{5-[5-(trifluorometil)-2-furanil]-1,2,4-oxadiazol-3-il}butil)-3,7-dihidro-1H-purino-2,6-diona	27	m/z 501 [MH]$^+$ TR 3.61 min
438		3-butil-8-cloro-1-{4-[5-(3-metil-2-furanil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purino-2,6-diona	27	m/z 447 [MH]$^+$ TR 3.43 min
439		3-butil-8-cloro-1-{4-[5-(1-metil-1H-pirazol-3-il)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purino-2,6-diona	25	m/z 447 [MH]$^+$ TR 3.02 min
440		3-butil-8-cloro-1-{4-[5-(1-metil-1H-pirazol-4-il)-1,2,4-oxadiazol-3-il)butil}-3,7-dihidro-1H-purino-2,6-diona	8	m/z 447 [MH]$^+$ TR 2.99 min
441		3-butil-8-cloro-1-{4-[5-(3-tienil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purino-2,6-diona	19	m/z 449 [MH]$^+$ TR 3.43 min
442		3-butil-8-cloro-1-{4-[5-(5-metil-1H-pirazol-3-il)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purino-2,6-diona	26	m/z 447 [MH]$^+$ TR 3.03 min

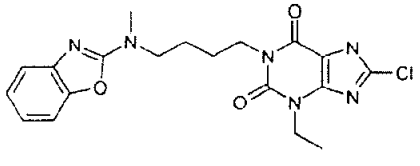
443		3-butil-8-cloro-1-{4-[5-(3-metil-2-tienil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purino-2,6-diona	27	m/z 463 [MH]$^+$ TR 3.62 min
444		3-butil-8-cloro-1-{4-[5-(1H-pirro1-2-il)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purino-2,6-diona	13	m/z 432 [MH]$^+$ TR 3.26 min
445		3-butil-8-cloro-1-{4-[5-(2-metil-3-tienil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purino-2,6-diona	18	m/z 463 [MH]$^+$ TR 3.64 min
446		3-butil-8-cloro-1-{4-[5-(4-metil-1,3-tiazol-5-il)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purino-2,6-diona	24	m/z 464 [MH]$^+$ TR 3.26 min
447		3-butil-8-cloro-1-{4-[5-(1H-pirazol-3-il)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purino-2,6-diona	20	m/z 433 [MH]$^+$ TR 3.00 min
448		3-butil-8-cloro-1-{4-[5-(3-etil-5-isoxazolil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purino-2,6-diona	20	m/z 462 [MH]$^+$ TR 3.43 min
449		3-butil-8-cloro-1-{4-[5-(5-etil-3-isoxazolil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purino-2,6-diona	23	m/z 462 [MH]$^+$ TR 3.46 min
450		3-butil-8-cloro-1-{4-[5-(1,3-tiazol-5-il)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purino-2,6-diona	20	m/z 450 [MH]$^+$ TR 3.13 min
451		3-butil-8,cloro-1-{4-[5-(1H-indazol-3-il)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purino-2,6-diona	24	m/z 483 [MH]$^+$ TR 3.50 min

452		1-{4-[5-(1-benzofuran-2-il)-1,2,4-oxadiazol-3-il]butil}-3-butil-8-cloro-3,7-dihidro-1H-purino-2,6-diona	6	m/z 483 [MH]$^+$ TR 3.72 min
453		3-butil-8-cloro-1-{4-[5-(5-metil-3-isoxazolil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purino-2,6-diona	13	m/z 448 [MH]$^+$ TR 3.30 min
454		3-butil-8-cloro-1-{4-[5-(2-metil-1,3-tiazol-4-il)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purino-2,6-diona	20	m/z 464 [MH]$^+$ TR 3.14 min
455		3-butil-8-cloro-1-{4-[5-(4-metil-1,2,3-tiadiazol-5-il)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purino-2,6-diona	14	m/z 465 [MH]$^+$ TR 3.40 min
456		3-butil-8-cloro-1-{4-[5-(3-metil-2-tioxo-2,3-dihidro-1H-imidazol-4-il)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purino-2,6-diona	16	m/z 479 [MH]$^+$ TR 3.08 min
457		3-butil-8-cloro-1-{4-[5-(1,2,5-tiadiazol-3-il)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purino-2,6-diona	24	m/z 451 [MH]$^+$ TR 3.27 min
458		3-butil-8-cloro-1-{4-[5-(3-furanil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purino-2,6-diona	21	m/z 433 [MH]$^+$ TR 3.29 min
459		3-butil-8-cloro-1-{4-[5-(1-metil-1H-pirazol-5-il)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purino-2,6-diona	23	m/z 447 [MH]$^+$ TR 3.22 min

460		3-butil-8-cloro-1-{4-[5-(1,3-tiazol-4-il)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purino-2,6-diona	20	m/z 450 $[MH]^+$ TR 3.06 min
461		*N*-(4-{3-[4-(3-butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1H-purin-1-il)butil]-1,2,4-oxadiazol-5-il}-3-clorofenil)-acetamida	23	m/z 534 $[MH]^+$ TR 3.44 min
462		*N*-(4-{3-[4-(3-butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1H-purin-1-il)butil]-1,2,4-oxadiazol-5-il}fenil)acetamida	16	m/z 500 $[MH]^+$ TR 3.23 min
463		3-butil-8-cloro-{4-[5-(2-tienil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purino-2,6-diona	27	m/z 449 $[MH]^+$ TR 3.45 min
464		3-butil-8-cloro-1-{4-[5-(1-metil-1H-pirrol-2-il)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purino-2,6-diona	15	m/z 446 $[MH]^+$ TR 3.45 min

EJEMPLO 465

1-{4-[1,3-Benzoxazol-2-il(metil)amino]butil}-8-cloro-3-etil-3,7-dihidro-1*H*-purina-2,6-diona



Una solución de 2-cloro-1,3-benzoxazol (0.46 g, 3 mmoles) en THF (20 ml) se trató con 1-metilpirrolidina (0.26 g, 3 mmoles) y la mezcla de

reacción se calentó a reflujo durante 6 hr, después se enfrió y se evaporó a sequedad. La purificación por cromatografía instantánea [Isco Companion, cartucho Redisep de 12 g, gradiente de elución de ciclohexano a ciclohexano/éter dietílico (3:2)] reveló 0.52 g (73% rendimiento) de *N*-(4-clorobutil)-*N*-metil-1,3-benzoxazol-2-amina como un aceite incoloro.

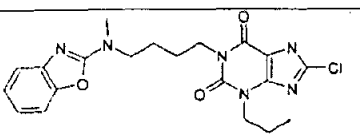
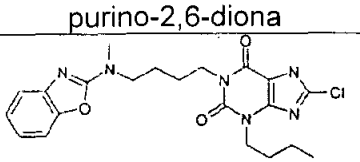
CL/EM: m/z 239 $[MH]^+$, TR 3.12 min.

Una solución de 8-cloro-3-etil-7-(2-propen-1-il)-3,7-dihidro-1*H*-purina-2,6-diona (0.112 g, 0.44 mmoles) en DMF (10 ml) se trató sobre carbonato de potasio (0.08 g, 0.6 mmoles) y *N*-(4-clorobutil)-N-metil-1,3-benzoxazol-2-amina (0.12g, 0.5 mmoles). La mezcla de reacción se calentó a 75°C durante 18 hr y después se enfrió a temperatura ambiente. La mezcla se desgasificó mediante la aplicación repetida de vacío seguido por rellenado con nitrógeno gaseoso y después se trató con tetrakis(trifenilfosfin)paladio(0) (0.03 g, 0.026 mmoles) y morfolina (0.5 ml, 5.7 mmoles). Se agitó durante 4 hr bajo una atmósfera de nitrógeno a temperatura ambiente, tiempo después del cual la mezcla se evaporó a sequedad y el residuo se dividió entre cloroformo (40 ml) y cloruro de amonio acuoso saturado (40 ml). La fase orgánica se evaporó a sequedad y el residuo se disolvió en metanol (5 ml) y se añadió a un cartucho de SPE de aminopropilo 5g que se lavó subsecuentemente con metanol y el producto se eluyó con una solución al 5% de ácido acético en metanol. Las fracciones que contenían producto combinado se evaporaron a sequedad y el producto se purificó por MDAP para dar el compuesto del título como un sólido blanco (0.043 g, 23%).

CL/EM: m/z 417 $[MH]^+$, TR 2.91 min.

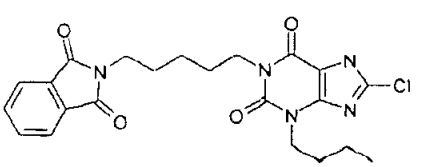
Los siguientes compuestos (cuadro 29) se prepararon por un método análogo al del ejemplo 465.

CUADRO 29

Ejemplo	Estructura	Precursor	Rend. (mg)	CL/EM
466	 1-{4-[1,3-benzoxazol-2-il(metil)amino]butil}-8-cloro-3-propi1-3,7-dihidro-1H-purino-2,6-diona	8-cloro-7-(2-propen-1-il)-3-propil-3,7-dihidro-1H-purino-2,6-diona	47	m/z 431 $[MH]^+$ TR 3.09 min
467	 1-{4-[1,3-benzoxazol-2-il(metil)amino]butil}-3-butil-8-cloro-3,7-dihidro-1H-purino-2,6-diona	3-butil-8-cloro-7-(2-propen-1-il)-3,7-dihidro-1H-purino-2,6-diona	61	m/z 445 $[MH]^+$ TR 3.28 min

EJEMPLO 468

3-Butil-8-cloro-1-[5-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)pentil]-3,7-dihidro-1*H*-purina-2,6-diona



Una solución de 3-butil-8-cloro-7-(2-propen-1-il)-3,7-dihidro-1*H*-

purina-2,6-diona (0.5 g, 1.8 mmoles) en DMF (20 ml) se trató sobre carbonato de potasio (0.3 g, 2.1 mmoles) y 1,5-dibromopentano (1.2 ml, 8.9 mmoles) y después se calentó a 50°C durante 2 hr. La mezcla se enfrió y se evaporó a sequedad. El residuo se dividió entre acetato de etilo (30 ml) y bicarbonato de sodio acuoso saturado (30 ml). La fase acuosa se extrajo con acetato de etilo adicional (30 ml) y los compuestos orgánicos combinados se secaron sobre sulfato de magnesio, se filtraron y se evaporaron a sequedad. El producto se purificó por cromatografía instantánea [Isco Companion, cartucho Redisep 40g, gradiente de elución de ciclohexano a ciclohexano/acetato de etilo (1:1)] para revelar 0.663 g (87%) de 1-(5- bromopentil)-3-butil-8-cloro-7-(2-propen-1-il)-3,7-dihidro-1*H*-purina-2,6-diona como un aceite incoloro.

CL/EM: m/z 431/433 $[MH]^+$, TR 3.76 min.

A una solución de 1-(5-bromopentil)-3-butil-8-cloro-7-(2-propen-1-il)-3,7-dihidro-1*H*-purina-2,6-diona (0.642 g, 1.5 mmoles) en DMF (10 ml) se añadió ftalimida de potasio (0.303 g, 1.6 mmoles) y la mezcla se calentó a 50°C durante 2 hr, después se enfrió. La mezcla se desgasificó mediante la aplicación repetida de vacío seguido por rellenado con nitrógeno gaseoso y después se trató con tetrakis(trifenilfosfin)paladio(0) (0.173 g, 0.15 mmoles) y morfolina (1.3 ml, 15 mmoles). La mezcla se dejó reposar a temperatura ambiente bajo un manto de nitrógeno durante 18 hr tiempo después del cual la mezcla se evaporó y el residuo se dividió entre cloroformo (30 ml) y cloruro de amonio acuoso saturado (30 ml). La fase acuosa se extrajo con cloroformo adicional (30 ml) y los compuestos orgánicos combinados se secaron sobre

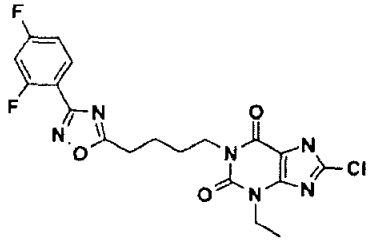
sulfato de magnesio, se filtraron y se evaporaron. El residuo se disolvió en metanol (5 ml) y se añadió a un cartucho de SPE de aminopropilo 10g que se lavó subsecuentemente con metanol y el producto se eluyó con una solución al 5% de ácido acético en metanol. Las fracciones que contenían producto se evaporaron y después se purificaron por MDAP para dar *N*-[5-(3-butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1*H*-purin-1-il)pentil]-2-(4-morfolinilcarbonil)-benzamida como un sólido blanco (0.137 g, CL/EM: m/z 545 $[MH]^+$, TR 2.77min) y el compuesto del título como un sólido blanco (0.239 g, 35%).

CL/EM: m/z 458 $[MH]^+$, TR 3.33 min.

EJEMPLO 469

8-Cloro-1-{4-[3-(2,4-difluorofenil)-1,2,4-oxadiazol-5-il]butil}-3-etil-3,7-dihidro-1*H*-purina-2,6-diona

a) 8-Cloro-1-{4-[3-(2,4-difluorofenil)-1,2,4-oxadiazol-5-il]butil}-3-etil-3,7-dihidro-1*H*-purina-2,6-diona

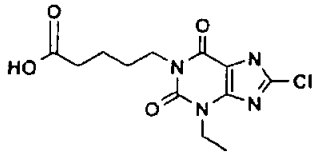


Una solución de ácido 5-(8-cloro-3-etil-2,6-dioxo-2,3,6,7-tetrahidro-1*H*-purin-1-il)pentanoico (0.05 g, 0.16 mmoles) en DMSO (1 ml) se trató con CDI (0.029 g, 0.18 mmoles) y la mezcla se agitó a temperatura

ambiente durante 1 hr. Subsecuentemente, la mezcla se trató con 2,4-difluorobenzamidoxima (0.03 g, 0.18 mmoles) y después se calentó a 120°C durante 30 min. El producto se purificó a partir de la mezcla cruda usando MDAP. Las fracciones que contenían producto se evaporaron usando una corriente de nitrógeno y la goma incolora resultante se trituró en éter y se secó para revelar el compuesto del título como un sólido blanco (50 mg, 70%).

CL/EM: m/z 451 $[MH]^+$, TR 2.23 min.

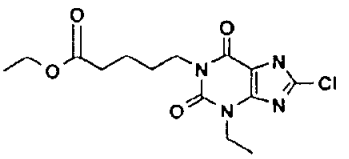
b) Acido 5-(8-cloro-3-etil-2,6-dioxo-2,3,6,7-tetrahidro-1*H*-purin-1-il)pentanoico



Una solución de 5-(8-cloro-3-etil-2,6-dioxo-2,3,6,7-tetrahidro-1*H*-purin-1-il)pentanoato de etilo (2.3 g, 6.7 mmoles) en metanol (75 ml) se trató con agua (3 ml) e hidróxido de litio (0.481 g, 20.1 mmoles) y la mezcla se agitó a 40°C durante 17 hr. La mezcla se evaporó a sequedad y el residuo se trató con 50 ml de acetato de etilo y 50 ml de agua. Las 2 fases se separaron y la fase acuosa se ajustó a pH 5 usando ácido clorhídrico acuoso 2M. El producto precipitado se filtró y se secó para dar ácido 5-(8-cloro-3-etil-2,6-dioxo-2,3,6,7-tetrahidro-1*H*-purin-1-il)pentanoico como un sólido blanco (1.99 g, 95%).

CL/EM: m/z 315 $[MH]^+$, TR 2.34 min.

c) 5-(8-Cloro-3-etil-2,6-dioxo-2,3,6,7-tetrahidro-1*H*-purin-1-il) pentanoato de etilo

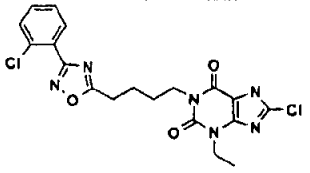
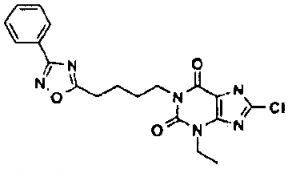
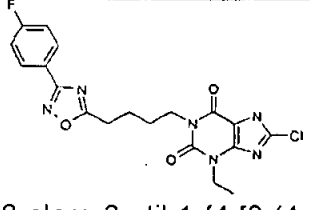
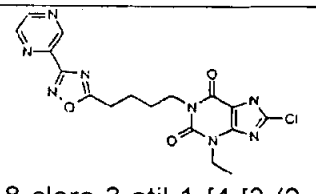


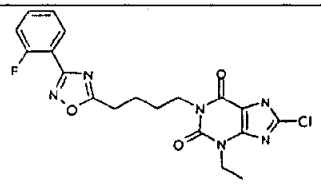
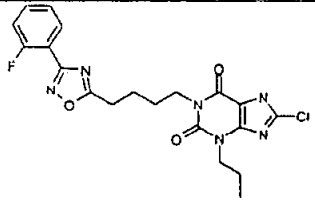
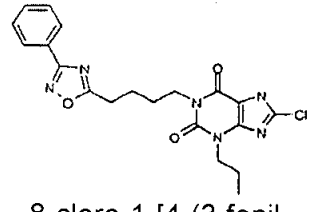
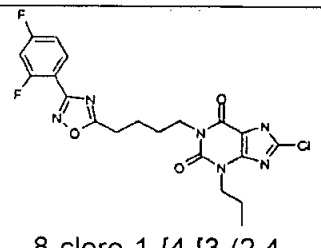
Una solución de 8-cloro-7-(2-propen-1-il)-3-etil-3,7-dihidro-1*H*-purina-2,6-diona (3 g, 11.8 mmoles) en DMF (40 ml) se trató sobre carbonato de potasio (1.9 g, 14.1 mmoles) y 5-bromopentanoato de etilo (2.24 ml, 14.1 mmoles) y la mezcla se calentó en una atmósfera de nitrógeno a 70°C durante 5 hr y después se enfrió. La mezcla se desgasificó mediante la aplicación repetida de vacío seguido por rellenado con nitrógeno gaseoso y después se trató con tetrakis(trifenilfosfin)paladio(0) (1.36 g, 1.1 mmoles) y morfolina (10.3 ml, 1 18 mmoles). La mezcla se agitó en una atmósfera de nitrógeno durante 4 hr y después se evaporó a sequedad. El residuo se dividió entre 100 ml de acetato de etilo y 100 ml de agua. La fase acuosa se volvió a extraer con 100 ml de acetato de etilo y los compuestos orgánicos combinados se secaron sobre sulfato de magnesio, se filtraron y se evaporaron. El residuo se trituró en éter dietílico, se filtró y se secó para revelar el compuesto 5-(8-cloro-3- etil-2,6-dioxo-2,3,6,7-tetrahidro-1H-purin-1-il)pentanoato de etilo como un sólido blanco (2.3 g, 57%).

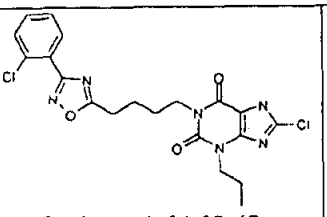
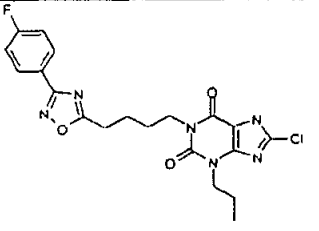
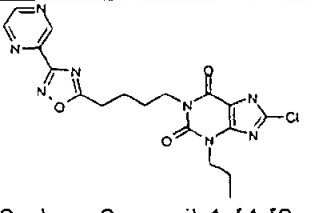
CL/EM: m/z 343 $[MH]^+$, TR 2.73 min.

Los siguientes compuestos (cuadro 30) se prepararon por un método análogo al del ejemplo 469.

CUADRO 30

Ejemplo	Estructura	Precursor	Rend. (mg)	CL/EM
470	 8-cloro-1-{4-[3-(2-clorofenil)-1,2,4-oxadiazol-5-il]butil}-3-etil-3,7-dihidro-1H-purino-2,6-diona	ácido 5-(8-cloro-3-etil-2,6-dioxo-2,3,6,7-tetrahidro-1*H*-purin-1-il)pentanoico	33	m/z 449 $[MH]^+$ TR 3.27 min
471	 8-cloro-1-[4-(3-fenil-1,2,4-oxadiazol-5-il)butil]-3-etil-3,7-dihidro-1H-purino-2,6-diona	ácido 5-(8-cloro-3-etil-2,6-dioxo-2,3,6,7-tetrahidro-1*H*-purin-1-il)pentanoico	32	m/z 415 $[MH]^+$ TR 3.22 min
472	 8-cloro-3-etil-1-{4-[3-(4-fluorofenil)-1,2,4-oxadiazol-5-il]butil}-3,7-dihidro-1-purino-2,6-diona	ácido 5-(8-cloro-3-etil-2,6-dioxo-2,3,6,7-tetrahidro-1*H*-purin-1-il)pentanoico	31	m/z 433 $[MH]^+$ TR 3.26 min
473	 8-cloro-3-etil-1-{4-[3-(2-pirazinil)-1,2,4-oxadiazol-5-il]butil}-3,7-dihidro-1H-purino-2,6-diona	ácido 5-(8-cloro-3-etil-2,6-dioxo-2,3,6,7-tetrahidro-1*H*-purin-1-il)pentanoico	2	m/z 417 $[MH]^+$ TR 2.54 min

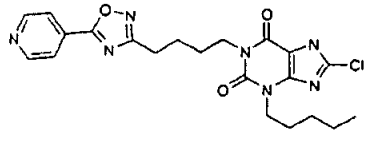
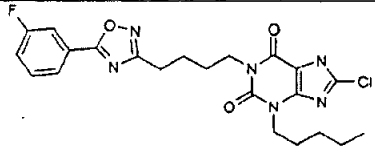
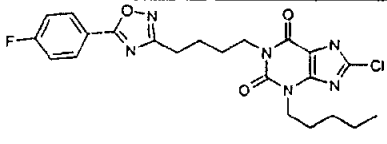
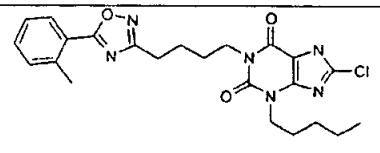
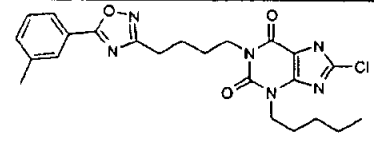
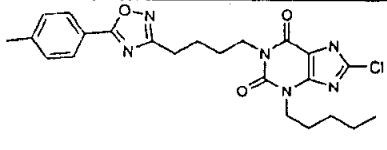
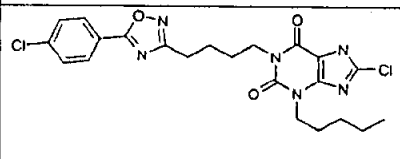
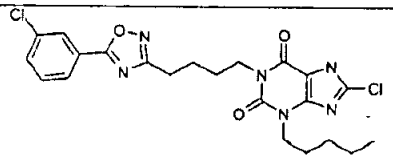
474	 8-cloro-3-etil-1-{4-[3-(2-fluorofenil)-1,2,4-oxadiazol-5-il]butil}-3,7-diihidro-1H-purino-2,6-diona	ácido 5-(8-cloro-3-etil-2,6-dioxo-2,3,6,7-tetrahidro-1*H*-purin-1-il)pentanoico	38	m/z 433 $[MH]^+$ TR 3.12 min
475	 8-cloro-1-{4-[3-(2-fluorofenil)-1,2.4-oxadiazol-5-il]butil}-3-propil-3,7-dihidro-1H-purino-2,6-diona	ácido 5-(8-cloro-3-propil-2,6-dioxo-2,3,6,7-tetrahidro-1*H*-purin-1-il)pentanoico	29	m/z 447 $[MH]^+$ TR 3.28 min
476	 8-cloro-1-[4-(3-fenil-1,2,4-oxadiazol-5-il)butil]-3-propil-3,7-dihidro-1H-purino-2,6-diona	ácido 5-(8-cloro-3-propil-2,6-dioxo-2,3,6,7-tetrahidro-1*H*-purin-1-il)pentanoico	11	m/z 429 $[MH]^+$ TR 3.35 min
477	 8-cloro-1-{4-[3-(2,4-difluorofenil)-1,2,4-oxadiazol-5-il]butil}-3-propil-3,7-dihidro-1H-purino-2,6-diona	ácido 5-(8-cloro-3-propil-2,6-dioxo-2,3,6,7-tetrahidro-1*H*-purin-1-il)pentanoico	32	m/z 465 $[MH]^+$ TR 3.40 min

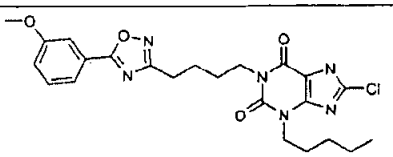
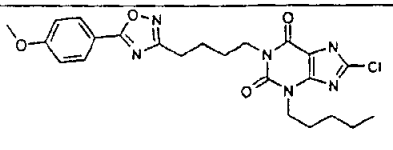
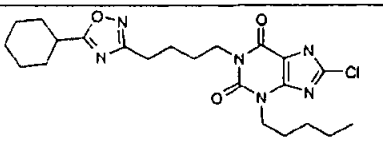
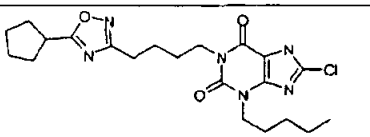
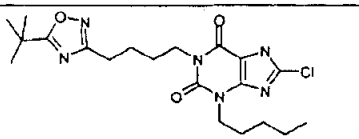
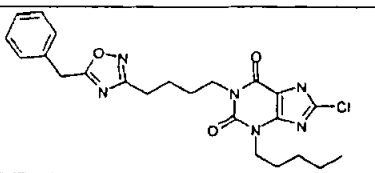
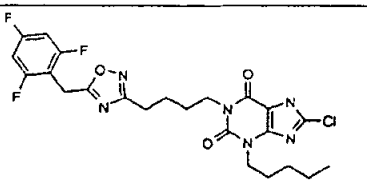
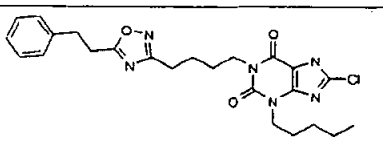
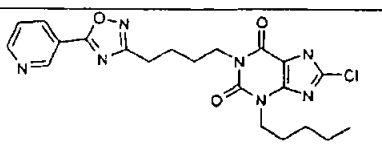
478	 8-cloro-1-{4-[3-(2-clorofenil)-1,2,4-oxadiazol-5-il]butil}-3-propil-3,7-dihidro-1H-purino-2,6-diona	ácido 5-(8-cloro-3-propil-2,6-dioxo-2,3,6,7-tetrahidro-1*H*-purin-1-il)pentanoico	25	m/z 463 $[MH]^+$ TR 3.40 min
479	 8-cloro-1-{4-[3-(4-fluorofenil)-1,2,4-oxadiazol-5-il]butyl}-3-propil-3,7-dihidro-1H-purino-2,6-diona	ácido 5-(8-cloro-3-propil-2,6-dioxo-2,3,6,7-tetrahidro-1*H*-purin-1-il)pentanoico	26	m/z 447 $[MH]^+$ TR 3.44 min
480	 8-cloro-3-propil-1-{4-[3-(2-pirazinil)-1,2,4-oxadiazol-5-il]butil}-3,7-dihidro-1H-purino-2,5-diona	ácido 5-(8-cloro-3-propil-2,6-dioxo-2,3,6,7-tetrahidro-1*H*-purin-1-il)pentanoico	25	m/z 431 $[MH]^+$ TR 3.09 min

Los siguientes compuestos (cuadro 31) se prepararon usando un método análogo al del ejemplo 158, usando el ácido apropiado.

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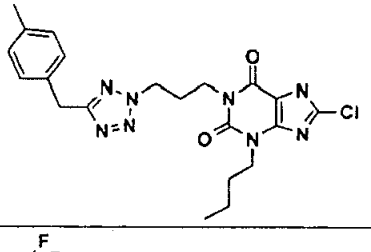
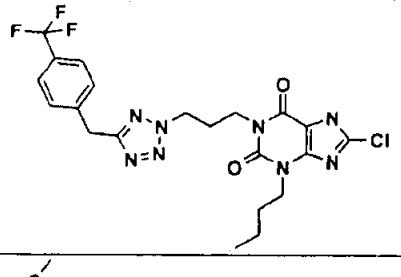
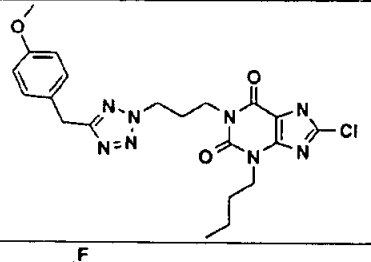
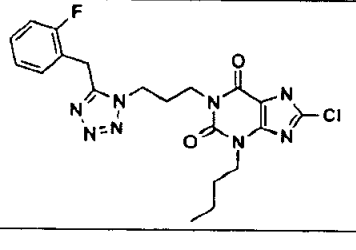
CUADRO 31

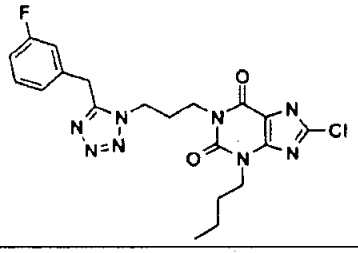
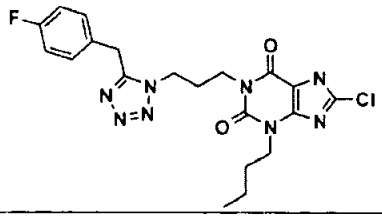
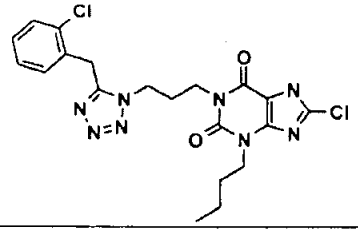
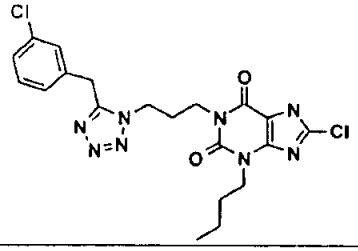
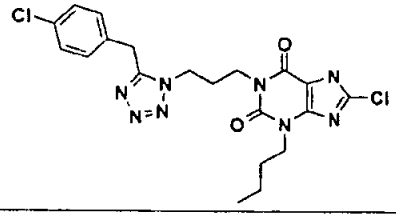
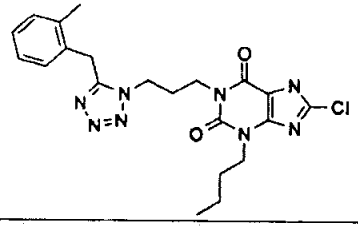
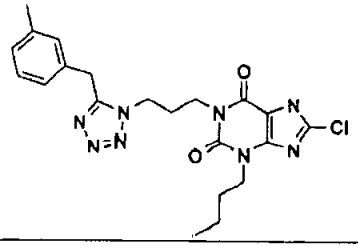
Ejemplo	Estructura	Nombre	Rend. (mg)	CL/EM:
481		8-cloro-3-pentil-1-{4-[5-(4-piridinil)-1,2,4-oxadiazol-3-il]butyl}-3,7-dihidro-1H-purino-2,6-diona	8.0	m/z 458 $[MH]^+$ TR 3.25 min
482		8-cloro-1-{4-[5-(3-fluorofenil)-1,2,4-oxadiazol-3-il]butil}-3-pentil-3,7-dihidro-1H-purino-2,6-diona	9.1	m/z 475 $[MH]^+$ TR 3.73 min
483		8-cloro-1-{4-[5-(4-fluorofenil)-1,2,4-oxadiazol-3-il]butil}-3-pentil-3,7-dihidro-1H-purin-2,6-diona	16.1	m/z 475 $[MH]^+$ TR 3.69 min
484		8-cloro-1-{4-[5-(2-metilfenil)-1,2,4-oxadiazol-3-il]butil}-3-pentil-3,7-dihidro-1H-purino-2,6-diona	22.9	m/z 471 $[MH]^+$ TR 3.82 min
485		8-cloro-1-{4-[5-(3-metilfenil)-1,2,4-oxadiazol-3-il]butil}-3-pentil-3,7-dihidro-1H-purino-2,6-diona	18.0	m/z 471 $[MH]^+$ TR 3.81 min
486		8-cloro-1-{4-[5-(4-metilfenil)-1,2,4-oxadiazol-3-il]butil}-3-pentil-3,7-dihidro-1H-purino-2,6-diona	25.0	m/z 471 $[MH]^+$ TR 3.80 min
487		8-cloro-1-{4-[5-(4-clorofenil)-1,2,4-oxadiazol-3-il]butil}-3-pentil-3,7-dihidro-1H-purino-2,6-diona	16.6	m/z 491 $[MH]^+$ TR 3.89 min
488		8-cloro-1-{4-[5-(3-clorofenil)-1,2,4-oxadiazol-3-il]butil}-3-pentil-3,7-dihidro-1H-purino-2,6-diona	12.8	m/z 491 $[MH]^+$ TR 3.91 min

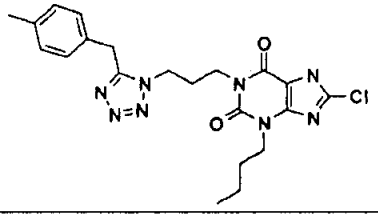
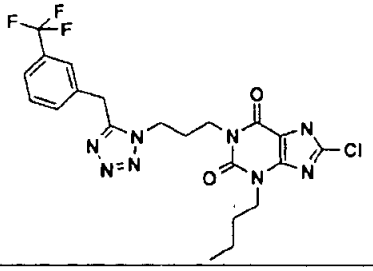
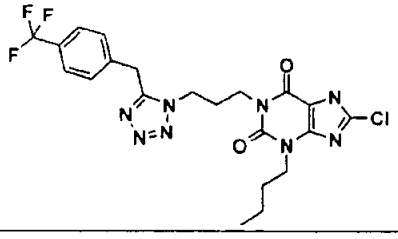
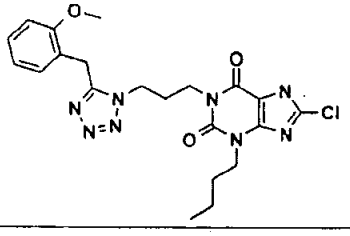
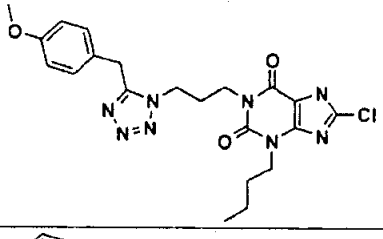
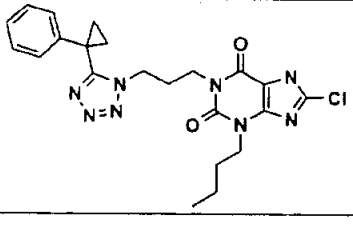
489		8-cloro-1-(4-{5-[3-(metiloxi)fenil]-1,2,4-oxadiazol-3-il]butil}-3-pentil-3,7-dihidro-1H-purino-diona	23.0	m/z 487 $[MH]^+$ TR 3.71 min
490		8-cloro-1-(4-{5-[4-(metiloxi)fenil]-1,2,4-oxadiazol-3-il}butil)-3-pentil-3,7-dihidro-1H--purino-diona	15.8	m/z 487 $[MH]^+$ TR 3.67 min
491		8-cloro-1-[4-(5-ciclohexil-1,2,4-oxadiazol-3-il)butil]-3-pentil-3,7-dihidro-1H-purino-2,6-diona	16.1	m/z 463 $[MH]^+$ TR 3.73 min
492		8-cloro-1-[4-(5-ciclopentil-1,2,4-oxadiazol-3-il)butyl]-3-pentil-3,7-dihidro-1H-purino-2,6-diona	11.7	m/z 449 $[MH]^+$ TR 3.59 min
493		8-cloro-1-{4-[5-(1,1-dimetiletil)-1,2,4-oxadiazol-3-il]butil}-3-pentil-3,7-dihidro-1H-purino-2,6-diona	19.8	m/z 437 $[MH]^+$ TR 3.52 min
494		8-cloro-3-pentil-1-{4-[5-(fenilmetil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purino-2,6-diona	21.0	m/z 471 $[MH]^+$ TR 3.55 min
495		8-cloro-3-pentil-1-(4-{5-[(2,4,6-trifluorofenil)metil]-1,2,4-oxadiazol-3-il}butil)-3,7-dihidro-1H-purino-2,6-diona	29.3	m/z 525 $[MH]^+$ TR 3.62 min
496		8-cloro-3-pentil-1-{4-[5-(2-feniletil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purino-2,6-diona	18.4	m/z 485 $[MH]^+$ TR 3.64 min
497		8-cloro-3-pentil-1-{4-[5-(3-piridinil)-1,2,4-oxadiazol-3-il]butil}-3,7-dlhidro-1H-purino-2,6-diona	8.2	m/z 458 $[MH]^+$ TR 3.23 min

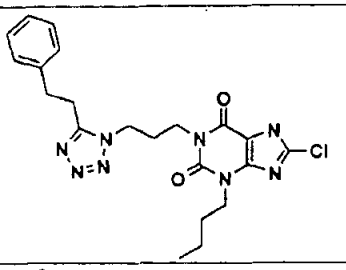
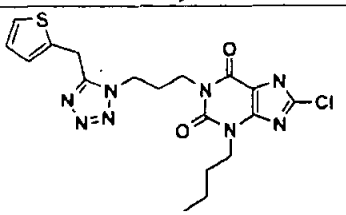
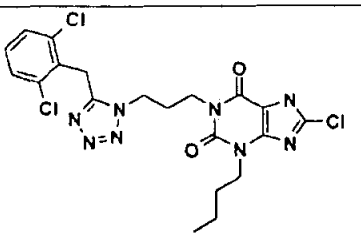
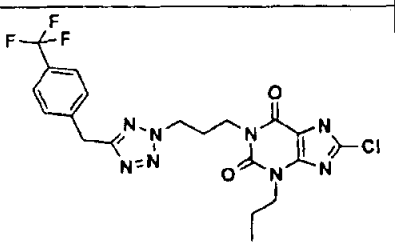
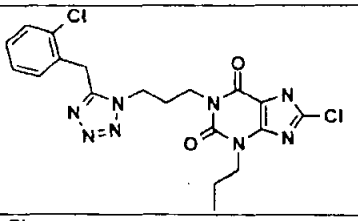
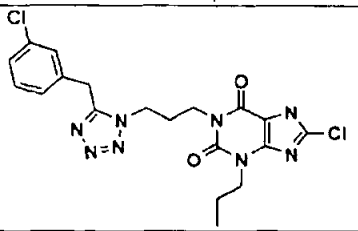
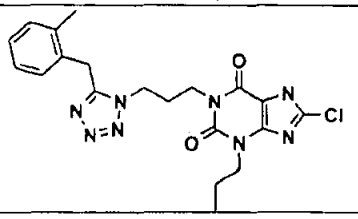
Los siguientes compuestos (cuadro 32) se prepararon usando un método análogo al del ejemplo 36, usando el tetrazol apropiado y metansulfonato de 3-[3-alquil-8-cloro-2,6-dioxo-7-(2-propen-1-il)-2,3,6,7-tetrahidro-1*H*-purin-1-il]propilo. MDAP se usó para purificar adicionalmente esos compuestos insuficientemente puros siguiendo la cromatografía de fase normal.

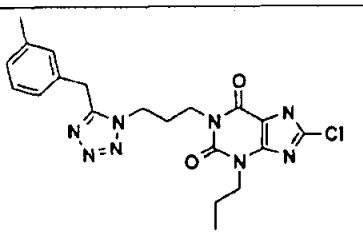
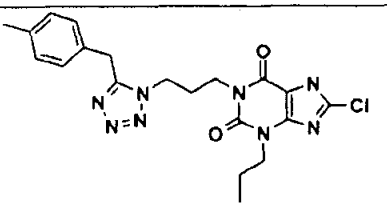
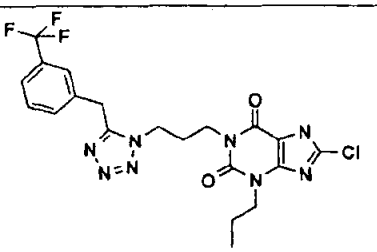
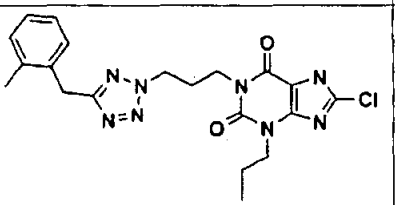
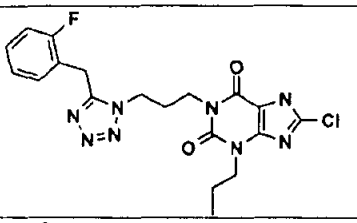
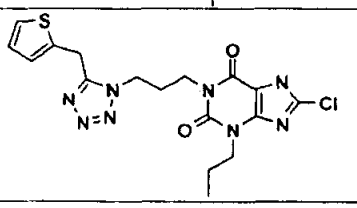
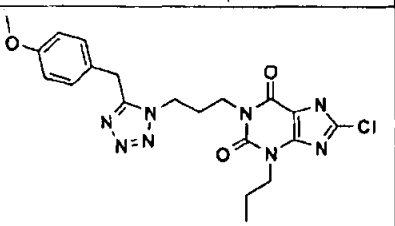
CUADRO 32

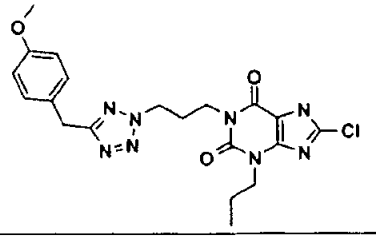
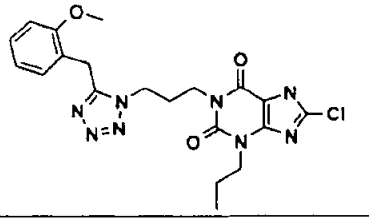
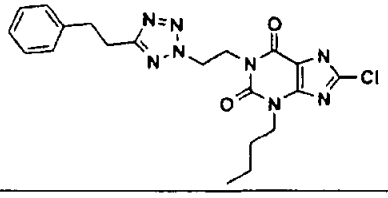
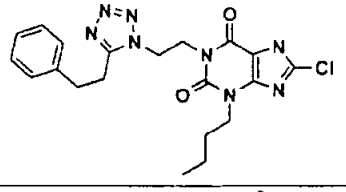
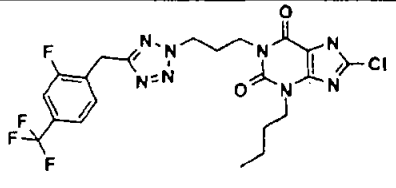
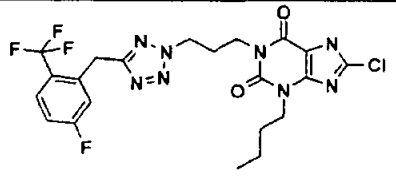
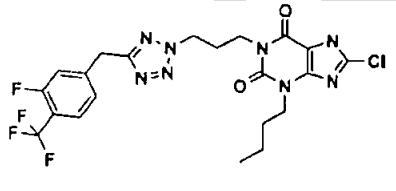
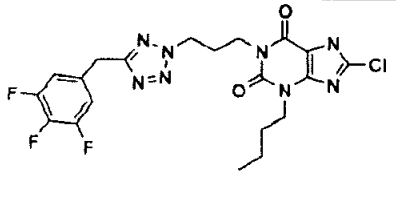
Ejemplo	Estructura	Nombre	Rend. (mg)	CL/EM:
498		3-butil-8-cloro-1-(3-{5-[(4-metilfenil)metil]-2H-tetrazol-2-il}propil)-3,7-dihidro-1H-purino-2,6-diona	35.1	m/z 457 $[MH]^+$ TR 3.40 min
499		3-butil-8-cloro-1-[3-[5-{[4-(trifluorometil)fenil]metil)-2H-tetrazol-2-il)propil]-3,7-dihidro-1H-purino-2,6-diona	43.6	m/z 511 $[MH]^+$ TR 3.52 min
500		3-butil-8-cloro-1-[3-(5-{[4-(metiloxi)fenil]-metil}-2H-tetrazol-2-il)propil]-3,7-dihidro-1H-purino-2,6-diona	38.2	m/z 473 $[MH]^+$ TR 3.24 min
501		3-butil-8-cloro-1-fluorofenil)metil]-1H-tetrazol-1-il}propil)-3,7-dihidro-1H-purino-2,6-diona	13.7	m/z 461 $[MH]^+$ TR 3.07 min

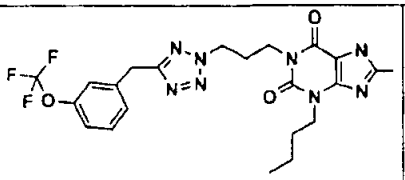
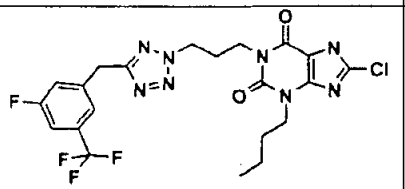
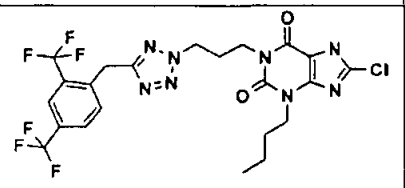
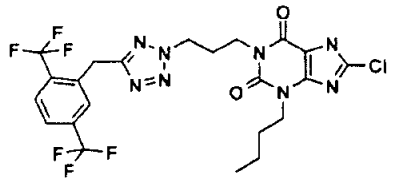
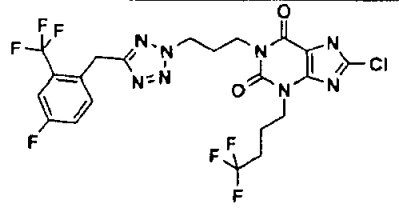
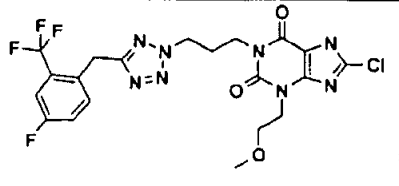
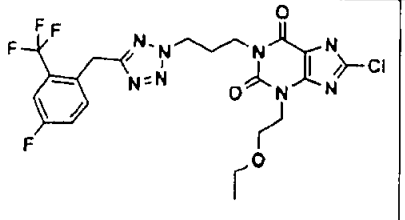
502		3-butil-8-cloro-1-(3-{5-[(3-fluorofenil)metil]-1H-tetrazol-1-il}propil)-3,7-dihidro-1H-purino-2,6-diona	15.0	m/z 461 $[MH]^+$ TR 3.10 min
503		3-butil-8-cloro-1-(3-{5-[(4-fluorofenil)metil]-1H-tetrazol-1-il}propil)-3,7-dihidro-1H-purino-2,6-diona	17.7	m/z 461 $[MH]^+$ TR 3.10 min
504		3-butil-8-cloro-1-(3-(5-[(2-clorofenil)metil]-1H-tetrazol-1-il}propil)-3,7-dihidro-1H-purino-2,6-diona	8.4	m/z 477 $[MH]^+$ TR 3.17 min
505		3-butil-8-cloro-1-(3-{5-[(3-clorofenil)metil]-1H-tetrazol-1-il}propil)-3,7-dihidro-1H-purino-2,6-diona	16.4	m/z 477 $[MH]^+$ TR 3.23 min
506		3-butil-8-cloro-1-(3-{5-[(4-clorofenil)metil]-1H-tetrazol-1-il}propil)-3,7-dihidro-1H-purino-2,6-diona	17.0	m/z 477 $[MH]^+$ TR 3.24 min
507		3-butil-8-cloro-1-metilfenil)metil]-1H-tetrazol-1-il}propil)-3,7-dihidro-1H-purino-2,6-diona	15.1	m/z 457 $[MH]^+$ TR 3.15 min
508		3-butil-8-cloro-1-(3-{5-[(3-metilfenil)metil]-1H-tetrazol-1-il}propil)-3,7-dihidro-1H-purino-2,6-diona	18.6	m/z 457 $[MH]^+$ TR 3.18 min

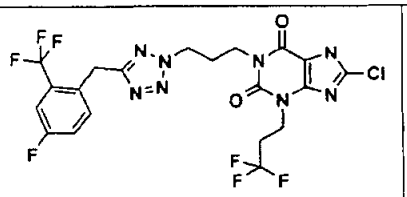
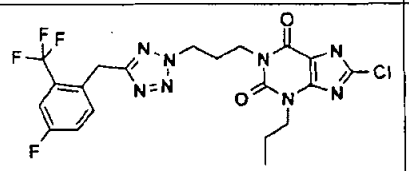
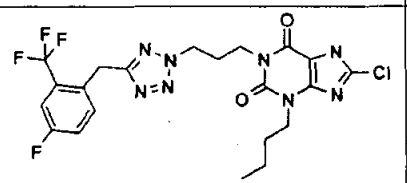
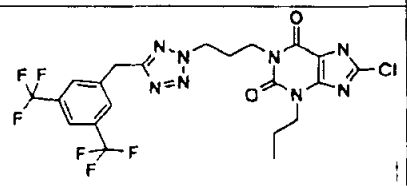
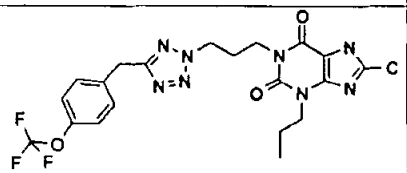
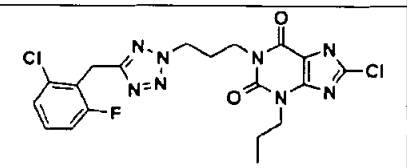
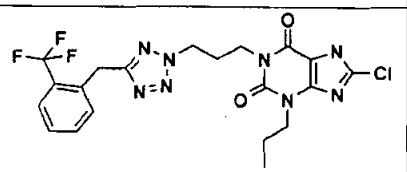
509		3-butil-8-cloro-1-(3-{5-[(4-metilfenil)metil]-1H-tetrazol-1-il}propil)-3,7-dihidro-1H-purino-2,6-diona	16.3	m/z 457 $[MH]^+$ TR 3.19 min
510		3-butil-8-cloro-1-[3-(-5-{[3-(trifluorometil)fenil]metil)-1H--tetrazol-1-il}propil)-3,7-dihidro-1H-purino-2,6-diona	17.7	m/z 511 $[MH]^+$ TR 3.31 min
511		3-butil-8-cloro-1-[3-(5-{[4-(trifluorometil)fenil]metil}-1H-tetrazol-1-il)propil]-3,7-dihidro-1H-purino-2,6-diona	21.6	m/z 511 $[MH]^+$ TR 3.33 min
512		3-butil-8-cloro-1-[3-(5-{[2-(metiloxi)fenil]-metil}-1H-tetrazol-1-il)propil]-3,7-dihidro-1H-purino-2,6-diona	16.3	m/z 473 $[MH]^+$ TR 3.10 min
513		3-butil-8-cloro-1-[3-(5-{[4-(metiloxi)fenil]-metil}-1H-tetrazol-1-il)propil]-3,7-dihidro-1H-purino-2,6-diona	20.8	m/z 473 $[MH]^+$ TR 3.05 min
514		3-butil-8-cloro-1-(3-[5-(1-fenilciclopropil)-1H-tetrazol—il]propil}-3,7-dihidro-1H-purino-2,6-diona	14.1	m/z 468 $[MH]^+$ TR 3.16 min

515		3-butil-8-cloro-1-{3-[5-(2-feniletil)-1H-tetrazol-1-il]propil}-3,7-dihidro-1H-purino-2,6-diona	21.0	m/z 457 $[MH]^+$ TR 3.15 min
516		3-butil-8-cloro-1-[3-[5-(2-tienilmetil)-1H-tetrazol-1-il]propil}-3,7-dihidro-1H-purino-2,6-diona	11.8	m/z 448 $[MH]^+$ TR 3.02 min
517		3-butil-8-cloro-1-(3-{5-[(2,6-diclorofenil)metil]-1H-tetrazol-1-il}propil)-3,7-dihidro-1H-purino-2,6-diona	12.4	m/z 512 $[MH]^+$ TR 3.27 min
518		8-cloro-3-propil-1-[3-(5-{[4-(trifluorometil)fenil]metil}-2H-ltetrazol-2-il)propil]-3,7-dihidro-1H-purino-2,6-diona	15.5	m/z 497 $[MH]^+$ TR 3.38 min
519		8-cloro-1-(3-{5-[(2-clorofenil)metil]-1H-tetrazol-1--cliclopropil)-3-propil-3,7-dihidro-1H-purino-2,6-diona	1.6	m/z 463 $[MH]^+$ TR 3.00 min
520		8-cloro-1-(3-{5-[(3-clorofenil)metil]-1H-tetrazol-1-il}propil)-3-propil-3,7-dihidro-1H-purino-2,6-diona	7.1	m/z 463 $[MH]^+$ TR 3.06 min
521		8-cloro-1-(3-{5-[(2-metilfenil)metil]-1H-tetrazol-1-il}propil)-3-propil-3,7-dihidro-1H-purino-2,6-diona	7.2	m/z 443 $[MH]^+$ TR 2.97 min

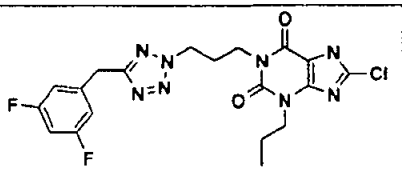
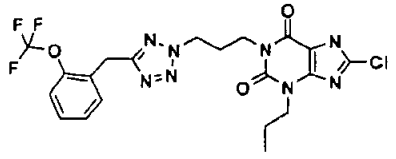
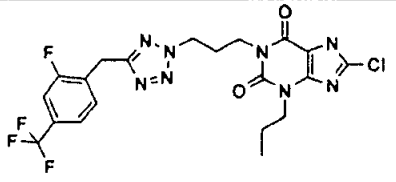
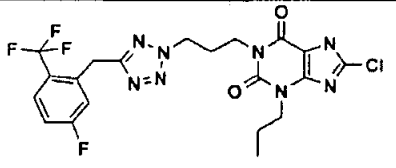
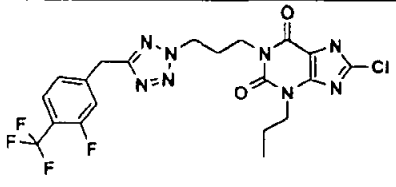
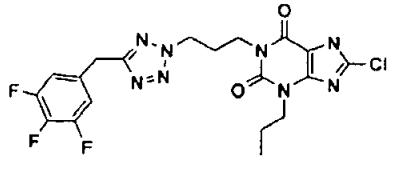
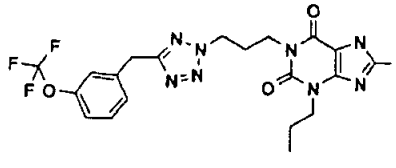
522		8-cloro-1-(3-{5-[(3-metilfenil)metil]-1H-tetrazol-1-il}propil)-3-propil-3,7-dihidro-1H-purino-2,6-diona	5.7	m/z 443 $[MH]^+$ TR 3.01 min
523		8-cloro-1-(3-{5-[(4-metilfenil)metil]-1H-tetrazol-1-il}propil)-3-propil-3,7-dihidro-1H-purino-2,6-diona	5.5	m/z 443 $[MH]^+$ TR 3.01 min
524		8-cloro-3-propil-1-[3-(5-{[3-(trifluorometil)fenil]metil}-1H-tetrazol-1-il)propil]-3,7-dihidro-1H-purino-2,6-diona	3.3	m/z 497 $[MH]^+$ TR 3.16 min
525		8-cloro-1-(3-{5-[(2-metilfenil)metil}-2H-tetrazol-2-il}propil)-3-propil-3,7-dihidro-1H-purino-2,6-diona	24.1	m/z 443 $[MH]^+$ TR 3.20 min
526		8-cloro-1-(3-{5-[(2-fluorofenil)metil]-1H-tetrazol-1-il}propil)-3-propil]-3,7-dihidro-1H-purino-2,6-diona	1.3	m/z 447 $[MH]^+$ TR 2.89 min
527		8-cloro-3-propil-1-{3-[5-(2-tienilmetil)-1H-tetrazol-1-il]propil)-3,7-dihidro-1H-purino-2,6-diona	5.2	m/z 435 $[MH]^+$ TR 2.83 min
528		8-cloro-1-[3-(5-{[4-(metiloxi)fenil]-metil)-1H-tetrazol-1-il)propil]-3-propil-3,7-dihidro-1H-purino-2,6-diona	1.2	m/z 459 $[MH]^+$ TR 2.87 min

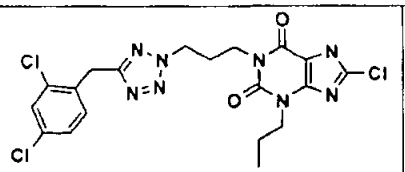
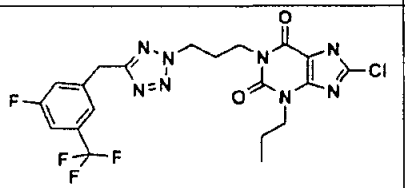
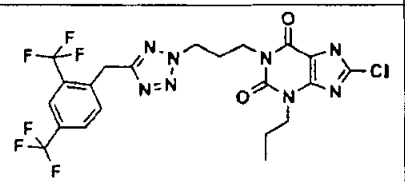
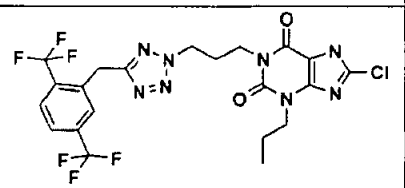
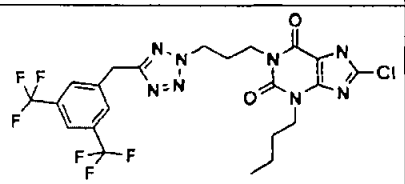
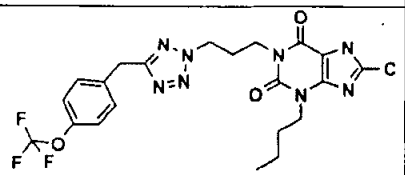
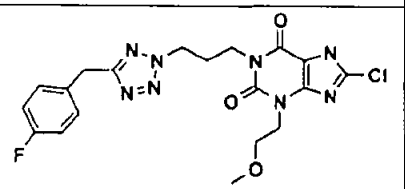
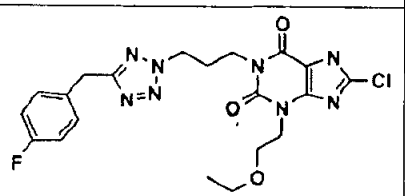
529		8-cloro-1-[3-(5-{[4-(metiloxi)fenil]metil}-2H-tetrazol-2-il)propil]-3-propil-3,7-dihidro-1H-purino-2,6-diona	19.7	m/z 459 $[MH]^+$ TR 3.07 min
530		8-cloro-1-[3-(5-{[2-(metiloxi)fenil]metil}-1H-tetrazol-il)propil]-3-propil-3,7-dihidro-1H-purino-2,6-diona	1.9	m/z 459 $[MH]^+$ TR 2.92 min
531		3-butil-8-cloro-1-{2-[5-(2-feniletil)-2H-tetrazol-2-il]etil}-3,7-dihidro-1H-purino-2,6-diona	44.0	m/z 443 $[MH]^+$ TR 3.31 min
532		3-butil-8-cloro-1-{2-[5-(2-feniletil)-1H-tetrazol-1-il]etil}-3,7-dihidro-1H-purino-2,6-diona	10.4	m/z 443 $[MH]^+$ TR 3.12 min
533		3-butil-8-cloro-1-[3-(5-{[2-fluoro-4-(trifluorometil)fenil]metil}-2H-tetrazol-2-il)propil]-3,7-dihidro-1H-purino-2,6-diona	24.5	m/z 529 $[MH]^+$ TR 3.22 min
534		3-butil-8-cloro-1-[3-(5-{[5-fluoro-2-(trifluorometil)fenil]metil}-2H-tetrazol-2-il)propil]-3,7-dihidro-1H-purino-2,6-diona	25.3	m/z 529 $[MH]^+$ TR 3.51 min
535		3-butil-8-cloro-1-[3-(5-{[3-fluoro-4-(trifluorometil)fenil]metil}-2H-tetrazol-2-il)propil]-3,7-dihidro-1H-purino-2,6-diona	11.5	m/z 529 $[MH]^+$ TR 3.56 min
536		3-butil-8-cloro-1-(3-{5-[(3,4,5-trifluorofenil)metil]-2H-tetrazol-2-il}propil)-3,7-dihidro-1H-purino-2,6-diona	19.4	m/z 497 $[MH]^+$ TR 3.45 min

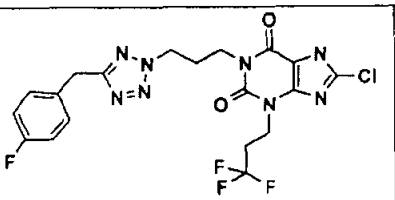
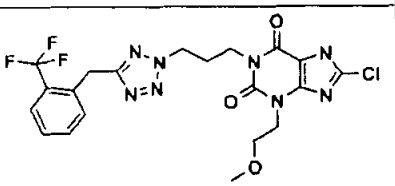
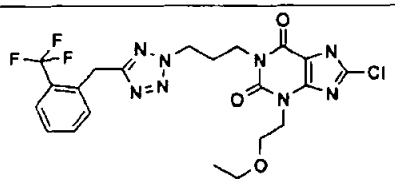
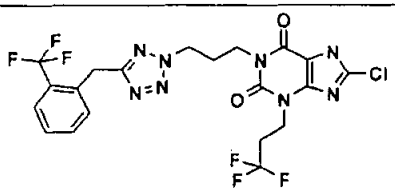
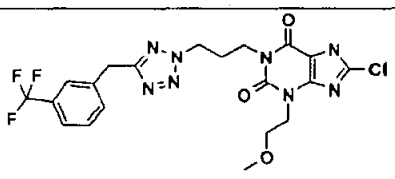
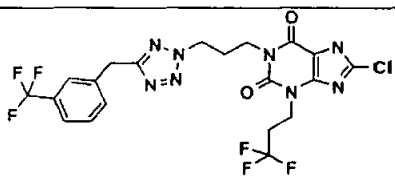
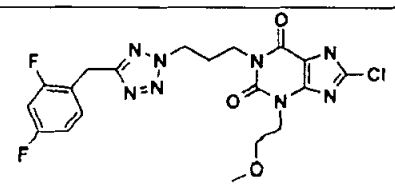
537		3-butil-8-cloro-1-{3-[5-({3-(trifluorometil)oxi]fenil)metil)-2H-tetrazol-2-il]propil}-3,7-dihidro-1H-purino-2,6-diona	27.2	m/z 527 $[MH]^+$ TR 3.55 min
538		3-butil-8-cloro-1-[3-(5-{[3-fluoro-5-(trifluorometil)fenil]metil}-2H-tetrazol-2-il)propil]-3,7-dihidro-1H-purino-2,6-diona	19.8	m/z 529 $[MH]^+$ TR 3.56 min
539		1-[3-(5-{[2,4-bis(trifluorometil)fenil]metil}-2H-tetrazol-2-il)propil]-3-butil-8-cloro-3,7-dihidro-1H-purino-2,6-diona	36.6	m/z 579 $[MH]^+$ TR 3.72 min
540		1-[3-(5-{[2,5-bis(trifluorometil)fenil]rnetil}-2H-tetrazol-2-il)propil]-3-butil-8-cloro-3,7-dihidro-1H-purino-2,6-diona	50.3	m/z 579 $[MH]^+$ TR 3.65 min
541		8-cloro-1-[3-(5-{[4-fluoro-2-(trifluorometil)fenil]metil}-2H-tetrazol-2-il)propil]-3-(4,4,4-trifluorobutil)-3,7-dihidro-1H-purino-2,6-diona	25.0	m/z 583 $[MH]^+$ TR 3.50 min
542		8-cloro-1-[3-(5-{[4-fluoro-2-(trifluorometil)fenil]metil}-2H-tetrazol-2-il)propil]-3-[2-(metiloxi)etil]-3,7-dihidro-1H-purino-2,6-diona	23.0	m/z 531 $[MH]^+$ TR 3.16 min
543		8-cloro-3-[2-(etiloxi)etil]-1-[3-(5-([4-fluoro-2-(triflubrometil)fenil]metil}-2H-tetrazol-2-il)propil]-3,7-dihidro-1H-purino-2,6-diona	13.1	m/z 545 $[MH]^+$ TR 3.30 min

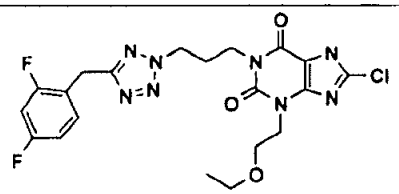
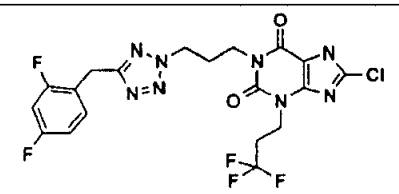
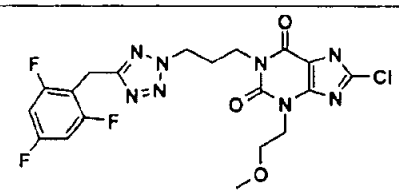
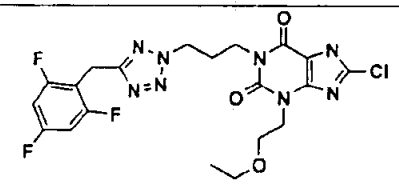
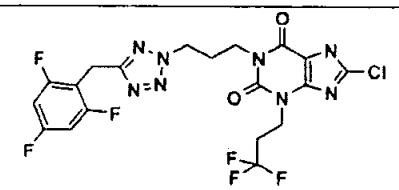
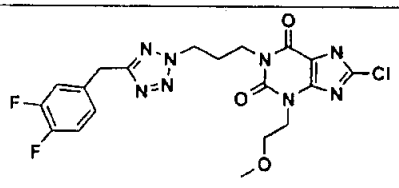
544		8-cloro-1-[3-(5-([4-fluoro-2-(trifluorometil)fenil]metil}-2H-tetrazol-2-il)propil]-3-(3,3,3-trifluoropropil)-3,7-dihidro-1H-purino-2,6-diona	36.3	m/z 569 $[MH]^+$ TR 3.46 min
545		8-cloro-1-[3-(5-{[4-fluoro-2-(trifluorometil)fenil]metil}-2H-tetrazol-2-il)propil]-3-propil-3,7-dihidro-1H-purino-2,6-diona	32.0	m/z 515 $[MH]^+$ TR 3.37 min
546		3-butil-8-cloro-1-[3-(5-{[4-fluoro-2-(trifluorometil)fenil]metil}-2H-tetrazol-2-il)propil]-3,7-dihidro-1H-purino-2,6-diona	30.3	m/z 529 $[MH]^+$ TR 3.53 min
547		1-[3-(5-{[3,5-bis(trifluorometil)fenil]metil}-2H-tetrazol-2-il)propil]-8-cloro-3-propil-3,7-dihidro-1H-purino-2,6-diona	22.9	m/z 565 $[MH]^+$ TR 3.54 min
548		8-cloro-3-propil-1-{3-[5-{[4-[(trifluorometil)oxi]fenil}metil]-2H-tetrazol-2-il]propil]-3,7-dihidro-1H-purino-2,6-diona	21.6	m/z 513 $[MH]^+$ TR 3.42 min
549		8-cloro-1-(3-{5-[(2-cloro-6-fluorofenil)metil]-2H-tetrazol-2-il}propil)-3-propil-3,7-dihidro-1H-purino-2,6-diona	12.4	m/z 481 $[MH]^+$ TR 3.20 min
550		8-cloro-3-propil-1-[3-(5-{[2-(trifluorometil)fenil]metil}-2H-tetrazol-2-il)propil]-3,7-dihidro-1H-purino-2,6-diona	17.7	m/z 497 $[MH]^+$ TR 3.26 min

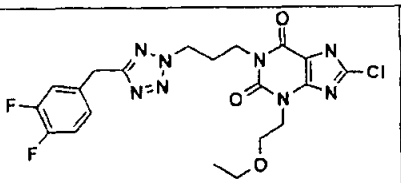
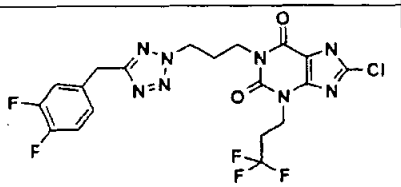
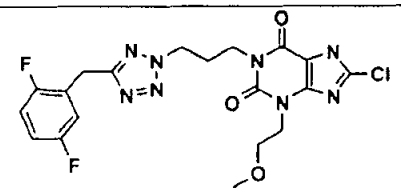
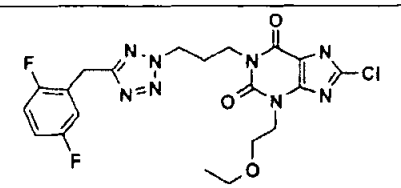
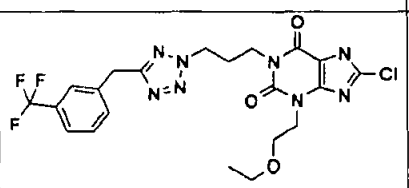
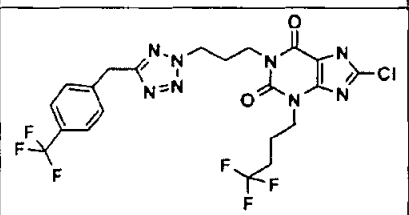
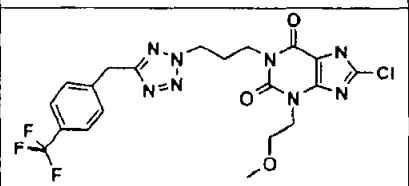
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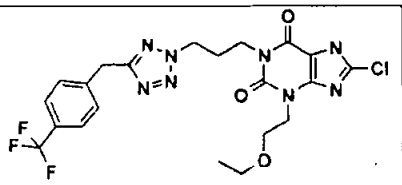
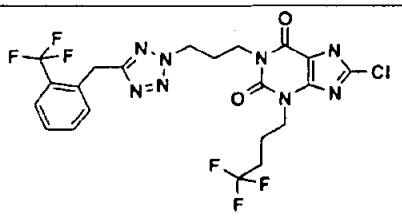
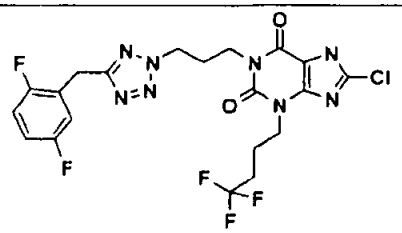
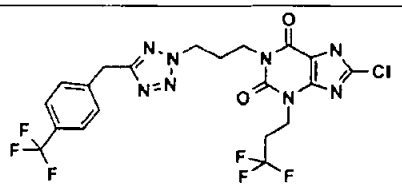
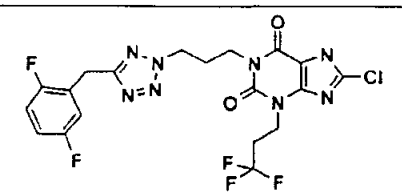
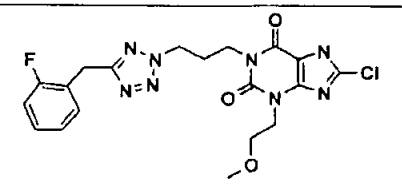
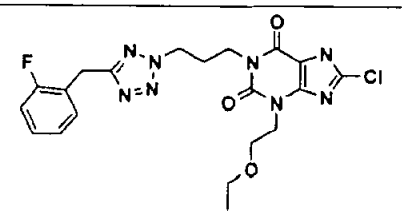
551		8-cloro-1-(3-{5-[(3,5-difluorofenil)metil]-2H-tetrazol-2-il}propil)-3-propil-3,7-dihidro-1H-purino-2,6-diona	21.6	m/z 465 $[MH]^+$ TR 3.16 min
552		8-cloro-3-propil-1-{3-[5-({2-(trifluorometil)oxi]fenil}metil)-2H-tetrazol-2-il}propil)-3,7-dihidro-1H-purino-2,6-diona	22.3	m/z 513 $[MH]^+$ TR 3.27 min
553		8-cloro-1-[3-(5-{[2-fluoro-4-(trifluorometil)fenil]metil}-2H-tetrazol-2-il)propil]-3-propil-3,7-dihidro-1H-purino-2,6-diona	9.7	m/z 515 $[MH]^+$ TR 3.40 min
554		8-cloro-1-[3-(5-{[5-fluoro-2-(trifluorometil)fenil]metil}-2H-tetrazol-2-il)propil]-3-propil-3,7'-dihidro-1H-purino-2,6-diona	26.8	m/z 515 $[MH]^+$ TR 3.26 min
555		8-cloro-1-[3-(5-{[3-fluoro-4-(trifluorometil)fenil]metil)-2H-tetrazol-2-il}propil)-3-propil-3,7-dihidro-1H-purino-2,6-diona	20.7	m/z 515 $[MH]^+$ TR 3.31 min
556		8-cloro-3-propil-1-(3-{5-[(3,4,5-trifluorofenil)metil]-2H-tetrazol-2-il}propil)-3,7-dihidro-1H-purino-2,6-diona	10.2	m/z 483 $[MH]^+$ TR 3.23 min
557		8-cloro-3-propil-1-{3-[5-({3-[(trifluorometil)oxi]fenil}metil)-2H-tetrazol-2-il}propil]-3,7-dihidro-1H-purino-2,6-diona	9.8	m/z 513 $[MH]^+$ TR 3.35 min

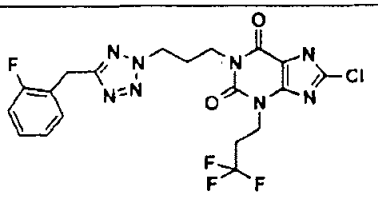
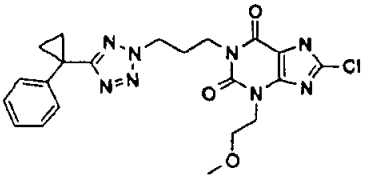
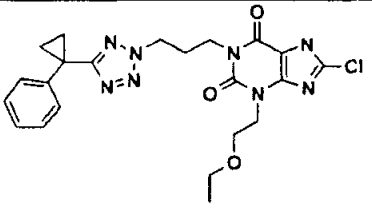
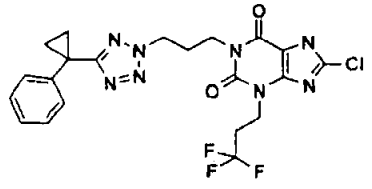
558		8-cloro-1-(3-{5-[(2,4-diclorofenil)metil]-2H-tetrazol-2-il}propil)-3-propil-3,7-dihidro-1H-purino-2,6-diona	27.6	m/z 497 $[MH]^+$ TR 3.40 min
559		8-cloro-1-[3-(5-{[3-fluoro-5-(trifluorometil)fenil]metil)-2H-tetrazol-2-il)propil]-3-propil-3,7-dihidro-1H-purino-2,6-diona	17.6	m/z 515 $[MH]^+$ TR 3.23 min
560		1-[3-(5-{[2,4-bis(trifluorometil)fenil]metil}-2H-tetrazol-2-il)propil]-8-cloro-3-propil-3,7-dihidro-1H-purino-2,6-diona	21.0	m/z 565 $[MH]^+$ TR 3.40 min
561		1-[3-(5-{[2,5-bis(trifluorometil)fenil]metil)-2H-tetrazol-2-il)propil]-8-cloro-3-propil-3,7-dihidro-1H-purino-2,6-diona	9.7	m/z 565 $[MH]^+$ TR 3.50 min
562		1-[3-(5-{[3,5-bis(trifluorometil)fenil]metil}-2H-tetrazol-2-il)propil]-3-butil-8-cloro-3,7-dihidro-1H-purino-2,6-diona	28.1	m/z 579 $[MH]^+$ TR 3.68 min
563		3-butil-8-cloro-1-[(trifluorometil)oxi]fenil}metil)-2H-tetrazol-2-il]propil)-3,7-dihidro-1H-purino-2,6-diona	32.1	m/z 527 $[MH]^+$ TR 3.57 min
564		8-cloro-1-(3-{5-[(4-fluorofenil)metil]-2H-tetrazol-2-il}propil)-3-[2-(metiloxi)etil}-3,7-dihidro-1H-purino-2,6-diona	15.0	m/z 463 $[MH]^+$ TR 2.89 min
565		8-cloro-3-[2-(etiloxi)etil]-1-(3-{5-[(4-fluorofenil)metil]-2H-tetrazol-2-il}propil)-3,7-dihidro-1H-purino-2,6-diona	12.6	m/z 477 $[MH]^+$ TR 3.03 min

566		8-cloro-1-(3-{5-[(4-fluorofenil)metil]-2H-tetrazol-2-il}propil)-3-(3,3,3-trifluoropropil)-3,7-dihidro-1H-purino-2,6-diona	17.8	m/z 501 $[MH]^+$ TR 3.21 min
567		8-cloro-3-[2-(metiloxi)etil]-1-[3-(5-{[2-(trifluorometil)fenil]metil}-2H-tetrazol-2-il)propil]-3,7-dihidro-1H-purino-2,6-diona	14.2	m/z 513 $[MH]^+$ TR 3.10 min
568		8-cloro-3-[2-(etiloxi)etil]-1-[3-(5-{[2-(trifluorometil)fenil]metil}-2H-tetrazol-2-il)propil]-3,7-dihidro-1H-purino-2,6-diona	20.8	m/z 527 $[MH]^+$ TR 3.18 min
569		8-cloro-1-[3-(5-{[2-(trifluorometil)fenil]metil}-2H-tetrazol-2-il)propil]-3-(3,3,3-trifluoropropil)-3,7-dihidro-1H-purino-2,6-diona	35.8	m/z 551 $[MH]^+$ TR 3.35 min
570		8-cloro-3-[2-(metiloxi)etil]-1-[3-(5-{[3-(trifluorometil)fenil]metil}-2H-tetrazol-2-il)propil]-3,7-dihidro-1H-purino-2,6-diona	15.3	m/z 513 $[MH]^+$ TR 3.14 min
571		8-cloro-1-[3-(5-{[3-(trifluorometil)fenil]metil}-2H-tetrazol-2-il)propil]-3-(3,3,3-trifluoropropil)-3,7-dihidro-1H-purino-2,6-diona	29.4	m/z 551 $[MH]^+$ TR 3.42 min
572		8-cloro-1-(3-{5-[(2,4-difluorofenil)metil]-2H-tetrazol-2-il}propil)-3-[2-(metiloxi)etil]-3,7-dihidro-1H-purino-6-diona	17.8	m/z 481 $[MH]^+$ TR 2.96 min

573		8-cloro-1-(3-{5-[(2,4-difluorofenil)metil]-2H-tetrazol-2-il}propil)-3-[2-(etiloxi)etil]-3,7-dihidro-1H-purino-2,6-diona	14.4	m/z 495 $[MH]^+$ TR 2.86 min
574		8-cloro-1-(3-(5-[(2,4-difluorofenil)metil]-2H-tetrazol-2-il}propil)-3-(3,3.3-trifluoropropil)-3,7-dihidro-1H-purino-2,6-diona	29.9	m/z 519 $[MH]^+$ TR 3.19 min
575		8-cloro-3-[2-(metiloxi)etil]-1-(3-{5-[(2.4,6-trifluorofenil)metil]-2H-tetrazol-2-il}propil)-3,7-dihidro-1H-purino-2,6-diona	21.3	m/z 499 $[MH]^+$ TR 2.93 min
576		8-cloro-3-[2-(etiloxi)etil]-1-(3-{5-[(2,4,6-trifluorofenil)metil]-2H-tetrazol-2-il}propil)-3,7-dihidro-1H-purino-2,6-diona	15.5	m/z 513 $[MH]^+$ TR 2.93 min
577		8-cloro-1-(3-{5-[(2,4,6-trifluorofenil)metil]-2H-tetrazol-2-il}propil)-3-(3,3,3-trifluoropropil)-3,7-dihidro-1H-purino-2,6-diona	32.3	m/z 537 $[MH]^+$ TR 3.29 min
578		8-cloro-1-(3-{5-[(3,4-difluorofenil)metil]-2H-tetrazol-2-il}propil)-3-[2-(metiloxi)etil}-3,7-dihidro-1H-purino-2,6-diona	14.5	m/z 481 $[MH]^+$ TR 2.97 min

579		8-cloro-1-(3-{5-[(3,4-difluorofenil)metil]-2H-tetrazol-2-il}propil)-3-[2-(etiloxi)etil]-3,7-dihidro-1H-purino-2,6-diona	7.2	m/z 495 $[MH]^+$ TR 3.06 min
580		8-cloro-1-(3-{5-[(3,4-difluorofenil)metil]-2H-tetrazol-2-il}propil)-3-(3,3,3-trifluoropropil)-3,7-dihidro-1H-purino-2,6-diona	27.8	m/z 519 $[MH]^+$ TR 3.27 min
581		8-cloro-1-(3-{5-[(2,5-difluorofenil)metil]-2H-tetrazol-2-il}propil)-3-[2-(metiloxi)etil]-3,7-dihidro-1H-purina-2,6-diona	17.1	m/z 481 $[MH]^+$ TR 2.89 min
582		8-cloro-1-(3-{5-[(2,5-difluorofenil)metil]-2H-tetrazol-2-il}propil)-3-[2-(etiloxi)etil]-3,7-dihidro-1H-purino-2,6-diona	13.5	m/z 495 $[MH]^+$ TR 3.05 min
583		8-cloro-3-[2-(etiloxi)etil]-1-3-(5-{[3-(trifluorometil)fenil]metil}-2H-tetrazol-2-il)propil]-3,7-dihidro-1H-purino-2,6-diona	14.6	m/z 527 $[MH]^+$ TR 3.26 min
584		8-cloro-3-(4,4,4-trifluorobutil)-1-[3-(5-{[4-(trifluorometil)fenil]metil}-2H-tetrazol-2-il)propil]-3,7-dihidro-1H-purino-2,6-diona	12.1	m/z 565 $[MH]^+$ TR 3.51 min
585		8-cloro-3-[2-(metiloxi)etil]-1-[3-(5-{[4-(trifluorometil)fenil]metil)-2H-tetrazol-2-il)propil]-3,7-dihidro-1H-purino-2,6-diona	17.3	m/z 513 $[MH]^+$ TR 3.17 min

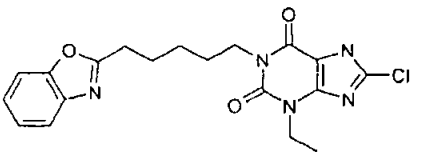
586		8-cloro-3-[2-(etiloxi)etil]-1-[3-(5-{[4-(trifluorometil)fenil]metil}-2H-tetrazol-2-il)propil]-3,7-dihidro-1H-purino-2,6-diona	15.2	m/z 527 $[MH]^+$ TR 3.30 min
587		8-cloro-3-(4,4,4-trifluorobutil)-1-[3-(5-{[2-(trifluorometil)fenil]metil}-2H-tetrazol-2-il)propil]-3,7-dihidro-1H-purino-2,6-diona	5.8	m/z 565 $[MH]^+$ TR 3.46 min
588		8-cloro-1-(3-{5-[(2,5-difluorofenil)rnetil]-2H-tetrazol-2-il}propil)-3-(4,4,4-trifluorobutil)-3,7-dihidro-1H-purino-2,6-diona	14.7	m/z5337 $[MH]^+$ TR 3.34 min
589		8-cloro-1-[3-(5-{[4-(trifluorometil)fenil]metil}-2H-tetrazol-2-il)propil]-3-(3,3,3-trifluoropropil)-3,7-dihidro-1H-purino-2,6-diona	26.1	m/z 551 $[MH]^+$ TR 3.46 min
590		8-cloro-1-(3-{5-[(2,5-difluorofenil)metil]-2H-tetrazol-2-il}propil)-3-(3,3,3-trifluoropropil)-3,7-dihidro-1H-purino-2,6-diona	18.0	m/z 519 $[MH]^+$ TR 3.29 min
591		8-cloro-1-(3-{5-[(2-fluorofenil)metil]-2H-tetrazol-2-il}propil)-3-[2-(metiloxi)etil]-3,7-dihidro-1H-purino-2,6-diona	3.4	m/z 463 $[MH]^+$ TR 2.84 min
592		8-cloro-3-[2-(etiloxi)etil]-1-(3-{5-[(2-fluorofenil)metil]-2H-tetrazol-2-il}propil)-3,7-dihidro-1H-purino-2,6-diona	8.2	m/z 477 $[MH]^+$ TR 2.85 min

593		8-cloro-1-(3-{5-[(2-fluorofenil)metil]-2H-tetrazol-2-il}propil)-3-(3,3,3-trifluoropropil)-3,7-dihidro-1H-purino-2,6-diona	32.7	m/z 501 $[MH]^+$ TR 3.25 min
594		8-cloro-3-[2-(metiloxi)etil]-1-(3-[5-(1-fenilciclopropil)-2H-tetrazol-2-il]propil}-3,7-dihidro-1H-purino-2,6-diona	10.2	m/z 471 $[MH]^+$ TR 2.93 min
595		8-cloro-3-[2-(etitoxi)etil]-1-fenilciclopropil)-2H-tetrazol-2-il]propil)-3,7-dihidro-1H-purino-2,6-diona	15.2	m/z 485 $[MH]^+$ TR 2.96 min
596		8-cloro-1-{3-[5-(1-fenilciclopropil)-2H-tetrazol-2-il]propil}-3-(3,3,3-trifluoropropil)-3,7-dihidro-1H-purino-2,6-diona	4.6	m/z 509 $[MH]^+$ TR 3.00 min

EJEMPLO 597

1-[5-(1,3-Benzoxazol-2-il)pentil]-8-cloro-3-etil-3,7-dihidro-1*H*-purina-2,6-diona

a) 1-[5-(1,3-Benzoxazol-2-il)pentil]-8-cloro-3-etil-3,7-dihidro-1*H*-purina-2,6-diona

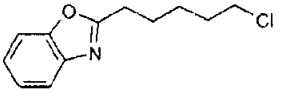


a) Una solución de 3-etil-8-cloro-7-(2-propen-il)-3,7-dihidro-1H-purina-2,6-diona (0.095 g, 0.37 mmoles) en DMF (10 ml) se trató sobre carbonato de potasio (0.0615 g, 0.45 mmoles) y 2-(5-cloropentil)-1,3-benzoxazol (0.091 g, 0.41 mmoles) y la mezcla se calentó a 70°C durante 4.5 hr. La mezcla se enfrió y se desgasificó mediante la aplicación repetida de vacío a la mezcla de reacción y rellenado subsecuente con nitrógeno gaseoso y después se trató con tetrakis(trifenilfosfin)paladio(0) (0.043 g, 0.037 mmoles) y morfolina (0.32 ml, 3.7 mmoles) y la mezcla se agitó durante 4 hr en una atmósfera de nitrógeno. La mezcla se evaporó a sequedad y el residuo se dividió entre 25 ml de acetato de etilo y 25 ml de salmuera. La fase acuosa se volvió a extraer con 25 ml de acetato de etilo y los compuestos orgánicos combinados se secaron sobre sulfato de magnesio, se filtraron y se evaporaron. El residuo se disolvió en 5 ml de metanol y se añadió a un SPE de aminopropilo 5 g que se lavó subsecuentemente con metanol y el producto

se eluyó con una solución al 5% de ácido acético en metanol. Las fracciones que contenían producto se pusieron en acervo y se evaporaron para revelar una goma incolora que se trituró con éter dietílico y se secó para dar el compuesto del título como un sólido blanco (0.0538 g, 36%).

CL/EM: m/z 402 $[MH]^+$, TR 3.06 min

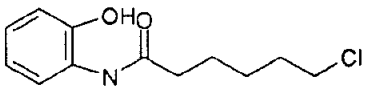
b) 2-(5-Cloropentil)-1,3-benzoxazol



6-Cloro-N-(2-hidroxifenil)hexanamida (0.95 g, 3.9 mmoles) se trató con tolueno (20 ml) y ácido 4-toluensulfónico monohidratado (0.05 g, 0.26 mmoles) y la mezcla se calentó en el microondas a 160°C durante 1 hr, después se enfrió y se evaporó. El residuo se dividió entre 25 ml de acetato de etilo y 25 ml de bicarbonato de sodio acuoso saturado. La fase acuosa se extrajo dos veces más con 25 ml de acetato de etilo y los compuestos orgánicos combinados se secaron sobre sulfato de magnesio, se filtraron y se evaporaron a sequedad. El producto después se purificó por cromatografía instantánea (gradiente de elución: ciclohexano a ciclohexano/acetato de etilo 1:1) para dar 2-(5-cloropentil)-1,3- benzoxazol como un aceite incoloro que se solidificó en reposo (0.47 g, 53%).

CL/EM: m/z 224 $[MH]^+$, TR 3.32min

c) 6-cloro-*N*-(2-hidroxifenil)hexanamida

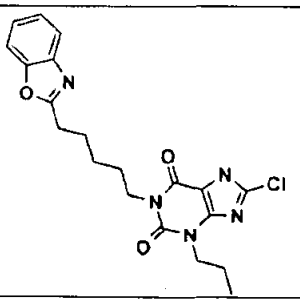


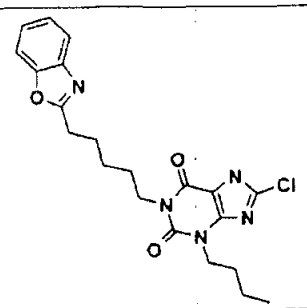
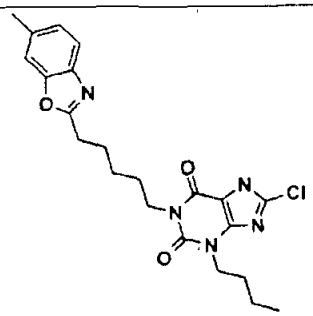
2-Aminofenol (0.5 g, 4.6 mmoles) se agitó en acetato de etilo (15 ml) y se trató gota a gota con cloruro de 6-clorohexanoilo (0.664 ml, 5.5 mmoles) y después gota a gota con trietilamina (0.95 ml, 6.9 mmoles). Después de 1 hr, la mezcla se lavó con 2 x 25 ml de bicarbonato de sodio acuoso saturado y la fase orgánica se secó sobre sulfato de magnesio, se filtró y se evaporó a sequedad para dar 6-cloro-*N*-(2-hidroxifenil)hexanamida como un sólido café pálido (0.05 g, 86%).

CL/EM: m/z 242 $[MH]^+$, TR 2.95 min.

Los siguientes compuestos (cuadro 33) se prepararon usando un método análogo al del ejemplo 597.

CUADRO 33

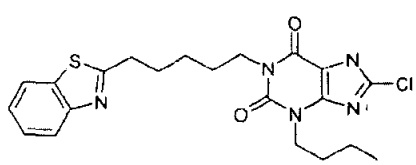
Ejemplo	Estructura	Nombre	Rend. (mg)	CL/EM:
598		1-[5-(1,3-benzoxazol-2-il)pentil]-8-cloro-3-propil-3,7-dihidro-1H-purino-2,6-diona	60.5	m/z 416 $[MH]^+$ TR 3.23 min

599		1-[5-(1,3-benzoxazol-2-il)pentil]-3-butil-8-cloro-3,7-dihidro-1H-purino-2,6-diona	55.1	m/z 428 $[MH]^+$ TR 3.42 min
600		3-butil-8-cloro-1-[5-(6-metil-1,3-benzoxazol-2-il)pentil]-3,7-dihidro-1H-purino-2,6-diona	68.9	m/z 444 $[MH]^+$ TR 3.56 min

EJEMPLO 601

1-[5-(1,3-Benzotiazol-2-il)pentil]-3-butil-8-cloro-3,7-dihidro-1*H*-purina-2,6-diona

a) 1-[5-(1,3-Benzotiazol-2-il)pentil]-3-butil-8-cloro-3,7-dihidro-1*H*-purina-2,6-diona

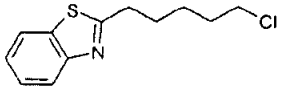


Una solución de 3-butil-8-cloro-7-(2-propen-1-il)-3,7-dihidro-1*H*-purina-2,6-diona (0.053 g, 0.19 mmoles) en DMF (5 ml) se trató sobre carbonato de potasio (0.026 g, 0.19 mmoles) y 2-(5-cloropentil)-1,3-benzotiazol (0.0498 g, 0.21 mmoles) y la mezcla se calentó a 60°C durante 3

días. La mezcla se enfrió y se desgasificó mediante la aplicación repetida de vacío a la mezcla de reacción y rellenado subsecuente con nitrógeno gaseoso y después se trató con tetrakis(trifenilfosfin)paladio(0) (0.0294 g, 0.025 mmoles) y morfolina (0.164 ml, 1.9 mmoles) y la mezcla se agitó durante 18 horas en una atmósfera de nitrógeno. La mezcla se evaporó a sequedad y el residuo se dividió entre 25 ml de acetato de etilo y 25 ml de bicarbonato de sodio acuoso saturado. La fase orgánica se secó sobre sulfato de magnesio, se filtró y se evaporó. El residuo se disolvió en 5 ml de metanol y se añadió a un SPE de aminopropilo de 5 g que se lavó subsecuentemente con metanol y el producto se eluyó con una solución al 5% de ácido acético en metanol. Las fracciones que contenían producto se pusieron en acervo y se evaporaron y el residuo se sometió a purificación por MDAP para dar el compuesto del título como un sólido blanco (0.0101 g, 12%).

CL/EM: m/z 446 $[MH]^+$, TR 3.55 min.

b) 2-(5-Cloropentil)-1,3-benzotiazol



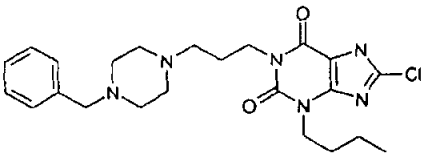
Una solución enfriada con hielo de 2-aminotiofenol (0.376 ml, 3.54 mmoles) en THF anhidro (5 ml) se trató con diisopropiletilamina (0.62 ml, 3.54 mmoles) seguido por cloruro de 6-clorohexanoilo (0.36 ml, 2.95 mmoles). La mezcla se agitó a temperatura ambiente durante 2 hr, después se calentó a

reflujo durante 19 hr y después se enfrió y se diluyó con DCM (10 ml). La solución se lavó con 10 ml de ácido clorhídrico acuoso 2M, 10 ml de hidróxido de sodio acuoso 2M y 10 ml de salmuera; se secó sobre sulfato de magnesio, se filtró y se evaporó para revelar 0.4122 g de un aceite amarillo pálido. El producto se purificó por cromatografía instantánea usando un gradiente de elución de ciclohexano a ciclohexano/acetato de etilo (7:3) para dar 2-(5-cloropentil)-1,3-benzotiazol como un aceite incoloro (0.0541 g, 6%).

CL/EM: m/z 240 $[MH]^+$, TR 3.48 min.

EJEMPLO 602

3-Butil-8-cloro-1-{3-[4-(fenilmetil)-1-piperazinil]propil}-3,7-dihidro-1*H*-purina-2,6-diona



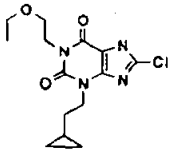
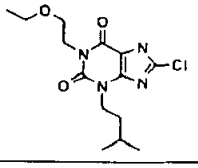
Una solución de metansulfonato de 3-[3-butil-8-cloro-2,6-dioxo-7-(2-propen-1-il)-2,3,6,7-tetrahidro-1*H*-purin-1-il]propilo (0.08 g, 0.19 mmoles) en DMF (5 ml) se trató sobre carbonato de potasio (0.08 g, 0.6 mmoles) y 1-bencilpiperazina (0.04 g, 0.23 mmoles) y después se calentó a 70°C durante 2 hr. La mezcla se enfrió, se evaporó a sequedad y se dividió entre 10 ml de DCM y 10 ml de agua. La fase orgánica se evaporó a sequedad y el residuo se disolvió en THF anhidro (5 ml). La solución se desgasificó cuidadosamente mediante la aplicación repetida de vacío a la mezcla de reacción y rellenado

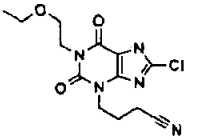
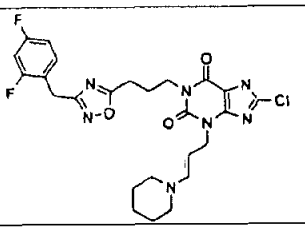
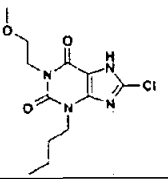
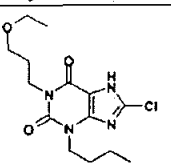
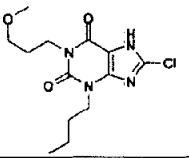
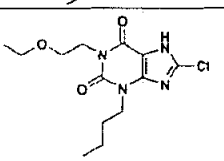
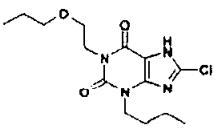
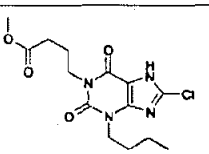
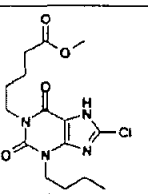
subsecuente con nitrógeno gaseoso y después se trató con tetrakis-(trifenilfosfin)paladio(0) (0.010 g, 0.009 mmoles) y morfolina (0.200 ml, 2.3 mmoles) y la mezcla se agitó durante 2 hr en una atmósfera de nitrógeno. La mezcla se evaporó y el residuo se recogió en 5 ml de metanol y se añadió a un cartucho de SPE de aminopropilo 2g que después se lavó con metanol y el producto eluido, usando una solución al 3% de ácido acético en metanol. Las fracciones que contenían producto se pusieron en acervo y se evaporaron a sequedad. El producto después se purificó por cromatografía instantánea usando un gradiente de elución de DCM/2% de ácido acético a DCM/20% de MeOH/2% de ácido acético y el producto final se secó por congelamiento a partir de 1,4-dioxano para dar el compuesto del título como un sólido blanco (0.021 g, 24%).

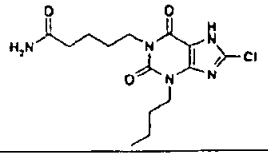
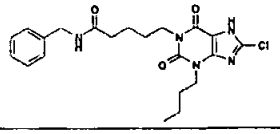
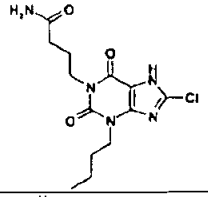
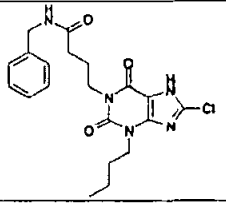
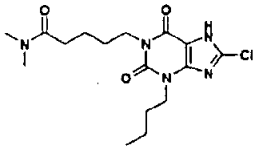
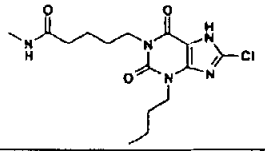
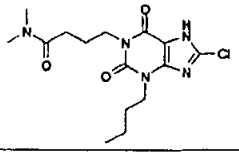
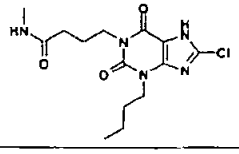
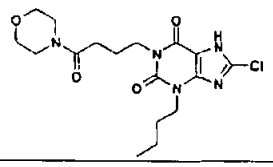
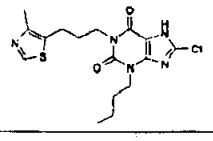
CL/EM: m/z 459 $[MH]^+$, TR 2.37 min.

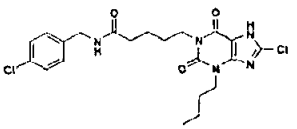
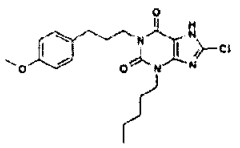
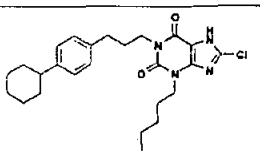
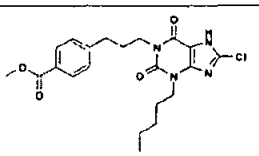
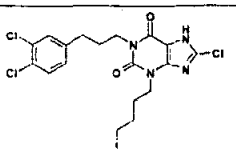
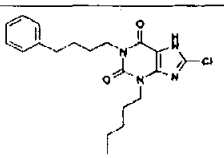
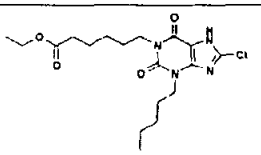
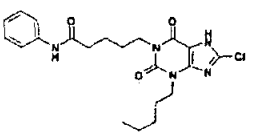
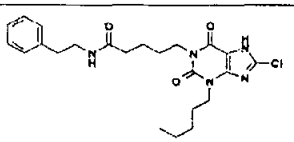
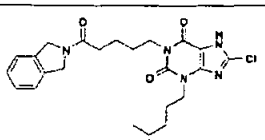
Los siguientes compuestos (cuadro 34) se prepararon por la metodología general apropiada descrita antes.

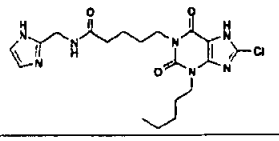
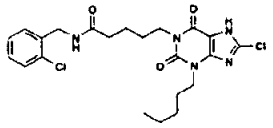
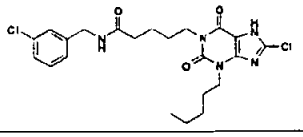
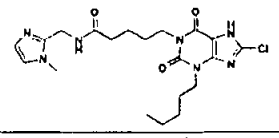
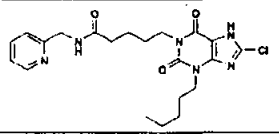
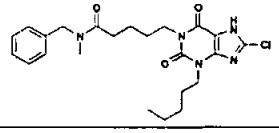
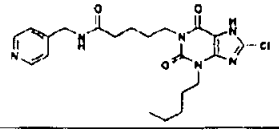
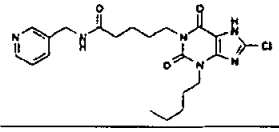
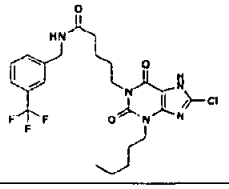
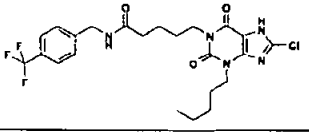
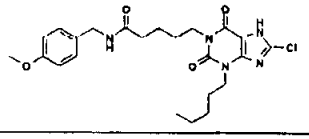
CUADRO 34

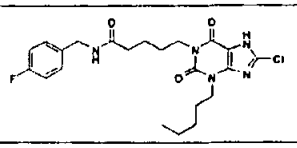
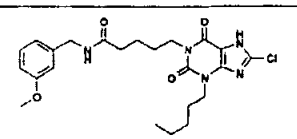
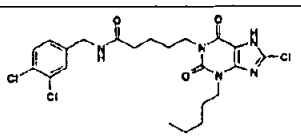
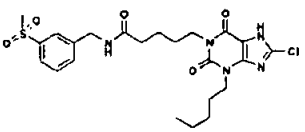
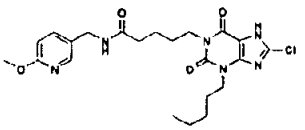
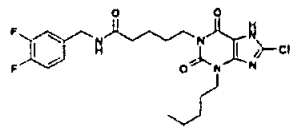
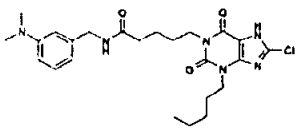
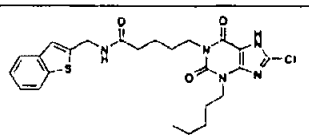
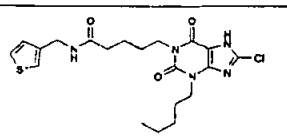
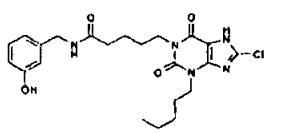
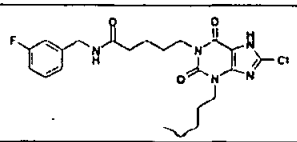
Ejemplo	Estructura	Nombre	CL/EM
603		8-cloro-3-(2-ciclopropiletil)-1-[2-(etiloxi)etil]-3,7-dihidro-1H-purino-2,6-diona	m/z 327 $[MH]^+$ TR 2.80min
604		8-cloro-1-[2-(etiloxi)etil]-3-(3-metilbutil)-3.7-dihidro-1H-purino-2.6-diona 257	Mlz 329 $[MH]^+$ TR 3.02min

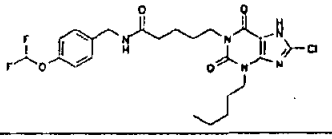
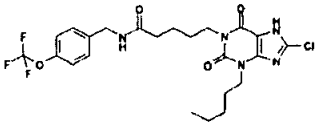
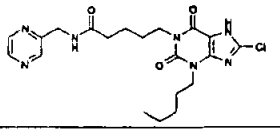
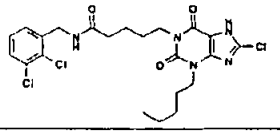
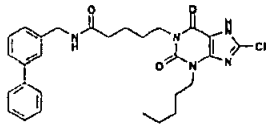
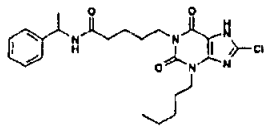
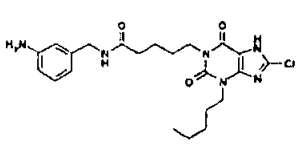
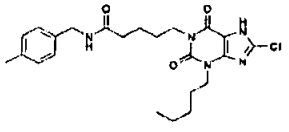
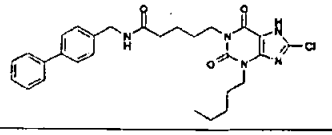
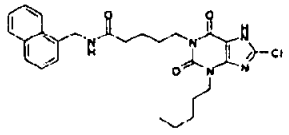
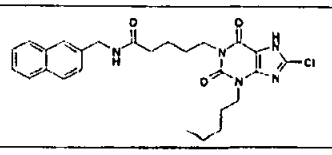
605		4-{8-cloro-1-[2-(etiloxi)etil}-2,6-dioxo-1,2,6,7-tetrahidro-3H-purino-3-il}butanonitrilo	m/z 326 $[MH]^+$ TR 2.33min
606		8-cloro-1-(3-{3-[(2,4-difluorofenil)metil]-1,2,4-oxadiazol.5-il}propil)-3[3-(1-piperidinil)propil]-3,7-dihidro-1H-purino-2,6-diona	m/z 548 $[MH]^+$ TR 2.44min
607		3-butil-8-cloro-1-[2-(metiloxi)etil]-3,7-dihidro-1H-purino-2,6-diona	m/z 301 $(MH)^+$ TR 2.31 min
608		3-butil-8-cloro-1-[3-(etiloxi)propil]-3,7-dihidro-1H-purino-2,6-diona	m/z 329 $[MH]^+$ TR 2.95 min
609		3-butil-8-cloro-1-[3-(metiloxi)propil]-3,7-dihidro-1H-purino-2,6-diona	m/z 315 $[MH)^+$ TR 2.36 min
610		3-butil-8-cloro-1-[2-(etiloxi)etil]-3,7-.dihidro-1H-purino-2,6-diona	m/z 315 $[MH]^+$ TR 2.34 min
611		3-butil-8-cloro-1-[2-(propiloxi)etil]-3,7-dihidro-1H-purino-2,6-diona	m/z 329 $[MH]^+$ TR 2.71 min
612		4-(3-butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1H-purin-1-il)butanoato de metilo	m/z 343 $[MH]^+$ TR 2.56 mjn
613		5-(3-butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1H-purin-1-il)pentanoato de metilo	m/z 357 $[MH]^+$ TR 2.66 min

614		5-(3-butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1H-purin-1-il)pentanamida	m/z 342 $[MH]^+$ TR 2.41 min
615		5-(3-butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1H-purin-1-il)-N-(fenilmetil)pentanamida)	m/z 432 $[MH]^+$ TR 2.97 min
616		4-(3-butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1H-purin-1-il)butanamida	m/z 328 $[MH]^+$ TR 2.34 mjn
617		4-(3-butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1H-purin-1-il)-N-(fenilmetil)butanamida	m/z 418 $[MH]^+$ TR 2.93 min
618		5-(3-butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1H-purin-1-il)-N,N-dimetilpentanamida	m/z 370 $[MH]^+$ TR 2.26 min
619		5-(3-butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1H-purin-1-il)-N-metilpentanamida	m/z 356 $[MH]^+$ TR 2.56 min
620		4-(3-butil-8-cloro-2,6-djoxo-2,3,6,7-tetrahidro-1H-purin-1-il)-N,N-dimetilbutanamida	m/z 356 $[MH]^+$ TR 2.59 min
621		4-(3-butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1H-purin-1-il)-N-metilbutanamida	m/z 342 $[MH]^+$ TR 2.48 min
622		3-butil-8-cloro-1-(4-morfolin-4-il-4-oxobutil)-3,7-djhidro-1H-purino-2,6-diona	m/z 398 $[MH]^+$ TR 2.58 min
623		3-butil-8-cloro-1-[3-(4-metil-1,3-tiazol-5-il)propil]-3,7-dihidro-1H-purino-2,6-diona	m/z 382 $[MH]^+$ TR 3.00 min

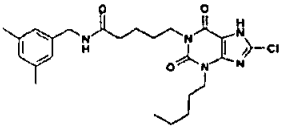
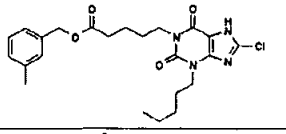
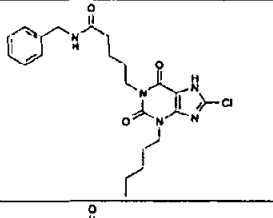
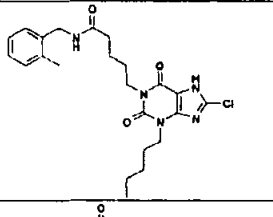
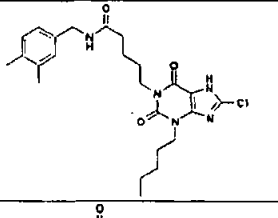
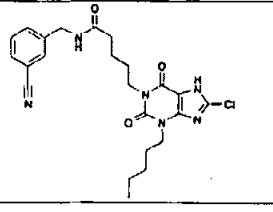
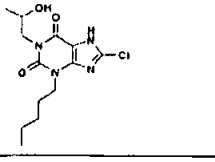
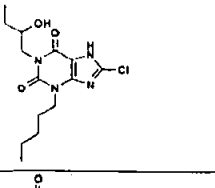
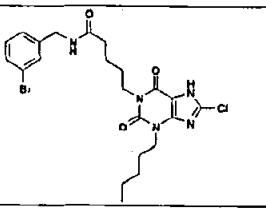
624		5-(3-butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1H-purin-1-il)-N-((4-clorofenil)metil]-pentanamida	m/z 466 $[MH]^+$ TR 3.26 min
625		8-cloro-1-{3-[4-(metiloxi)fenil]propil}-3-pentil-3,7-dihidro-1H-purino-2,6-diona	m/z 405 $[MH]^+$ TR 3.65 min
626		8-cloro-1-[3-(4-ciclohexllfenil)propil]-3-pentil-3,7-dlhidro-1H-purino-2,6-diona	m/z 457 $[MH]^+$ TR 4.42 min
627		4-[3-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)propil]benzoato de metilo	m/z 433 $[MH]^+$ TR 3.59 min
628		8-cloro-1-[3-(3,4-dlclorofenil)propil]-propil]-3-pentil-3,7-dihidro-1H-puino-2,6-diona	m/z 443 $[MH]^+$ TR 4.03 min
629		8-cloro-3-pentil-1-(4-fenilbutil)-3,7-dihidro-1H-purino-2,6-diona	m/z 389 $[MH]^+$ TR 3.87 min
630		6-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)hexanoato de etilo	m/z 399 $[MH]^+$ TR 3.47 min
631		5-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)-N-fenilpentanamlda	m/z 432 $[MH]^+$ TR 3.36 min
632		5-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)-N-(2-feniletil)pentanamida	m/z 460 $[MH]^+$ TR 3.29 min
633		8-cloro-1-15-(1,3-dihidro-2H-isoíndol-2-il)-5-oxopentil]-3-pentil-3,7-dihidro-1H-purino-2,6-diona	m/z 458 $[MH]^+$ TR 3.35 min

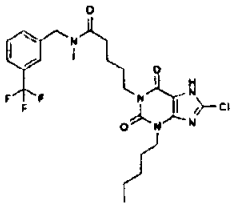
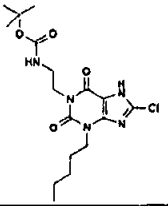
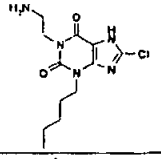
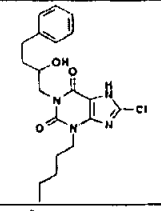
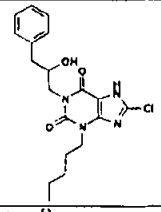
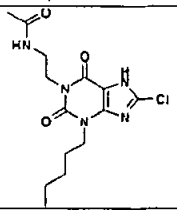
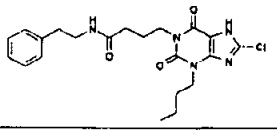
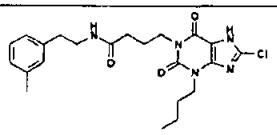
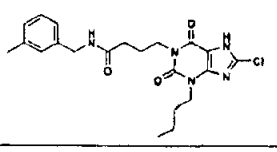
634		5-(8-cloro-2,6-dioxo-3- pentil-2,3,6,7-tetrahidro-1H-purin-1-il)-N-(1H-imidazol-2-ilmetil)pentanamida	m/z 436 $[MH]^+$ TR 2.32 min
635		5-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)-N-[(2-clorofenil)metil]pentan amida	m/z 480 $[MH]^+$ TR 2.77 min
636		5-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)-N-[(3-clorofenil)metil]pentan amida	m/z 480 $[MH]^+$ TR 3.42mín
637		5-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)-N-[(1-metil-1H-imidazol-2-il)metil]pentanamida	m/z 450 $[MH]^+$ TR 2.32 min
638		5-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)-N-(piridin-2-ilmetil)pentanamida	m/z 447 $[MH]^+$ TR 2.70 min
639		5-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)-N-metil-N-(fenilmetil)pentanamida	m/z 460 [MH]+ TR 3.38 min
640		5-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)-N-(piridin-4-ilmetil)pentanamida	m/z 447 $[MH]^+$ TR 2.42 min
641		5-(8-cloro-2.6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)-N-{piridin-3-ilmetil)pentanamida	m/z 447 $[MH]^+$ TR 2-54 min
642		5-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)-N-{[3-(trifluorometil)fenil]metil}pentanamida	m/z 514 $[MH]^+$ TR 3.45 min
643		5-{8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)-N-{[4-{trifluorometil)fenil]metil)il} pentanamida	m/z 514 $[MH]^+$ TR 3.47 min
644		5-{8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)-N-{[4-(metiloxi)fenil)metil} pentanamida	m/z 476 $[MH]^+$ TR 2.67 min

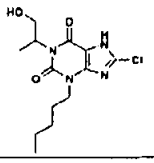
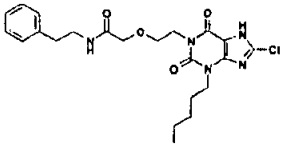
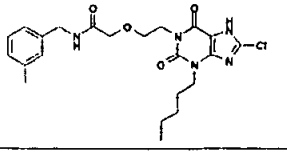
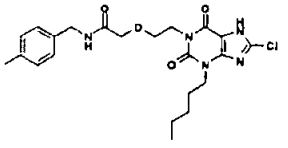
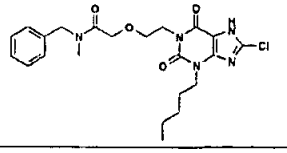
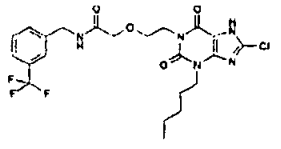
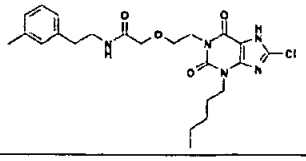
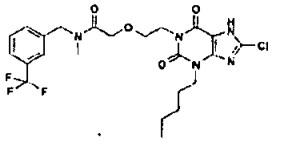
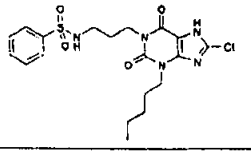
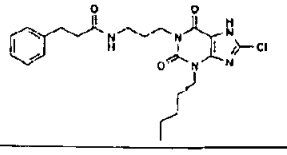
645		5-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)-N-[(4-fluorofenil)metil]pentanamida	m/z 464 $[MH]^+$ TR 3.26 min
646		5-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)-N-{[3-(metiloxi)fenil]metil} pentanamida	m/z 476 $[MH]^+$ TR 3.21 min
647		5-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)-N-[(3,4-diclorofenil)metil]pentanamida	m/z 514 $[MH]^+$ TR 3.56 min
648		5-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)-N-{[3-(metilsulfonil)fenil]metil} pentanamida	m/z 524 $[MH]^+$ TR 2.97 min
649		5-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)-N-{[6-(metiloxi)piridin-3-il] metil}pentanamida	m/z 477 $[MH]^+$ TR 3.01 min
650		5-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)-N-[(3,4-difluorofenil)metil] pentanamida	m/z 482 $[MH]^+$ TR 3.33 min
651		5-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)-N-{[3-(dimetilamino)fenil]metil} pentanamida	m/z 489 $[MH]^+$ TR 3.01 min
652		N-(1-benzotien-2-ilmetil)-5-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)pentanamida	m/z 502 $[MH]^+$ TR 3.48 min
653		5-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)-N-(3-tienilmetil) pentanamida	m/z 452 $[MH]^+$ TR 3.18 min
654		5-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)-N-(3-hidroxifenil)metil]penta namida	m/z 462 $[MH]^+$ TR 3.04 min
655		5-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)-N-(3-fluorofenil)metil] pentanamida	m/z 464 $[MH]^+$ TR 3.28 min

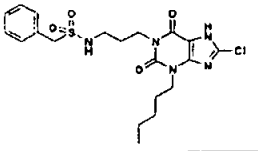
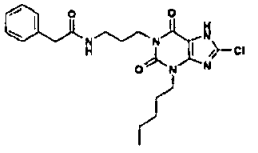
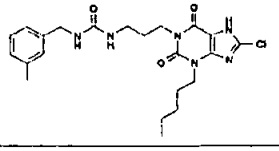
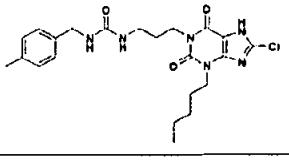
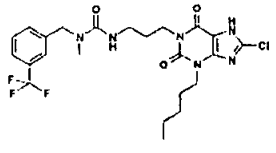
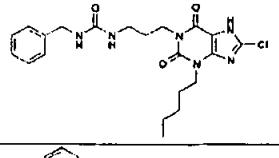
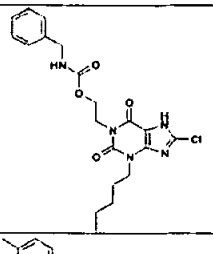
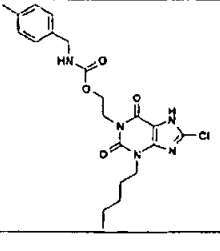
656		5-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)-N-({4-((difluorometil)oxi] fenil}metil)pentanamida	m/z 512 $[MH]^+$ TR 3.34 min
657		5-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)-N-({4-(trifluorometil)oxi] fenil}metil)pentanamida	m/z 530 $[MH]^+$ TR 3.50 min
658		5-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)-N-(pirazin-2-ilmetil)pentanamida	m/z 448 $[MH]^+$ TR 2.74 min
659		5-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)-N-[(2,3-djclorofenil)metil) pentanamida	m/z 514 $[MH]^+$ TR 3.55 min
660		N-(bifenil-3-ilmetil)-5-(8-cloro-2 6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)pentanamida	m/z 522 $[MH]^+$ TR 3.61 min
661		5-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)-N-(1-feniletil)pentanamida	m/z 460 $[MH]^+$ TR 3.30 min
662		N-[(3-aminofenil)metil]-5-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)pentanamida	m/z 461 $[MH]^+$ TR. 2.79 min
663		5-(8-cloro-2,6.dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)-N-[(4-metilfenil)metil]pentan amida	m/z 460 $[MH]^+$ TR 3.36 min
664		N-(bifenil-4-ilmetil)-5-(8-cloro-2 6-dloxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)pentanamida	m/z 522 $[MH]^+$ TR 3.63 min
665		5-(8-cloro-2.6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)-N-(naftalen-1-ilmetil)pentanamida	m/z 496 $[MH]^+$ TR 3.48 min
666		5-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)-N-(naftalen-2-ilmetil)pentanamida	m/z 496 $[MH]^+$ TR 3.50 min

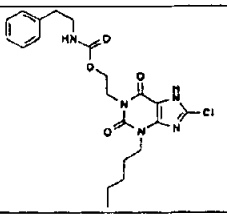
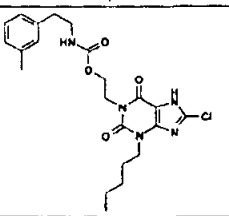
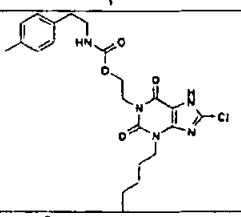
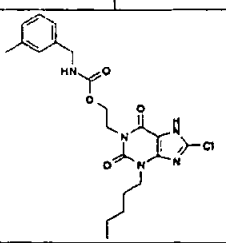
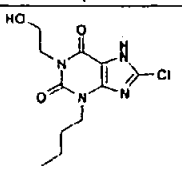
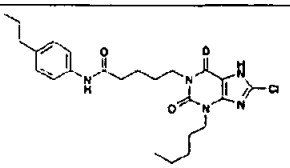
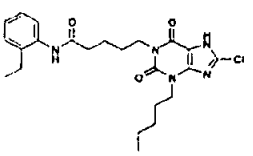
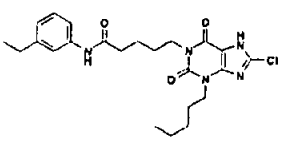
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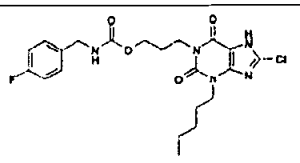
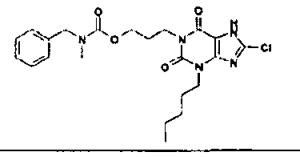
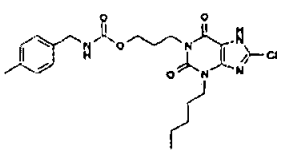
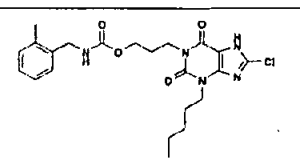
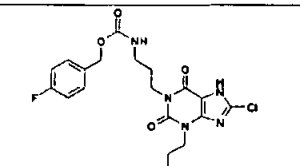
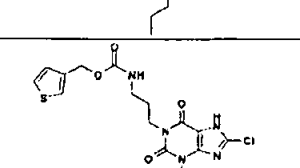
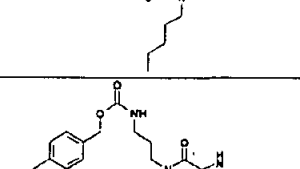
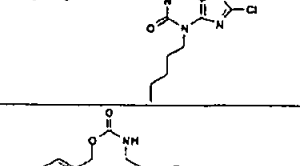
667		5-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)-N-[(3,5-dimetilfenil)metil) pentanamida	m/z 474 $[MH]^+$ TR 3.48 min
668		5-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)pentanoato de (3-metilfenil)metilo	m/z 461 $[MH]^+$ TR 3.78 min
669		5-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)-N-(fenilmetil)pentanamida	m/z 446 $[MH]^+$ TR 3.12 min
670		5-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)-N-[(2-metilfenil)metil]pentan amida	m/z 460 [MH]+ TR 3.22min
671		5-(8-cloro-2;6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)-N-[(3,4-dimetilfenil)metil)pentanamida	m/z 474 $[MH]^+$ TR 3.34 min
672		5-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)-N-[(3-cianofenil)metil] pentanamida	m/z 471 $[MH]^+$ TR 3.14 min
673		8-cloro-1-(2-hidroxipropil)-3-pentil-3,7-dihidro-1H-purino-2,6-diona	m/z 315 [MH]+ TR 2.73 min
674		8-cloro-1-(2-hidroxibutil)-3-pentil-3,7-dihidro-1H-purino-2,6-diona	m/z 329 $[MH]^+$ TR 2.91 min
675		N-[(3-bromofenil)metil]-5-(8-cloro-2,6-dioxo-3-pentil-2,6,7-tetrahidro-1H-purin-1-il)pentanamida	m/z 524 $[MH]^+$ TR 3.43 min

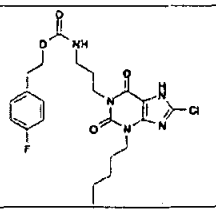
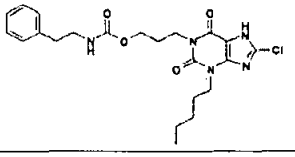
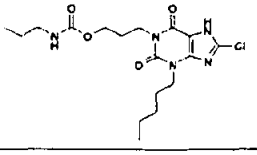
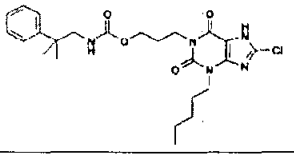
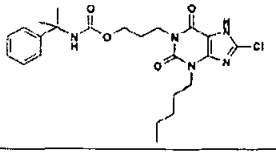
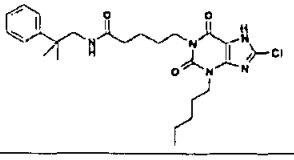
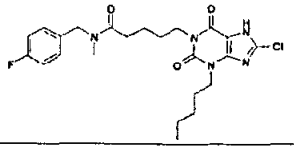
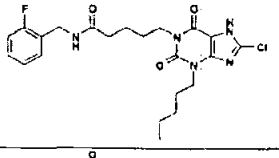
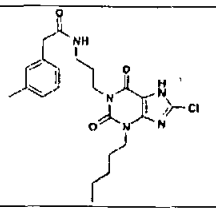
676		5-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)-N-metil-N-{[3-(trifluorometil)fenil]metil}pentanamida	m/z 528 $[MH]^+$ TR 3.55 min
677		[2-(8-cloro-2,6-dloxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)etil]carbamato de 1,1-dimetiletilo	m/z 400 $[MH]^+$ TR 3.21 m/n
678		1-(2-aminoetil)-8-cloro-3-pentil-3,7-dihidro-1H-purino-2,6-diona	m/z 300 $[MH]^+$ TR 2.14 min
679		8-cloro-1-(2-hidroxi-4-fenilbutil)-3-pentil-3,7-dihidro-1H-purino-2,6-diona	m/z 405 $[MH]^+$ TR 3.43 min
680		8-cloro-1-(2-hidroxi-3-fenilpropil)-3-pentil-3,7-dihidro-1H-purino-2,6-diona	m/z 391 $[MH]^+$ TR 3.17 min
681		N-[2-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)etil]acetamida	m/z 342 $[MH]^+$ .TR 2.61 min
682		4-(3-butil-8-cloro-2,6- djoxo-2,3,6,7-tetrahidro-1H-purin-1-il)-N-(2-feniletil)butanamida	m/z 432 $[MH]^+$ TR 3.06 min
683		4-(3-butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1H-purin-1-il)-N-[2-(3-metilfenil)etil]butanamida	m/z 446 $[MH]^+$ TR 3.19 min
684		4-(3-butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1H-purin-1-il)-N-[(3-metilfenil)metil] butanamida	m/z 432 $[MH]^+$ TR 3.14 min

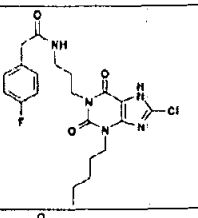
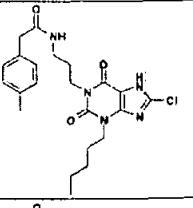
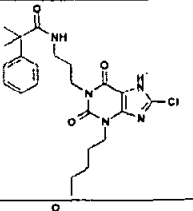
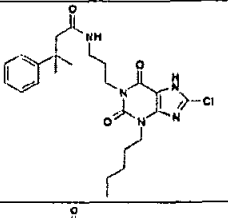
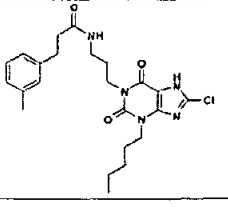
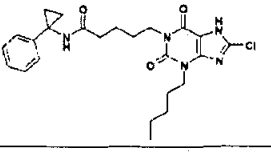
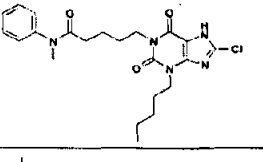
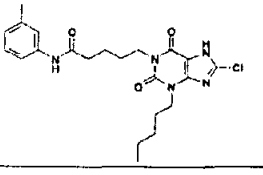
685		8-cloro-1-(2-hidroxi-1-metiletil)-3-pentil-3,7-dihidro-1H-purino-2,6-diona	m/z 315 $[MH]^+$ TR 2.80 min
686		2-{[2-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)etil]oxi}-N-(2-feniletil)acetamida	m/z 462 $[MH]^+$ TR 3.23 min
687		2-{[2-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)etil]oxi}-N-[(3-metilfenil)metil]acetamida	m/z 462 $[MH]^+$ TR 3.28 min
688		2-{[2-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)etil]oxi}-N-[(4-metilfenil)metil]acetamida	m/z 462 $[MH]^+$ TR 3.27 min
689		2-{[2-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)ethil]oxi}-N-metil-N-(fenilmetil)acetamida	m/z 462 $[MH]^+$ TR 3.27 min
690		2-{[2-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)etil]oxi}-N-{[(trifluorometil)fenil]metil} acetamida	m/z 516 $[MH]^+$ TR 3.39 min
691		2{[-2-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)etil]oxi}-N-[2-(3-metilfenil)etil]acetamida	m/z 476 $[MH]^+$ TR 3.36 min
692		2-{[2-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)etil]oxi}-N-metil-N-{[3-(trifluorometil)fenil]metil} acetamida	m/z 530 $[MH]^+$ TR 3.41 min
693		N-[3-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)propil)benceno-sulfonamida	m/z 454 $[MH]^+$ TR 3.29 min
694		N-{3-(8-cloro-2 6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)propil]-3-fenilpropanamida	m/z 446 $[MH]^+$ TR 3.27 min

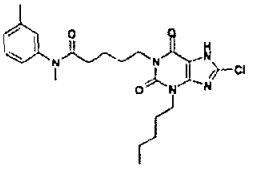
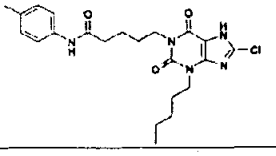
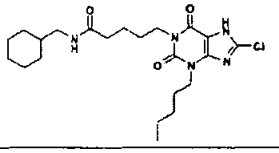
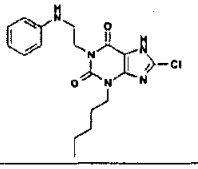
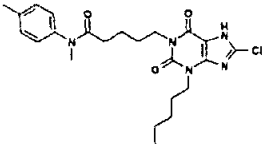
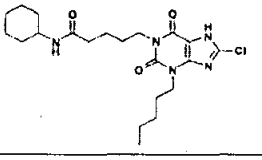
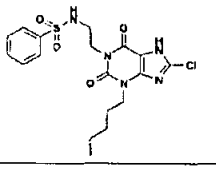
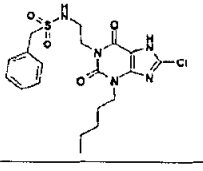
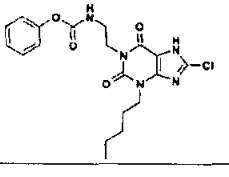
695		N-[3-(8-cloro-2 ,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)propil]-1-fenilmetansulfonamida	m/z 468 $[MH]^+$ TR 3.29 min
696		N-[3-(8-cloro-2 6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)propil)-2-fenilacetamida	m/z 432 $[MH]^+$ TR 3.18 min
697		1-[3-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)propil)-3-[(3-metilfenil)metil]urea	m/z 461 $[MH)^+$ TR 3.29 min
698		1-[3-(8-cloro-2,6-dioxo-3-pentil-2,3.6,7-tetrahidro-1H-purin-1-il)propil]-3-[(4-metilfe nil)metil]urea	m/z 461 $[MH]^+$ TR 3.29 min
699		3-[3-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)propil]-1-metil-1-{[3-(trifluorometil)fenil)metil}urea	m/z 529 $[MH]^+$ TR 3.51 min
700		1-[3-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)propil]-3-(fenilmetil)urea	m/z 447 $[MH]^+$ TR 3.17 min
701		(fenilmetil)carbamato 2-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)etilo	m/z 434 $[MH]^+$ TR 3.24 min
702		[(4-metilfenil}metil]carbamato de 2-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il}etilo	m/z 448 $[MH]^+$ TR 3.34 min

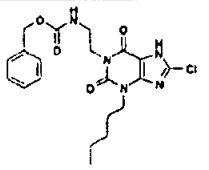
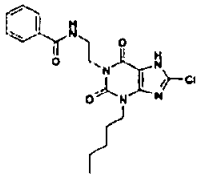
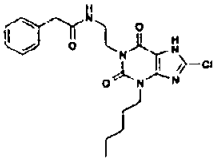
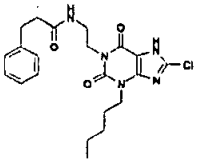
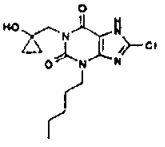
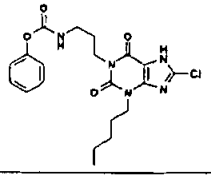
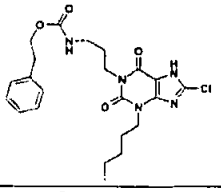
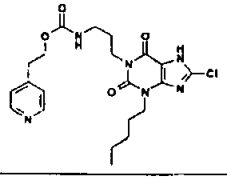
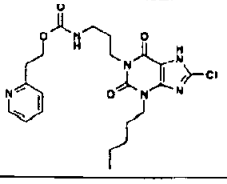
703		{2-feniletil)carbamato de 2-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)etilo	m/z 448 $[MH]^+$ TR 3.34 min
704		[2-(3-metilfenil)etil)carbamato de 2-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)etilo	m/z 462 $[MH]^+$ TR 3.48 min
705		[2-{4-metilfenil)etil]carbamato de 2-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)etilo	m/z 462 $[MH]^+$ TR 3.48 min
706		[{3-metilfenil)metil]carbamato de 2-{8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)etilo	m/z 448 $[MH]^+$ TR 3.37 min
707		3-butil-8-cloro-1-(2-hidroxietil)-3,7.dihidro-1H-purjno-2,6-diona	m/z 287 $[MH]^+$ TR 2.42 min
708		5-{8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)-N-(4-propilfenil)pentanamida	m/z 474 $[MH]^+$ TR 3.73 min
709		5-{8-cloro-2,6-dioxo-3-.pentil-2,3,6,7-tetrahidro-1H-purin-1-il)-N-(2-etilfenil)pentanamida	m/z 460 $[MH]^+$ TR 3.41 min
710		5-(8-cloro-26-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)-N-(3-H]etilfenil)pentanamida	m/z 460 $[M]^+$ TR 3.58 min

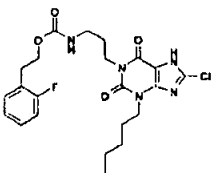
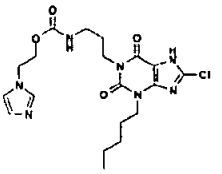
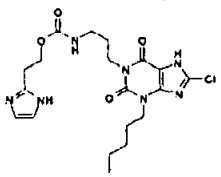
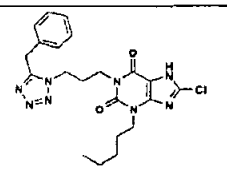
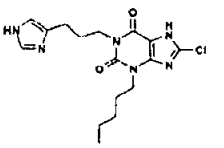
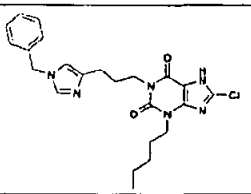
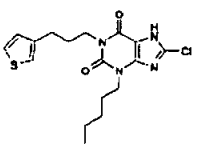
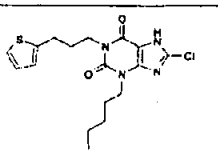
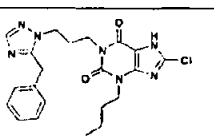
711		[(4-fluorofenil)metil]carbamato de 3-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)propilo	m/z 466 $[MH]^+$ TR 3.43 min
712		metil(fenilmetil)carbamato de 3-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)propilo	m/z 462 $[MH]^+$ TR 3.54 mjn
713		[(4-metilfenil)metil]carbamato 3-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)propilo	
714		[(2-metilfenil)metil]carbamato de 3-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)propilo	m/z 462 $[MH]^+$ TR 3.50 min
715		[3-(8-cloro-2 6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)propil]carbamato de (4-fluorofenil)metilo	m/z 466 $[MH]^+$ TR 3.36 min
716		[3-(8-cloro 2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)propil]carbamato de 3-tienilmetilo	m/z 454 $[MH]^+$ .TR 3.27 min
717		{3-(8-cloro-2 6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)propil]carbamato de (4-metilfenil)metilo	m/z 462 $[MH]^+$ TR 3.45 min
718		[3-(8-cloro-2 6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)propil]carbamato de (2-metilfenil)metilo	m/z 462 $[MH]^+$ TR 3.42 min

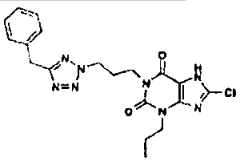
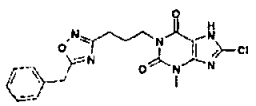
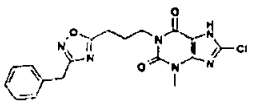
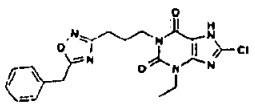
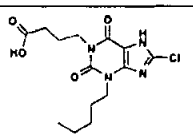
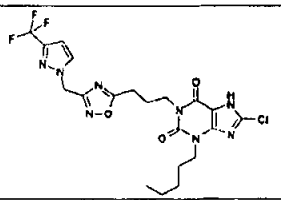
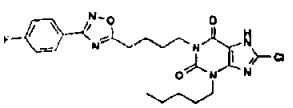
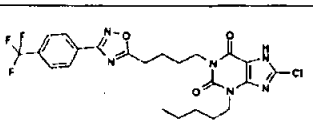
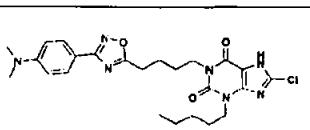
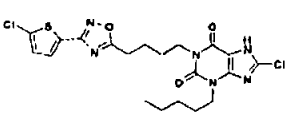
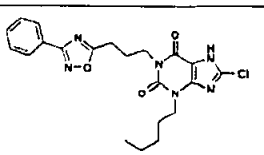
719		[3-(8-cloro-2 6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)propil]carbamato de 2-(4-fluorofenil)etilo	m/z 480 $[MH]^+$ RT 3.49 min
720		(2-feniletil)carbamato de 3-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)propilo	m/z 462 $[MH]^+$ TR 3.50 min
721		propilcarbamato de 3-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)propilo	m/z 400 [MH]+ RT 3.20 min
722		(2-metil-2-fenilpropil)carbamato de 3-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro- 1H-purin-1-il)propilo	m/z 490 $[MH]^+$ TR 3.66 min
723		(1-metil-1-feniletil)carbamato de 3-(8-cloro-2,6-dioxo-3- pentil-2,3,6,7-tetrahidro-1H-purin-1-il)propilo	m/z 476 $[MH]^+$ TR 3.59 min
724		5-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)-N-(2-metil-2-fenilpropil)pentanamida	m/z 488 $[MH]^+$ TR 3.53 min
725		5-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)-N-[{4-fluorofenil)metil]-N-metilpentanamida	m/z 478 $[MH]^+$ TR 3.46 min
726		5-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro- 1H-purin-1-il)-N-[(2-fluorofenil)metil]pentanamida	m/z 464 $[MH]^+$ TR 3.32 mjn
727		N-[3-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purln-1-il)propil]-2-(3-metilfenil)acetamida	m/z 446 $[MH]^+$ TR 3.37 min

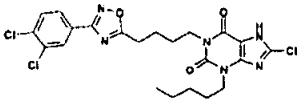
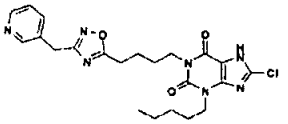
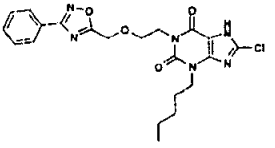
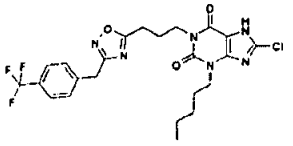
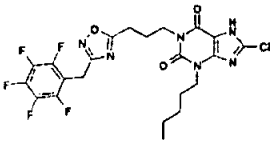
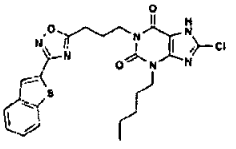
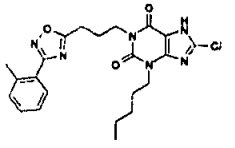
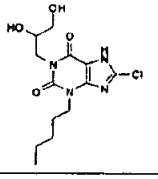
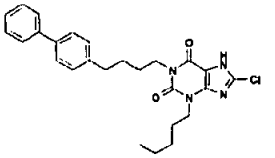
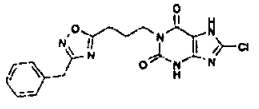
728		N-[3-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)propil]-2-{4-fluorofenil)acetamida	m/z 450 $[MH]^+$ TR 3.28 min
729		N-[3-{8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)propil]-2-(4-metilfenil)acetam¡da	m/z 446 $[MH]^+$ TR 3.36 min
730		N-[3-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)propil]-2-metil-2-fenilpropanamida	m/z 460 $[MH]^+$ TR 3.50 min
731		N-[3-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)propil)-3-metil-3-fenilbutanamida	m/z 474 [MH]+ TR 3.51 min
732		N-(3-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)propil]-3-(3-metilfenil)propanamida	m/z 460 $[MH]^+$ TR 3.45 min
733		5-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)-N-(1-fenilciclopropil)pentanamida	m/z 472 $[MH]^+$ TR 3.29 min
734		5-(8-cloro-26-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)-N-metil-N-fenilpentanamjda	m/z 446 $[MH]^+$ TR 3.27 min
735		5-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)-N-(3-metilfenil)pentanamida	m/z 446 $[MH]^+$ TR 3.41 min

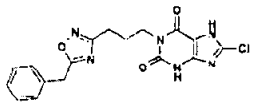
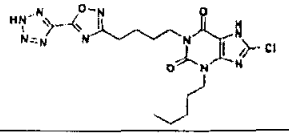
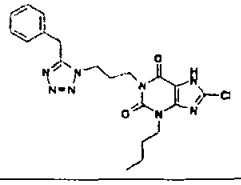
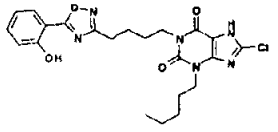
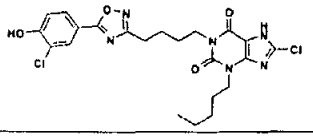
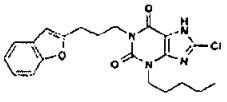
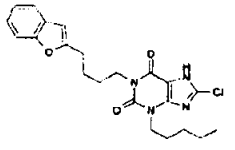
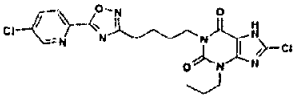
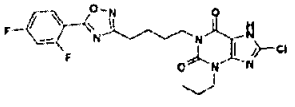
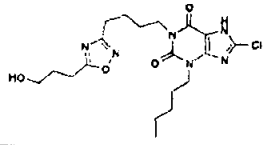
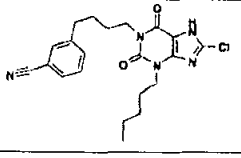
736		5-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)-N-metil-N-(3-metilfenil)pentanamida	m/z 460 $[MH]^+$ TR 3.41 min
737		5-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)-N-(4-metilfenil)pentanamida	m/z 446 $[MH]^+$ TR 3.40 min
738		5-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)-N-(ciclohexilmetil)pentanamida	m/z 452 $[MH]^+$ TR 3.40 min
739		8-cloro-3-pentil-1-[2-(fenilamino)etil)-3,7-dihidro-1H-purino-2,6-diona	m/z 376 $[MH]^+$ TR 3.55 min
740		5-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)-N-metil-N-(4-metilfenil)pentanamida	m/z 460 [MH]+ TR 3.41min
741		5-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)-N-ciclohexilpentanamida	m/z 438 $[MH]^+$ TR 3.25 min
742		N-[2-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)etil]bencensulfonamida	m/z 440 $[MH]^+$ TR 3.08 min
743		N-[2-(8-cloro-2,6.dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)etil]-1-fenilmetansulfonamida	m/z 454 $[MH]^+$ TR 3.15 min
744		[2-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)etil]carbamato de fenilo	m/z 420 $[MH]^+$ TR 3.18 min

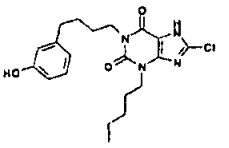
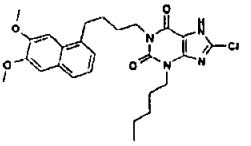
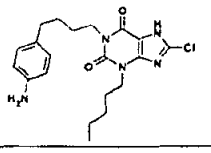
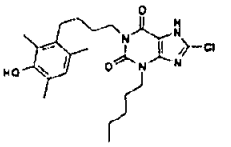
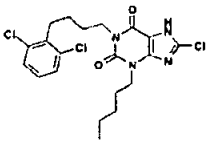
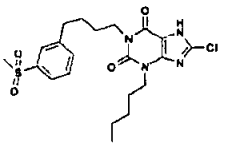
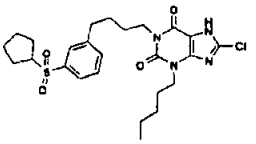
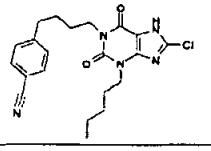
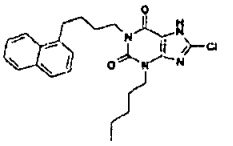
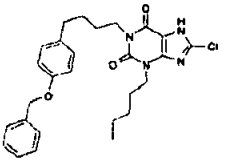
745		[2-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)etil]carbamato de fenilmetilo	m/z 434 $[MH]^+$ TR 3.23 min
746		N-[2-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)etil]benzamida	m/z 404 $[MH]^+$ TR 3.04 min
747		N-[2-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)etil]-2-fenilacetamida	m/z 418 $[MH]^+$ TR 2.99 min
748		N-[2-(8-cloro-2,6-dioxo-3- pentil-2,3,6,7-tetrahidro-1H-purin-1-il)etil]-3-fenilpropanamida	m/z 432 $[MH]^+$ TR 3.14 min
749		8-cloro-1-[(1-hidroxiciclopropil)metil]-3-pentil-3,7-djhidro-1H-purino-2,6-diona	m/z 327 $[MH]^+$ TR 2.82 min
750		[3-(8-cloro-2,6-dioxo.3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)propil]carbamato de fenilo	m/z 434 $[MH]^+$ TR 3.31 min
751		[3-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)propil]carbamato de 2-feniletilo	m/z 462 $[MH]^+$ TR 3.48 min
752		[3-(8- cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)propil]carbamato de 2-piridin-4-iletilo	m/z 463 $[MH]^+$ TR 2.44 min
753		[3-(8-cloro-2 6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)propil]carbamato de 2-piridin-2-iletilo	m/z 463 $[MH]^+$ TR 2.44 min

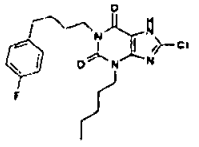
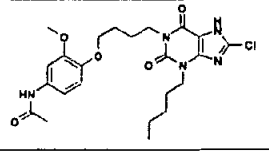
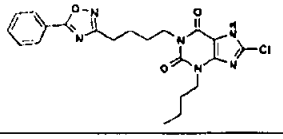
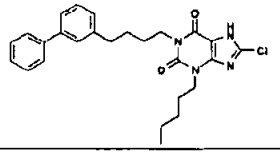
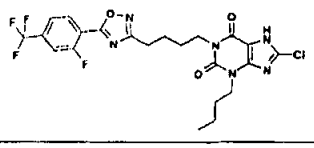
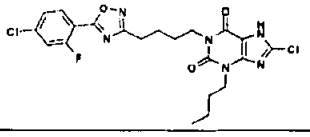
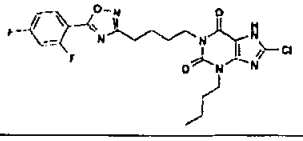
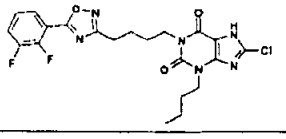
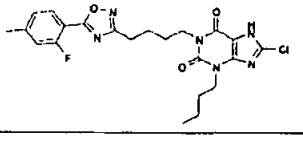
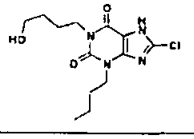
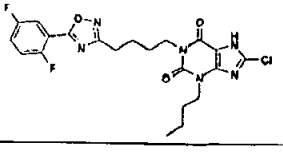
754		[3-(8-cloro-2 6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purrn-1-il)propil}carbamato de 2-(2-f1uorofenil)etilo	m/z 480 $[MH]^+$ TR 3.46 min
755		[3-(8-cloro-2 6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)propil]carbamato de 2-(1H-imidazol-1-il)etilo	m/z 452 [MH]+ TR 2.30 min
756		[3-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)propil]carbamato de 2-(1H-imidazol-2-il)etilo	m/z 452 $[MH]^+$ TR 2.31 min
757		8-cloro-3-pentil-1-{3-[5-(fenilmetil)-1-tetrazol-1-il]propil}-3,7-dlhidro-purino-2,6-diona	m/z 457 $[MH]^+$ 1H-TR 3.32 min
758		8-cloro-1-[3-(1H-imidazol-4-il)propil]-3-pentil-3,7-dihidro-1H-purino-2,6-diona	m/z 365 $[MH]^+$ TR 2.27 min
759		8-cloro-3-pentil-1-{3-[1-(fenilmetil)-1H-imidazol-4-il]propil}-3,7-dihidro-1H-purino-2.6-diona	m/z 455 $[MH]^+$ TR 2.61 min
760		8-cloro-3-pentil-1-[3-(3-tienil)propil]-3,7-dihidro-1H-purino-2,6-diona	m/z 381 $[MH]^+$ TR 3.61 min
761		8-cloro-3-pentil-1-[3-(2-tienil)propil]-3,7-dihidro-1H-purino-2,6-diona	m/z 381 $[MH]^+$ TR 3.69 min
762		3-butil-8-cloro-1-{3-[5-(fenilmetil)-1H-1,2,4-tiazol-1-il]propil}-3,7-dihidro-1H-purino-2,6-diona	m/z 442 $[MH]^+$ TR 2.94 min

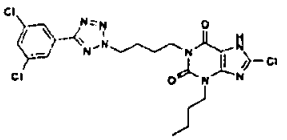
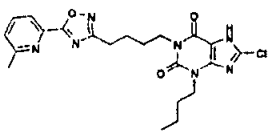
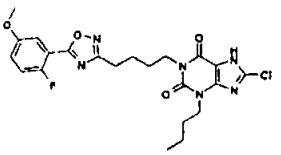
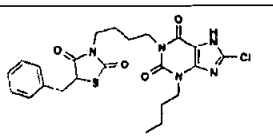
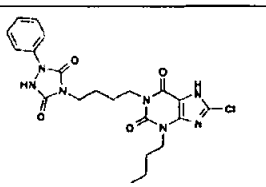
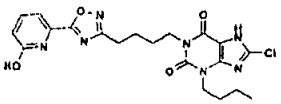
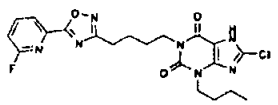
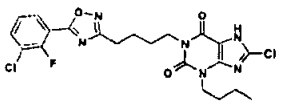
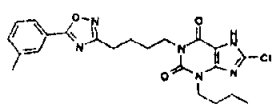
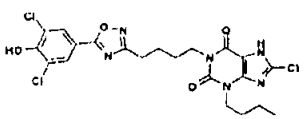
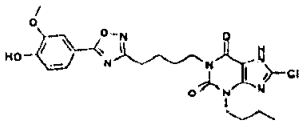
763		8-cloro-1-{3-(5-(fenilmetil)-2H-tetrazol-2-il]propil}-3-propil-3,7dihidro-1H-purino-2,6-diona	m/z 429 $[MH]^+$ TR 3.14 min
764		8-cloro-3-metil-1-{3-[5-(fenilmetil}-1,2,4-oxadlazol-3-il]propil}-3,7-dihidro-1H-purino-2,6-diona	m/z 401 $[MH]^+$ TR 2.88 min
765		8-cloro-3-metil-1-{3-[3-(fenilmetil)-1,2,4-oxadlazol-5-il]propil}-3,7-dihidro-1H-purino-2,6-diona	m/z 401 $[MH]^+$ TR 2.89 min
766		8-cloro-3-etil-1-{3-[5-(fenilmetil)-1,2,4-oxadlazol-3-il]propil}-3,7-dihidro-1H-purino-2,6-diona	m/z 415 $[MH]^+$ TR 2.97 min
767		ácido 4-(8-cloro-2,6-dioxo-3-pentil-2,3.6,7-tetrahidro-1H-purin-1-il)butanoico	m/z 343 $[MH]^+$ TR 2.81 min
768		8-cloro-3-pentil-1-[3-(3-{[3-(trifluorometil)-1H-pirazol-1-il]metil}-1,2,4-oxadiazol-5-il)propil]-3,7-dihidro-1H-purino-2,6-diona	m/z 515 $[MH]^+$ TR 3.43 min
769		8-cloro-1-{4-[3-(4-fluorofenil)-1,2,4-oxadiazol-5-il]butil}-3-pentil-3,7-dihidro-1H-purino-2,6-diona	m/z 475 $[MH]^+$ TR 3.71 min
770		8-cloro-3-pentil-1-(4-{3-[4-(trifluorometil)fenil]-1,2,4-oxadiazol-5-il}butil)-3,7-dihidro-1H-purino-2,6-diona	m/z 525 $[MH]^+$ TR 3.92 min
771		8-cloro-1-(4-{3-[4-(dimetilamino)fenil]-1,2,4-oxadiazol-5-il}butil)-3-pentil-3,7-dihidro-1H-purino-2,6-diona	m/z 500 $[MH]^+$ TR 3.73 min
772		8-cloro-1-{4-[3-(5-cloro-2-tienil)-1,2,4-oxadiazol-5-il]butil}-3-pentil-3,7-dihidro-1H-purino-2,6-diona	m/z 497 $[MH]^+$ TR 3.88 min
773		8-cloro-3-pentil-1-[3-(3-fenil-1,2,4-oxadiazol-5-il)propil]-3,7-dihidro-1H-purino-2,6-diona	m/z 443 $[MH]^+$ TR 3.51 min

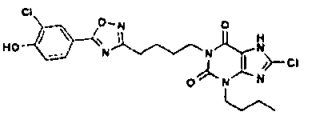
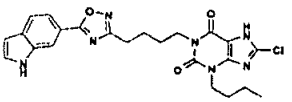
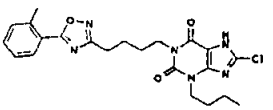
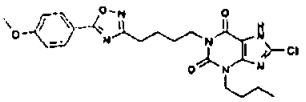
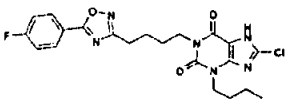
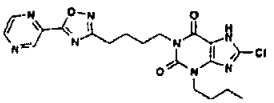
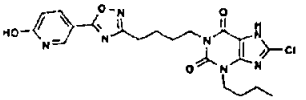
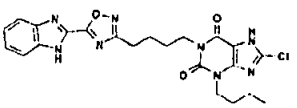
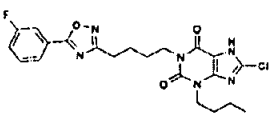
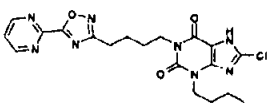
774		8-cloro-1-{4-[3-(3,4-diclorofenil)-1,2,4-oxadiazol-5-il]butil}-3-pentil-3,7-dihidro-1H-purino-2,6-diona	m/z 525 $[MH]^+$ TR 4.12 min
775		8-cloro-3-pentil-1-{4-[3-piridin-3-ilmetil)1,2,4-oxadiazol-5-il]butil}-3,7-dihidro-1H-purino-2,6-diona	m/z 472 $[MH]^+$ TR 2.90 min
776		8-cloro-3-pentil-1-(2-{[(3-fenil,1,2,4-oxadiazol-5-il)metil]oxi}etil)-3,7-dihidro-1H-purino-2,6-diona	m/z 459 $[MH]^+$ TR 3.45 min
777		8-cloro-3-pentil-1-[3-(3-{[4-(triftuorometil)fenil]metil}-1,2,4-oxadiazol-5-il)propil]-3,7-dihidro-1H-purino-2,6-diona	m/z 525 $[MH]^+$ TR 3.69 min
778		8-cloro-1-(3-{3-[(pentafluorofenil)metil]-1,2,4-oxadiazol-5-il}propil)-3-pentil-3,7-dihidro-1H-purino-2,6-diona	m/z 547 $[MH]^+$ TR 3.66 min
779		1-{3-[3-(1-benzotien-2-il)-1,2,4-oxadiazol-5-il]propil}-8-cloro-3-pentil-3,7-dihidro-purino-2,6-diona	m/z 499 $[MH]^+$ TR 3.77 min
780		8-cloro-1-{3-[3-(2-metilfenil)-1,2,4-oxadiazol-5-il]propil}-3-pentil-3,7-dihidro-1H-purino-2,6-diona	m/z 457 $[MH]^+$ TR 3.62 min
781		8-cloro-1-(2,3-dihidroxipropil)-3-pentil-3,7-dihidro-1H-purino-2,6-diona	m/z 331 $[MH]^+$ TR 2.48 min
782		1-(4-bifenil-4-ilbutil)-8-cloro-3-pentil-3,7-dihidro-1H-purino-2,6-diona	m/z 465 $[MH]^+$ TR 4.18 min
783		8-cloro-1-{3-[3-(fenilmetil)-1,2,4-oxadiazol-5-il]propil}-3,7-dihidro-1H-purino-2,6-diona	m/z 387 $[MH]^+$ TR 2.63 min

784		8-cloro-1-{3-[5-(fenilmetil)-1,2,4-oxadiazol-3-il]propil}-3,7-dihidro-1H-purino-2,6-diona	m/z 387 $[MH]^+$ TR 2.65 min
785		8-Cloro-3-pentil-1-{4-[5-(1H-tetrazol-5-il)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purino-2,6-diona	m/z 449 $[MH]^+$ TR 4.03 min
786		3-butil-8-cloro-1-{3-(5-(fenilmetil)-1H-tetrazol-1-il)propil}-3,7-dihidro-1H-purino-2,6-diona	m/z 443 $[MH]^+$ TR 3.11 min
787		8-cloro-1-{4-[5-{2-hidroxifenil)-1,2,4-oxadiazol-3-il]butil}-3-pentil-3,7-dihidro-1H-purino-2,6-diona	m/z 473 $[MH]^+$ TR 3.84 min
788		8-cloro-1-{4-[5-(3-cloro-4-hidroxifenil)-1,2,4-oxadiazol-3-il]butil}-3,pentil-3,7-dihidro-purino-2,6-diona	m/z 507 $[MH]^+$ TR 3.74 min
789		1-[3-(1-benzofuran-2-il)propil]-8-cloro-3-pentil-dihidro-1H-purino-2,6-diona	m/z 415 $[MH]^+$ TR 5.10 min
790		1-[4-(1-benzofuran-2-il)butil]-8-cloro-3-pentil-3,7-dihidro-1H-purino-2,6-diona	m/z 429 $[MH]^+$ TR 3.88 min
791		8-cloro-1-{4-[5-(5-cloropiridin-2-il)-1,2,4-oxadiazol-3-il]butil}-3-propil-3,7-dihidro-1H-purino-2,6-diona	m/z 464 $[MH]^+$ TR 3.30 min
792		8-cloro-1-{4-[5-{2,4-difluorofenil)-1,2,4-oxadiazol-3-il]butil}-3-propil-3,7-dihidro-1H-purino-2,6-diona	m/z 465 $[MH]^+$ TR 3.48 min
793		8-cloro-1-{4-[5-(3-hidroxipropil)-1,2,4-oxadiazol-3-il]butil}-3-pentil-3,7-dihidro-1H-purino-2,6-diona	m/z 439 $[MH]^+$ TR 2.93 min
794		3-[4-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)butil]benzonitrilo	m/z 414 $[MH]^+$ TR 3.62 min

795		8-cloro-1-[4-(3-hidroxifenil)butil]-3-pentil-3,7-dihidro-1H-purino-2,6-diona	m/z 405 $[MH]^+$ TR 3.48 min
796		1-{4-[6,7-bis(metiloxi)naftalen-1-il]butil}-8-cloro-3-pentil-3,7-dihidro-1H,purino-2,6-diona	m/z 499 $[MH]^+$ TR 3.78 min
797		1-[4-(4-aminofenil)butil]-8-cloro-3-pentil-3,7-dihidro-1H-purino-2,6-diona	m/z 404 $[MH]^+$ TR 3.02 min
798		8-cloro-1-[4-(3-hidroxi-2,4,6-trimetilfenil)butil]-3-pentil-3,7-dihidro-1H-purino-2,6-diona	m/z 447 $[MH]^+$ TR 3.78 min
799		8-cloro-1-[4-(2,6-diclorofenil)butil]-3-pentil-3,7-dihidro-1H-purino-2,6-diona	m/z 457 $[MH]^+$ TR 4.10 min
800		8-cloro-1-{4-[3-(metilsulfonil)fenil]butil}-3-pentil-3,7-dihidro-1H-purino-2,6-diona	m/z 467 $[MH]^+$ TR 3.33 min
801		8-cloro-1-{4-[3-(ciclopentilsulfonil)fenil]butil}-3-pentil-3,7-dihidro-1H-purino-2,6-diona	m/z 521 $[MH]^+$ TR 3.65 min
802		4-[4-(8-chloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1 il)butil]benzonitrilo	m/z 414 $[MH]^+$ TR 3.61 min
803		8-cloro-1-(4-naftalen-1-ilbutil)-3-pentil-3,7-dihidro-1H-purino-2,6-diona	m/z 439 $[MH]^+$ TR 4.00 min
804		8-cloro-3-pentil-1-(4-{4-[(fenilmetil)oxi]fenil}butil)-3,7-dihidro-1H-purino-2,6-diona	m/z 495 $[MH]^+$ TR 4.06 min

805		8-cloro-1-[4-(4-fluorofenil)butil]-3-pentil-3,7-dihidro-1H-purino-2,6-diona	m/z 407 $[MH]^+$ TR 3.78 min
806		N-[4-{[4-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)butiloxi}-3-(rnetiloxi)fenil]acetamida	m/z 492 $[MH]^+$ TR 3.09 min
807		3-butil-8-cloro-1-[4-(5-fenil-1,2,4-oxadiazol-3-il)butil]-3,7-dihidro-1H-purino-2,6-diona	m/z 443 $[MH]^+$ TR 3.49 min
808		1-(4-bifenil-3-ilbutil)-8-cloro-3-pentil-3,7-dihidro-1H-purino-2,6-diona	m/z 465 $[MH]^+$ TR 4.13 min
809		3-butil-8-cloro-1-(4-{5-[2-fluoro-4-(trlfluorometil)fenil]-1,2,4-oxadiazol-3-il}butil)-3,7-dihidro-1H-purino-2,6-diona	m/z 529 $[MH]^+$ TR 3.71 min
810		3-butil-8-cloro-1-{4-[5-(4-cloro-2-fluorofenil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purino-2,6-diona	m/z 495 $[MH]^+$ TR 3.64 min
811		3-butil-8-cloro-1-{4-[5-(2,4-difluorofenil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purino-2,6-diona	m/z 479 $[MH]^+$ TR 3.49 min
812		3-butil-8-cloro-1-{4-[5-(2,3-difluorofenil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purino-2,6-diona	m/z 479 $[MH]^+$ TR 3.53 min
813		3-butil-8-cloro-1-{4-[5-(2-fluoro-4-metilfenil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purino-2,6-diona	m/z 475 $[MH]^+$ TR 3.51 min
814		3-butil-8-cloro-1-(4-hidroxibutil)-3,7-dihidro-1H-purino-2,6-diona	m/z 315 $[MH]^+$ TR 2.54 min
815		3-butil-8-cloro-1-{4-[5-(2,5-difluorofenil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purino-2,6-diona	m/z 479 $[MH]^+$ TR 3.50 min

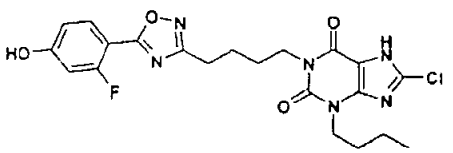
816		3-butil-8-cloro-1-{4-[5-(3,5-diclorofenil)-2H-tetrazol-2-il]butil}-3,7-dihidro-1H-purino-2,6-diona	m/z 511 $[MH]^+$ TR 3.92 min
817		3-butil-8-cloro-1-{4-[5-(6-metilpiridin-2-il)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purino-2,6-diona	m/z 458 $[MH]^+$ TR 3.12 min
818		3-butil-8-cloro-1-(4-{5-[2-fluoro-5-(metiloxi)fenil]-1,2,4-oxadiazol-3-il}butil)-3,7-dihidro-1H-purino-2,6-diona	m/z 491 $[MH]^+$ TR 3.51 min
819		3-butil-8-chloro-1-{4-[2,4-dioxo-5-(fenilmetil)-1,3-tiazolidin-3-il]butil}-3,7-dihidro-1H-purino-2,6-diona	m/z 504 $[MH]^+$ TR 3.36 min
820		3-butil-8-cloro-1-[4-(3,5-dioxo-1-fenil-1,2,4-triazolidin-4-il)butil]-3,7-dihidro-1H-purino-2,6-diona	m/z 474 $[MH]^+$ TR 2.91 min
821		3-butil-8-cloro-1-{4-[5-(6-oxo-1,6-dihidropiridin-2-il)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purino-2,6-diona	m/z 460 $[MH]^+$ TR 2.86 min
822		3-butil-8-cloro-1-{4-[5-(6-,fluoropiridin-2-il)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purino-2,6-diona	m/z 462 $[MH]^+$ TR 3.23 min
823		3-butil-8-cloro-1-{4-[5-(3-cloro-2-fluorofenil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purino-2,6-diona	m/z 495 $[MH]^+$ TR 3.69 min
824		3-butil-8-cloro-1-{4-[5-(3-metilfenil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purino-2,6-diona	m/z 457 $[MH]^+$ TR 3.67 min
825		3-butil-8-cloro,1-{4-[5-(3,5-dicloro-4-hidroxifenil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purino-2,6-diona	m/z 527 $[MH]^+$ TR 3.92 min
826		3-butil-8-cloro-1-(4-{5-[4-hidroxi-3-(metiloxi)fenil]-1,2,4-oxadiazol-3-il}butil)-3,7-dihidro-1H-purino-2,6-diona	m/z 489 $[MH]^+$ TR 3.27 min

827		3-butil-8-cloro-1-{4-[5-(3-cloro-4-hidroxifenil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purino-2,6-diona	m/z 493 $[MH]^+$ TR 3.61 min
828		3-butil-8-cloro-1-{4-[5-(1H-indol-6-il)-1,2,4-oxadiazol-3-il]butil},3,7-dihidro-1H-purino-2,6-diona	m/z 482 $[MH]^+$ TR 3.55 min
829		3-butil-8-cloro-1-{4-[5-(2-metilfenil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purino-2,6-diona	m/z 457 $[MH]^+$ TR 3.67 min
830		3-butil-8-cloro-1-(4-{5-[4-(metiloxi)fenil]-1,2,4-oxadiazol-3-il}butil)-3,7-dihidro-1H-purino-2,6-diona	m/z 473 $[MH]^+$ TR 3.51 min
831		3-butil-8-cloro-1-{4-[5-(4-fluorofenil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purino-2,6-diona	m/z 461 $[MH]^+$ TR 3.54 min
832		3-buti1-8-cloro-1-[4-(5-pirazin-2-il-1,2,4-oxadiazol-3-il)butil]-3,7-dihidro-1H-purino-2,6-diona	m/z 445 $[MH]^+$ TR 2.96 min
833		3-butil,8-cloro-1-{4-[5-(6-oxo-1,6-dihidropiridin-3-il)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purino-2,6-diona	m/z 460 $[MH]^+$ TR 2.78 min
834		1-{4-[5-(1H-benzimidazol-2-il)-1,2,4-oxadiazol-3-il]butil}-3-butil-8-cloro-3,7-dihidro-1H-purino-2,6-diona	m/z 483 $[MH]^+$ TR 3.22 min
835		3-butil-8-cloro-1-{4-[5-(3-fluorofenil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purino-2,6-diona	m/z 461 $[MH]^+$ TR 3.58 min
836		3-butil-8-cloro-1-[4-(5-pirimidin-2-il-1,2,4-oxadiazol-3-il)butil]-3,7-dihidro-1H-purino-2,6-diona	m/z 445 $[MH]^+$ TR 2.84 min

EJEMPLO 837

3-Butil-8-cloro-1-{4-[5-(2-fluoro-4-hidroxifenil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1*H*-purina-2,6-diona

a) 3-Butil-8-cloro-1-{4-[5-(2-fluoro-4-hidroxifenil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1*H*-purina-2,6-diona

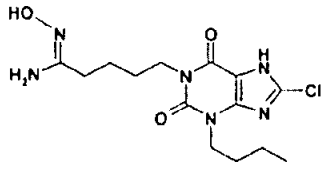


CDI (45 mg, 0.28 mmoles) en DMSO anhidro (0.5 ml) se añadió a ácido 2-fluoro-4-hidroxbenzoico (40 mg, 0.25 mmoles) y se agitó a t.a. durante 2 hr. Se añadió 5-(3-butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1*H*-purin-1-il)-*N*-hidroxipentanimidamida (100 mg, 0.28 mmoles) en DMSO (0.4 ml) y la mezcla resultante se calentó a 90°C durante 18 hr. La purificación por MDAP dio el compuesto del título como un sólido (38 mg, 28%).

CL/EM: m/z 477 $[MH]^+$, TR 3.39 min.

^{1}H RMN (DMSO-d_6) δ: 0.87 (t, 3H, J = 7Hz), 1.27 (m, 2H), 1.56-1.78 (m, 6H), 2.77 (t, 2H, J = 7Hz), 3.90 (m, 4H), 6.80 (m, 2H), 7.91 (t, 1H, J = 9Hz), 11.01 (s, 1H), 14.45 (br s, 1H).

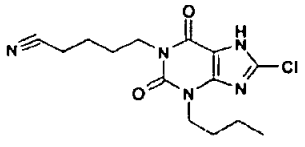
b) 5-(3-Butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1*H*-purin-1-il)-*N*-hidroxipentanimidamida



5-(3-Butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1*H*-purin-1-il)pentanonitrilo (8.5 g, 26 mmoles) se disolvió en EtOH (100 ml). Se añadió hidroxilamina (50% en agua; 2.6 ml, 39 mmoles) y la mezcla se calentó a 80°C durante 48 hr bajo nitrógeno. La mezcla de reacción se concentró bajo vacío, el sólido resultante se lavó con metanol y se secó para dar el compuesto del título como un sólido (5.9 g, 47%).

CL/EM: m/z 357 $[MH]^+$, TR 2.17 min.

c) 5-(3-Butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1*H*-purin-1-il)pentanonitrilo



5-Bromopentanonitrilo (4.54 ml, 39 mmoles) y carbonato de cesio (12.7 g) se añadieron a una solución de 3-butil-8-cloro-7-(2-propen-1-il)-3,7-dihidro-1*H*-purina-2,6-diona (10 g, 35 mmoles) en DMF (100 ml) y la mezcla se agitó bajo nitrógeno a 40°C durante la noche y se dejó enfriar.

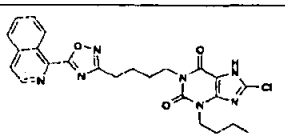
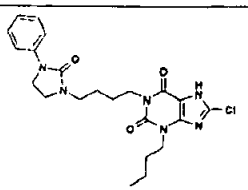
La mezcla se desgasificó después mediante la aplicación

sucesiva repetida de un vacío y después por presión de nitrógeno. La mezcla después se trató con tetrakis(trifenilfosfin)paladio(0) (2.86 g, 2.5 mmoles) y morfolina (30.8 ml, 350 mmoles). La mezcla se agitó en una atmósfera de nitrógeno durante 3 hr y después se dividió entre EtOAc y ácido clorhídrico acuoso 2M. La capa acuosa se separó y se extrajo con EtOAc (x2). Las fases orgánicas combinadas se concentraron bajo vacío para dar un sólido que se lavó con éter, se filtró y se secó. El filtrado se concentró y se purificó sobre una columna de aminopropilo eluyendo con MeOH seguido por 3% de AcOH/MeOH. Las fracciones que contenían producto se combinaron y se concentraron para dar un sólido, que se combinó con el producto filtrado. El compuesto del título se obtuvo como un sólido (10.5 g, 93%).

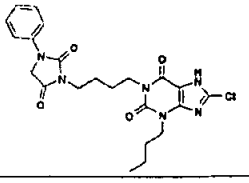
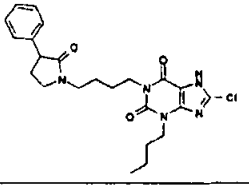
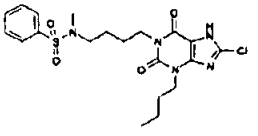
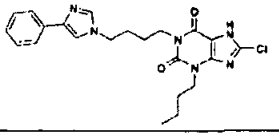
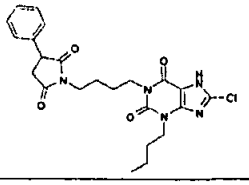
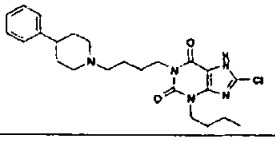
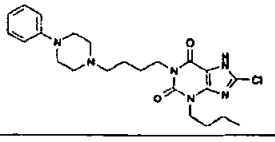
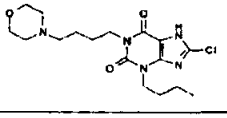
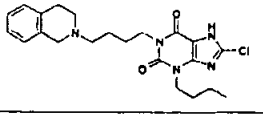
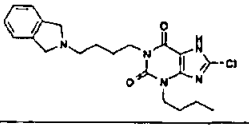
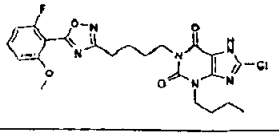
CL/EM: m/z 324 $[MH]^+$, TR 2.75 min.

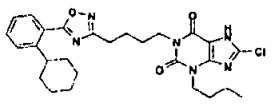
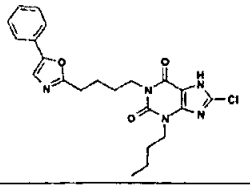
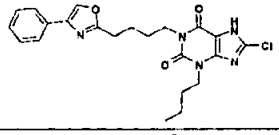
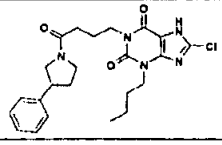
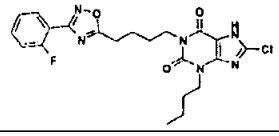
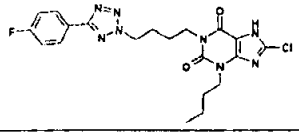
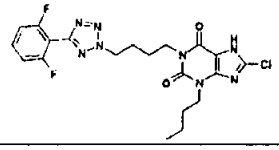
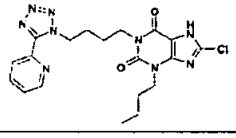
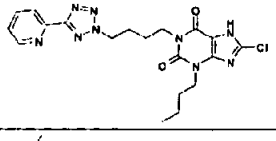
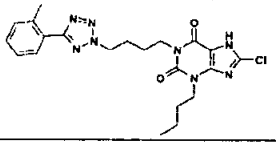
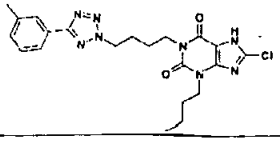
Los siguientes compuestos (cuadro 35) se prepararon usando un método análogo al del ejemplo 837, usando el ácido carboxílico apropiado.

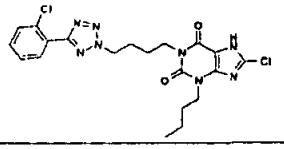
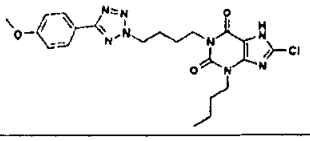
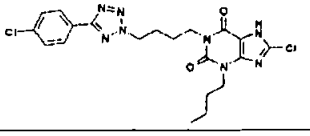
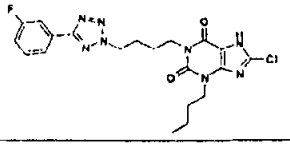
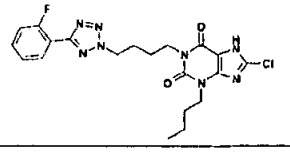
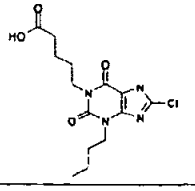
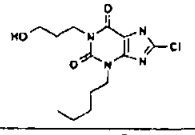
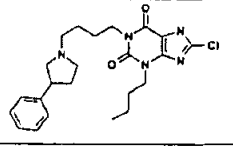
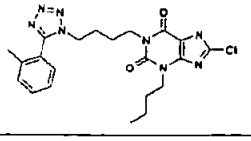
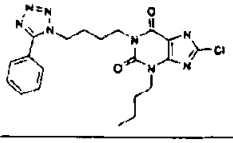
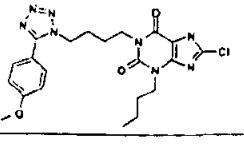
CUADRO 35

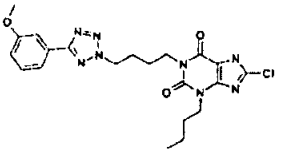
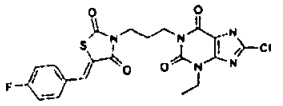
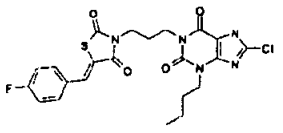
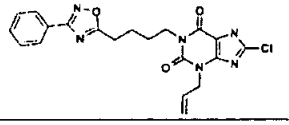
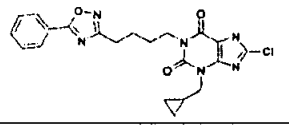
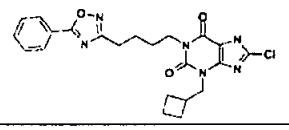
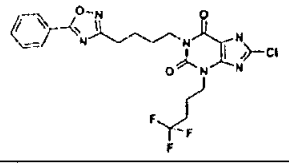
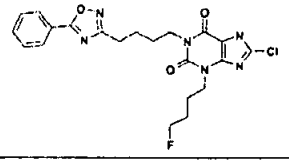
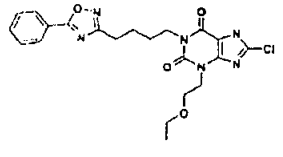
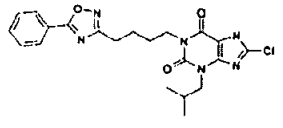
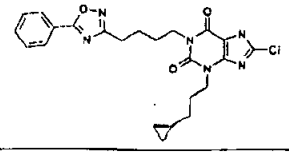
844		3-butil-8-cloro-1-[4-(5-ioquinolin-1-il-1,2,4-oxadiazol-3-il)butil]-3,7-dihidro-1H-purino-2,6-diona	m/z 494 $[MH]^+$ TR 3.49 min
845		3-butil-8-cloro-1-[4-(2-oxo-3-fenilimidazolidin-1-il)butil]-3,7-dihidro-1H-purino-2,6-diona	m/z 459 $[MH]^+$ TR 3.23 min

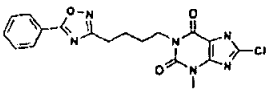
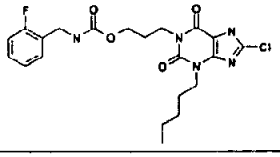
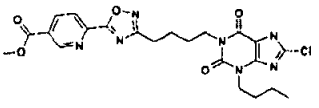
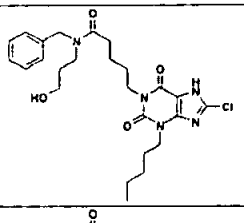
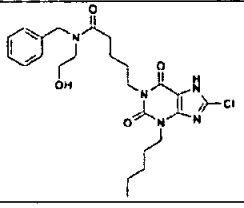
670

846		3-butil-8-cloro-1-[4-(2,5-dioxo-3-fenilimidazolidin-1-il)butil]-3,7-dihidro-1H-purino-2,6-diona	m/z 473 $[MH]^+$ TR 3.19 min
847		3-butil-8-cloro-1-[4-(2-oxo-fenilpirrolidin-1-il)butil]-3,7-dihidro-1H-purino-2,6-diona	m/z 458 $[MH]^+$ TR 3.12 min
848		N-[4-(3-butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1H-purin-1-il)butil]-N-metilbencensulfonamida	m/z 468 $[MH]^+$ TR 3.28 min
849		3-butil-8-cloro-1-[4-{4-fenil-1H-imidazol-1-il)butil]-3,7-dihidro,1H-purino-2,6-diona	m/z 441 $[MH]^+$ TR 2.60 min
850		3-butil-8-cloro-1-[4-(2,5-dioxo-3-fenilpirrolidin-1-il)butil]-3,7-dihidro-1H-purin-2,6-diona	m/z 471 $[MH]^+$ TR 3.20 min
851		3-butil-8-cloro-1-[4-(4-fenilpiperidin-1-il)butil]-3,7,dihidro-1H-purino-2,6-diona	m/z 458 $[MH]^+$ TR 2.56 min
852		3-butil-8-cloro-1-[4-(4-fenilpiperazin-1-il)butil]-3,7-dihidro-1H-purino-2,6- diona	m/z 459 $[MH]^+$ TR 2.49 min
853		3-butil-8-cloro-1-(4-morfolin-4-ilbutil)-3,7-dihidro-1H-purino-2,6-diona	m/z 384 $[MH]^+$ TR 2.11 min
854		3-butil-8-cloro-1-[4-(3,4-dihidroisoquinolin-2(1H)-il)butil}-3,7-dihidro-1H-purino-2,6-diona	m/z 430 $[MH]^+$ TR 2.40 min
855		3-butil-8-cloro-1-[4-(1,3-dihidro-2H-isoindol-2-il)butil]-3,7-dihidro-1H-purino-2,6-diona	m/z 416 $[MH]^+$ TR 2.33 min
856		3-butil-8-cloro-1-(4-{5-[2-fluoro-6-(metiloxi)fenil]-1,2,4-oxadiazol-3-il}butil)-3,7-dihidro-1H-purino-2,6-diona	m/z 491 $[MH]^+$ TR 3.33 min

857		3-butil-8-cloro-1-{4-[5-(2-ciclohexilfenil)-1,2,4-oxadiazol-3-il]butil}-3,7-dihidro-1H-purino-2,6-diona	m/z 525 $[MH]^+$ TR 4.18 min
858		3-butil-8-cloro-1-[4-(5-fenil-13-oxazol-2-il)butil]-3,7-dihidro-1H-purino-2,6-diona	m/z 442 $[MH]^+$ TR 3.46 min
859		3-butil-8-cloro-1-{4-(4-fenil-1,3-oxazol-2-il)butil]-3,7-dihidro-1H-purino-2,6-diona	m/z 442 $[MH]^+$ TR 3.48 min
860		3-butil-8-cloro-1-[4-oxo-4-(3-fenilpirrolidin-1-il)butil]-3,7-dihidro-1H-purino-2,6-diona	m/z 458 $[MH]^+$ TR 3.16 min
861		3-butil-8-cloro-1-{4-[3-(2-fluorofenil)-1,2,4-oxadiazol-5-il]butil}-3,7-dihidro-1H-purino-2,6-diona	m/z 461 $[MH]^+$ TR 3.45 min
862		3-butil-8-cloro-1-{4-[5-(4-fluorofenil)-2H-tetrazol-2-il)butil}-3,7-dihidro-1H-purino-2,6-diona	m/z 461 $[MH]^+$ TR 3.47 min
863		3-butil-8-cloro-1-{4-[5-(2,6-difluorofenil)-2H-tetrazol-2-il]butil}-3,7-dihidro-1H-purino-2,6-diona	m/z 479 $[MH]^+$ TR 3.32 min
864		3-butil-8-cloro-1-[4-(5-piridin-2-il-1H-tetrazol-1-il)butil]-3,7-dihidro-1H-purino-2,6-diona	m/z 444 $[MH]^+$ TR 2.94 min
865		3-butil-8-cloro-1-[4-(5-piridin-2-il-2H-tetrazol-2-il)butil]-3,7-dihidro-1H-purino-2,6-diona	m/z 444 $[MH]^+$ TR 3.07 min
866		3-butil-8-cloro-1-{4-[5-(2-metilfenil)-2H-tetrazol-2-il]butil}-3,7-,dihidro-1H-purino-2,6-diona	m/z 457 $[MH]^+$ TR 3.54 min
867		3-butil-8-cloro-1-{4-[5-(3-metilfenil)-2H-tetrazol-2-il]butil}-3,7-dihidro-1H-purino-2,6-diona	m/z 457 $[MH]^+$ TR 3.56 min

868		3-butil-8-cloro-1-{4-[5-(2-clorofenil)-2-tetrazol-2-il]butil}-3,7-dihidro-1H-purino-2,6-diona	m/z 477 $[MH]^+$ TR 3.68 min
869		3-butil-8-cloro-1-(4-{5-[4-(metiloxi)fenil]-2H-tetrazol-2-il}butil)-3,7-dihidro-1H-purino-2,6-diona	m/z 473 $[MH]^+$ TR 3.40 min
870		3-butil-8-cloro-1-{4-[5-(4-clorofenil)-2H-tetrazol-2-il]butil}-3,7-dihidro-1H-purino-2,6-diona	m/z 477 $[MH]^+$ TR 3.68 min
871		3-butil-8-cloro-1-{4-[5-(3-fluorofenil)-2H-tetrazol-2-il]butil}-3,7-dihidro-1H-purino-2,9-diona	m/z 461 $[MH]^+$ TR 3.51 min
872		3-butil-8-cloro-1-{4-[5-(2-fluorofenil)-2H-tetrazol-2-il]butil}-3,7-dihidro-1H-purino-2,6-diona	m/z 461 $[MH]^+$ TR 3.34 min
873		ácido 5-(3-butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1H-purin-1-il)pentanoico	m/z 343 $[MH]^+$ TR 2.76 min
874		ácido 5-(3-butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1H-purino-1-il)pentanoico	m/z 315 $[MH]^+$ TR 2.74 min
875		3-butil-8-cloro-1-[4-(3-fenil-1-pirrolidinil)butil]-3,7-dihidro-1H-purino-2,6-diona	m/z 444 $[MH]^+$ TR 2.51 min
876		3-butil-8-cloro-1-{4-[5-(2-metilfenil)-1H-tetrazol-1-il]butil}-3,7-dihidro-1H-purino-2,6-diona	m/z 457 $[MH]^+$ TR 3.16 min
877		3-butil-8-cloro-1-[4-(5-fenil-1H-tetrazol-1-il)butil]-3,7-dihidro-1H-purino-2,6-diona	m/z 443 $[MH]^+$ TR 3.08 min
878		3-butil-8-cloro-1-(4-{5-[4-(metiloxi)fenil)-1H-tetrazol-1-il}butil)-3,7-dihidro-1H-purino-2,6-diona	m/z 473 $[MH]^+$ TR 3.10 min

879		3-butil-8-cloro-1-(4-{5-[3-(metiloxi)fenil]-2H-tetrazol-2-il}butil)-3,7-dihidro-1H-purino-2,6-diona	m/z 473 $[MH]^+$ TR 3.40 min
880		8-cloro-3-etil-1-(3-{(5Z)-5-[(4-fluorofenil)metiliden]-2,4-dioxo-1,3-tiazolidin-3-il}propil)-3,7-dihidro-1H-purino-2,6-diona	m/z 478 $[MH]^+$ TR 3.31 min
881		3-butil-8-cloro-1-(3-{(5Z)-5-[(4-fluorofenil)metiliden]-2,4-dioxo-1,3-tiazolidin-3-il}propil)-3,7-dihidro-1H-purino-2,6-diona	m/z 506 $[MH]^+$ TR 3.63 min
882		8-cloro-1-[4-(3-fenil-1,2,4-oxadiazol-5-il)butil]-3-(2-propen-1-il)-3,7-dihidro-1H-purino-2,6-diona	m/z 427 $[MH]^+$ TR 3.20 min
883		8-cloro-3-(ciclopropilmetil)-1-[4-(5-fenil-1,2,4-oxadiazol-3-il)butil]-3,7-dihidro-1H-purino-2,6-diona	m/z 441 $[MH]^+$ TR 3.38 min
884		8-cloro-3-(ciclobutilmetil)-1-[4-(5-fenil-1,2,4-oxadiazol-3-il)butil}-3,7-dihidro-1H-purino-2,6-diona	m/z 455 $[MH]^+$ TR 3.53 min
885		8-cloro-1-[4-(5-fenil-1,2,4-oxadiazol-3-il)butil]-3-(4,4,4-trifluorobutil)-3,7-dihidro,1H,purino-2,6-diona	m/z 497 $[MH]^+$ TR 3.46 min
886		8-cloro-3-(4-fluorobutil)-1-[4-(5-fenil-1,2,4-oxadiazol-3-il)butil}-3,7-dihidro-1H-purino-2,6-diona	m/z 461 $[MH]^+$ TR 3.26 min
887		8-cloro-3-[2-(etiloxi)etil}-1-[4-(5-fenil-1,2,4-oxadiazol-3-il)butil]-3,7-dihidro-purino-2,6-diona	m/z 459 $[MH]^+$ TR 3.16 min
888		8-cloro-3-(2-metilpropil)-1-[4-(5-fenil-1,2,4-oxadiazol-3-il)butil]-3,7-dihidro-1H-purino-2,6-diona	m/z 443 $[MH]^+$ TR 3.44 min
889		8-cloro-3-(3-ciclopropilpropil)-1-[4-(5-fenil-1,2,4-oxadiazol-3-il)butil]-3,7-dihidro-1H-purino-2,6-diona	m/z 469 $[MH]^+$ TR 3.63 min

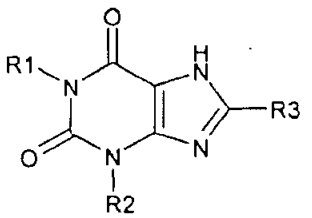
890		8-cloro-3-metil-1-[4-(5-fenil-1,2,4-oxadiazol-3-il)butil]-3,7-dihidro-1H-purino-2,6,diona	m/z 401 $[MH]^+$ TR 2.98 min
891		[(2-fluorofenil)metil]carbamato de 3-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)propilo	m/z 466 $[MH]^+$ TR 3.44 min
892		6-{3-[4-(3-butil-8-cloro-2,6-dioxo-2,3,6,7-tetrahidro-1H-purin-1-il)butil]-1,2,4-oxadiazol-5-il}-3-piridincarboxilato de metilo	m/z 502 $[MH]^+$ TR 3.22 min
893		5-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)-N-(3-hidroxipropil)-N-(fenilmetil)pentanamida	m/z 504 $[MH]^+$ TR 2.64 min
894		5-(8-cloro-2,6-dioxo-3-pentil-2,3,6,7-tetrahidro-1H-purin-1-il)-N-(2-hidroxietil)-N-(fenilmetil)pentanamida	m/z 490 $[MH]^+$ TR 3.13 min

Todas las publicaciones, incluyendo pero sin limitarse a patentes y solicitudes de patente, citadas en esta especificación se incorporan aquí por referencia como si cada publicación individual fuera específicamente e individualmente indicada para ser incorporada aquí por referencia

NOVEDAD DE LA INVENCION

REIVINDICACIONES

1.- Por lo menos una entidad química seleccionada de los compuestos de la fórmula (I)



(I)

y derivados farmacéuticamente aceptables de los mismos, en donde R^1 representa -(alquileno)$_m$-X-(alquileno)$_n$-Y; en donde X representa A, A1, A2 o un enlace directo; A representa un grupo seleccionado de cicloalquileno, cicloalquenileno, arilo, heteroarilo, heterociclilo, y -CH_2-OC(O)-; A1 representa un grupo seleccionado de -CH_2-O-$(CH_2)_q$arilo-O-, -CH_2-O-$(CH_2)_w$N(R^5)C(O)O-, -CH_2-N(R^5)C(O)O-, -CH_2-N(R^5)C(O)-, -CH_2-$(O)_p$-$(CH_2)_q$C(O)NR^5-, -CH_2-N(R^5)C(O)N(R^5)-, -CH_2-C(O)N($(CH_2)_w$OH)-, -CH_2-NR^5-S$(O)_2$-, CH_2-S$(O)_2$NR^5-, -CH_2-C(O)O-, -O-, -NR^5-, y -S-; A2 representa -CH(OH)-; Cuando X es A, A1 o A2, Y representa un grupo seleccionado de heteroarilo, heterociclilo, arilo, cicloalquilo, cicloalquenilo, -NH-arilo, -O$(CH_2)_n$-arilo, -O-heteroarilo, -OR^5, -C(O)OR^5, -C(O)O-arilo de C_6, -OC(O)R^4, -CH(arilo)$_2$, -CH(heteroarilo)$_2$, y –halogenoalquilo de C_{1-6}; cuando X es A1 y Y se selecciona de -O$(CH_2)_n$-arilo, -O-heteroarilo, -OR^5, -OC(O)R^4, y -NH-arilo, n es un entero seleccionado de 2,

3, 4 y 5; cuando X es A1 y Y es -halogenoalquilo de C_{1-6}, o cuando X es A2, n es un entero seleccionado de 2, 3, 4 y 5; cuando X es un enlace directo, (m + n) es un entero seleccionado de 2 a 10; cuando X es un enlace directo y (m + n) es un entero seleccionado de 3 a 10, Y representa un grupo seleccionado de $-C(O)(CH_2)_qOR^4$, -C(O)-arilo, -C(O)-heteroarilo, -C(O)-heterociclilo, heteroarilo, heterociclilo, arilo, sistema fusionado de 3 ó 4 anillos, $-CH(arilo)_2$, $-CH(heteroarilo)_2$, $-OR^5$, $-NR^5R^6$, $-NR^5C(O)OR^7$, $-(O)_pC(O)NR^5R^7$, y $-NR^5C(O)R^7$; cuando X es un enlace directo y (m + n) es 2, Y representa un grupo seleccionado de: $-OR^5$, $-NH_2$, y $-NR^5C(O)OR^8$; cuando Y incorpora un anillo, ese anillo puede ser opcionalmente sustituido por uno o más de alquilo de C_{1-6}, alquenilo de C_{2-6}, alquinilo de C_{2-6}, halógeno, $-(CH_2)_q NR^5R^7$, $-(CH_2)_q-(O)_p-(CH_2)_q-N(R^5)C(O)OR^8$, $-(CH_2)_q-N(R^5)C(O)R^8$, $-(CH_2)_q-(O)_p-(CH_2)_q-C(O)NR^5R^6$, $-(CH_2)_q-N(R^5)C(O)N(R^5)R^6$, $-(CH_2)_q-C(O)N((CH_2)_mOH)R^5$, $-(CH_2)_q-N(R^5)-S(O)_2R^8$, $-CH_2-S(O)_2N(R^5)R^6$, halogenoalquilo de C_{1-6}, $-OCF_3$, $-OCH(F)_2$, $-OCH_2F$, $-C(O)OR^5$, $-OR^5$, $-R^8CN$, -CN, $-SO_2R^9$, $-(CH_2)_n$heteroarilo, $-(CH_2)_n$heterociclilo, $-(CH_2)_n$cicloalquilo, $-(CH_2)_n$cicloalquenilo, y $-(CH_2)_n$arilo; siempre que cuando X es A1, A1 es -O- y Y es un anillo que es sustituido por arilo o heteroarilo, entonces m es un entero seleccionado de 3, 4 y 5; R^2 se selecciona de hidrógeno, alquilo de C_{1-10}, alquenilo de C_{2-10}, alquinilo de C_{2-10}, cicloalquilo, cicloalquenilo, heterociclilo, arilo y heteroarilo, cada uno de los cuales puede ser opcionalmente sustituido por uno o más de un grupo independientemente seleccionado de: alquilo de C_{1-10}, alquenilo de C_{2-10}, alquinilo de C_{2-10}, cicloalquilo, heterociclilo, arilo, heteroarilo, halogenoalquilo

de C_{1-6}, halógeno, -CN, $-OR^4$, $-(CH_2)_nCOR^4$, $-C(O)OR^4$, $-OCOR^4$, $-(CH_2)_nNR^5R^6$, $-(NH)_pCONR^5R^6$, $-OCONR^5R^7$, y $-NR^5C(O)OR^7$; R^3 representa un grupo seleccionado de halógeno y CN; R^4 se selecciona de hidrógeno, alquilo de C_{1-6}, alquenilo de C_{2-6}, alquinilo de C_{2-6}, $-(CH_2)_n$cicloalquilo, $-(CH_2)_n$cicloalquenilo, $-(CH_2)_n$heterociclilo, $-(CH_2)_n$ arilo, y $-(CH_2)_n$heteroarilo; R^5 y R^6 se seleccionan independientemente de hidrógeno y alquilo de C_{1-4}; R^7 representa un grupo seleccionado de H, alquilo de C_{1-6}, alquenilo de C_{2-6}, alquinilo de C_{2-6}, $-(CH_2)_n$cicloalquilo, $-(CH_2)_n$cicloalquenilo, $-(CH_2)_n$heterociclilo, $-(CH_2)_n$arilo y $-(CH2)_n$heteroarilo; R^8 representa un grupo seleccionado de alquilo de C_{1-4}; R^9 representa un grupo seleccionado de alquilo de C_{1-6}, alquenilo de C_{2-6}, alquinilo de C_{2-6}, $-(CH_2)_n$cicloalquilo, $-(CH_2)_n$cicloalquenilo, $-(CH_2)_n$heterociclilo, $-(CH_2)_n$arilo, $-(CH_2)_n$heteroarilo y CN; m representa un entero seleccionado de 1, 2, 3, 4 y 5; n representa un entero seleccionado de 0, 1 , 2, 3, 4 y 5; p representa un entero seleccionado de 0 y 1; q representa un entero seleccionado de 0, 1 y 2; t representa un entero seleccionado de 1 y 2; y w representa un entero seleccionado de 2, 3 y 4.

2.- Por lo menos una entidad química de conformidad con la reivindicación 1, caracterizada además porque X se selecciona de A y A1.

3.- Por lo menos una entidad química de conformidad con la reivindicación 1 ó 2, caracterizada además porque R^2 se selecciona de alquilo de C_{3-6}.

4.- Por lo menos una entidad química de conformidad con cualquiera de las reivindicaciones anteriores, caracterizada además porque X

se selecciona de A y A1, y A representa un grupo seleccionado de heteroarilo y heterociclilo, y A1 representa un grupo seleccionado de CH_2-O-$(CH_2)_wN(R^5)C(O)O$-, CH_2-$N(R^5)C(O)O$-, CH_2-$N(R^5)C(O)$-, CH_2-$(O)_p$-$(CH_2)_qC(O)NR^5$-, CH_2-$N(R^5)C(O)N(R^5)$-, CH_2-$C(O)N((CH_2)_mOH)$-, CH_2-NR^5-$S(O)_2$-, CH_2-$S(O)_2NR^5$- y CH_2-C(O)O-.

5.- Por lo menos una entidad química de conformidad con la reivindicación 4, caracterizada además porque X representa A y A representa un grupo seleccionado de heteroarilo.

6.- Por lo menos una entidad química de conformidad con la reivindicación 5, caracterizada además porque A representa un grupo seleccionado de heteroarilo que comprende un heteroátomo de nitrógeno.

7.- Por lo menos una entidad química de conformidad con cualquiera de las reivindicaciones anteriores, caracterizada además porque Y representa un grupo seleccionado de arilo, heteroarilo y O-arilo.

8.- Por lo menos una entidad química de conformidad con cualquiera de las reivindicaciones anteriores, caracterizada además porque R^3 representa halógeno.

9.- Por lo menos una entidad química de conformidad con cualquiera de las reivindicaciones anteriores, caracterizada además porque R^3 representa cloro.

10.- Por lo menos una entidad química de conformidad con cualquiera de las reivindicaciones anteriores para usarse en medicina humana o veterinara.

11.- Por lo menos una entidad química de conformidad con cualquiera de las reivindicaciones 1 a 9, para usarse en el tratamiento de trastornos de metabolismo de lípidos incluyendo dislipidemia e hiperlipoproteinemia y/o de enfermedades o condiciones inflamatorias.

12.- Por lo menos una entidad química de conformidad con cualquiera de las reivindicaciones 1 a 9 para usarse en el tratamiento de dislipidemia diabética, dislipidemia mixta, insuficiencia cardiaca, hpercolesteremia, enfermedad cardiovascular incluyendo aterosclerosis, arteriosclerosis, e hipertrigliceridemia, diabetes mellitus de tipo II, diabetes de tipo I, resistencia a la insulina, hiperlipidemia, anorexia nerviosa, obesidad, enfermedad de arteria coronaria, trombosis, angina, insuficiencia renal crónica, enfermedad vascular periférica o accidente vascular cerebral.

13.- Por lo menos una entidad química de conformidad con cualquiera de las reivindicaciones 1 a 9 para usarse en la fabricación de un medicamento para tratar dislipidemia diabética, dislipidemia mixta, insuficiencia cardiaca, hpercolesteremia, enfermedad cardiovascular incluyendo aterosclerosis, arteriosclerosis, e hipertrigliceridemia, diabetes mellitus de tipo II, diabetes de tipo I, resistencia a la insulina, hiperlipidemia, anorexia nerviosa, obesidad, enfermedad de arteria coronaria, trombosis, angina, insuficiencia renal crónica o accidente vascular cerebral.

14.- Un método para el tratamiento de un sujeto humano o animal que tiene una condición en donde la sub-activación del receptor de HM74A contribuye a la condición o en donde activación del receptor será

680

benéfica, dicho método comprende administrar a dicho sujeto humano o animal una cantidad efectiva de por lo menos una entidad química de conformidad con cualquiera de las reivindicaciones 1 a 9.

15.- El método de conformidad con la reivindicación 14, caracterizado además porque el sujeto humano o animal tiene un trastorno de metabolismo de lípidos incluyendo dislipidemia o hiperlipoproteinemia o una enfermedad o condición inflamatoria.

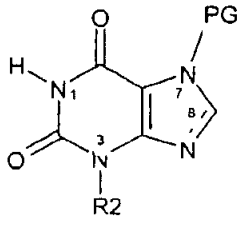
16.- Una formulación farmacéutica que comprende por lo menos una entidad química de cualquiera de las reivindicaciones 1 a 9 y por lo menos un diluyente, excipiente o vehículo farmacéuticamente aceptable.

17.- Una combinación para administración, en conjunto o por separado, secuencialmente o simultáneamente en formulaciones farmacéuticas separadas o combinadas, de dicha combinación que comprende por lo menos una entidad química de cualquiera de las reivindicaciones 1 a 9 junto con otro agente terapéuticamente activo.

18.- Una formulación farmacéutica que comprende: (i) por lo menos una entidad química de conformidad con cualquiera de las reivindicaciones 1 a 9; (ii) uno o más agentes terapéuticamente activos seleccionados de estatinas, fibratos, resinas de unión a ácidos biliares y ácido nicotínico; y (iii) uno o más diluyentes, excipientes o vehículos farmacéuticamente aceptables.

19.- Un método para la preparación de por lo menos una entidad química de cualquiera de las reivindicaciones 1 a 9, en el cual R^3 es halógeno

de un material de partida apropiado, por ejemplo compuesto(s) de la fórmula (II):



(II)

en donde PG = grupo protector, el método comprende: (i) alquilación en N1 de una xantina protegida con N7; (ii) alquilación en N3 de una xantina protegida con N7; (iii) halogenación en C8; y (iv) desprotección de N7; en cualquier orden proveyendo desprotección se lleva a cabo después de la alquilación.

RESUMEN DE LA INVENCION

La presente invención se refiere a compuestos de la fórmula (I), que son derivados de xantina, procedimientos para la fabricación de dichos derivados, formulaciones farmacéuticas que contienen los compuestos activos y el uso de los compuestos en terapia, por ejemplo, en el tratamiento de enfermedades en donde, bajo activación de receptor de HM74A, contribuye a la enfermedad o en donde la activación del receptor será benéfica.

JJ

P08/131F

LEYENDAS DE FIGURA

Figura 1

Intensity (counts) - Intensidad (conteos)

2Theta (°) - 2Teta (°)

Figura 2

Intensity (counts) - Intensidad (conteos)

2Theta (°) - 2Teta (°)

Figura 3

Intensity (counts) - Intensidad (conteos)

2Theta (°) - 2Teta (°)

Figure 1

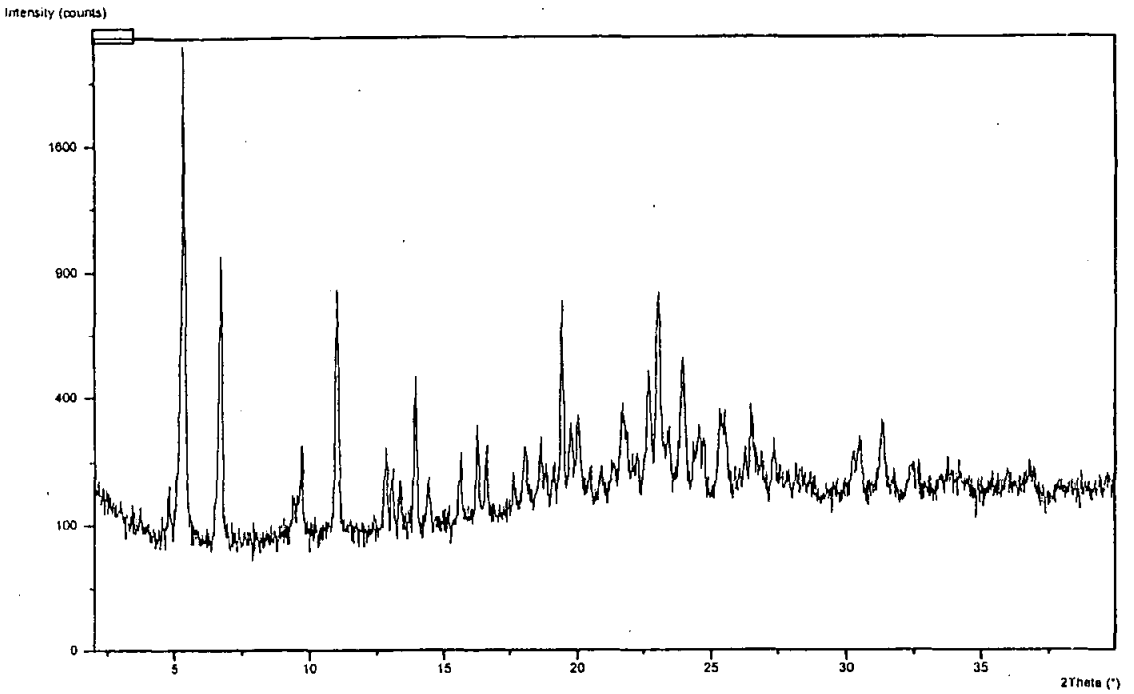


Figure 1: XRPD data of substantially crystalline 3-Butyl-8-chloro-1-{4-[5-(2-pyridinyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione form 1.

Figure 2

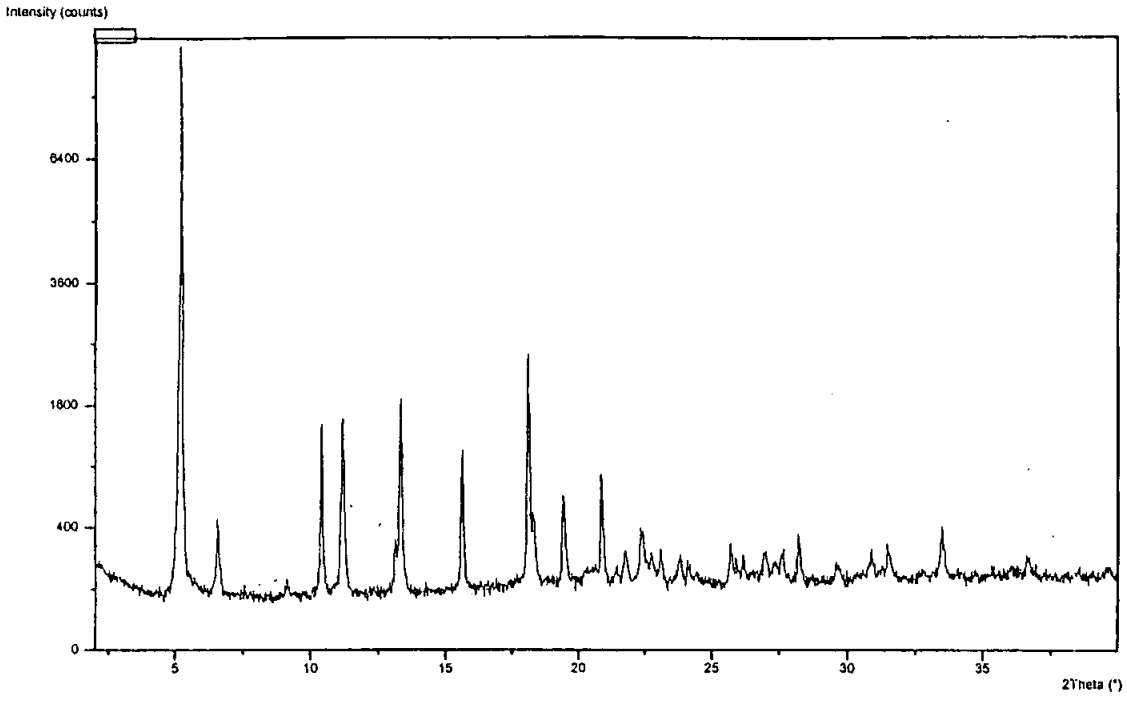


Figure 2: XRPD data of substantially crystalline 3-Butyl-8-chloro-1-{4-[5-(2-pyridinyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione form 2.

Figure 3

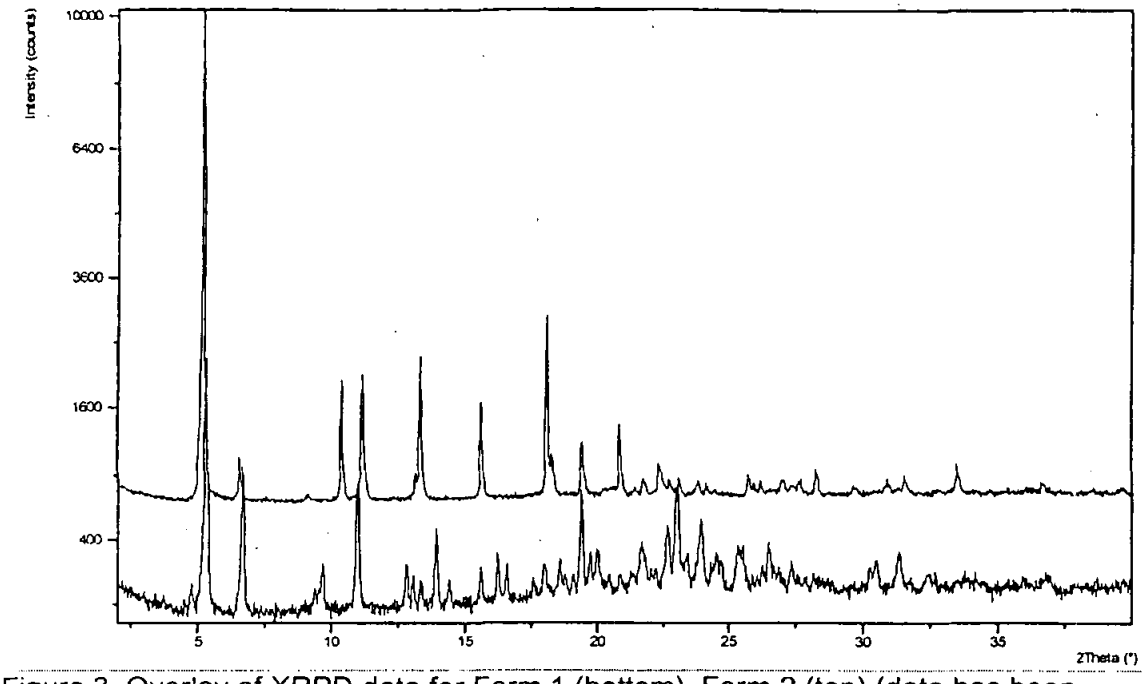


Figure 3 Overlay of XRPD data for Form 1 (bottom), Form 2 (top) (data has been offset for clarity).

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

To:

GLAXO SMITH KLINE
Attn. Easeman, Richard Lewis
Corporate Intellectual Property
(CN925.1)
980 Great West Road
Brentford, Middlesex TW8 9GS
GRANDE BRETAGNE

GlaxoSmithKline
Corporate IP
Received BRENTFORD
11 DEC 2006

ATTY
IPM : N/A | ON | UPDATED ON
ATTY CHECKED/FILE

Applicant's or agent's file reference LH/PB62046	Date of mailing *(day/month/year)* 12/12/2006 **FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/EP2006/007869	International filing date *(day/month/year)* 08/08/2006
Applicant SMITHKLINE BEECHAM CORPORATION	

1. [X] The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

   When? The time limit for filing such amendments is normally two months from the date of transmittal of the International Search Report.

   Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Fascimile No.: (41-22) 338.82.70

   For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

   [ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

   [ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

   Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

   The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

   Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

   In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

   See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the International Searching Authority	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	Petronella Elsackers

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the *PCT Applicant's Guide*, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report and the written opinion of the International Searching Authority, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims,description and drawings) may be amended during the international preliminary examination procedure, *there is usually no need to file amendments of the claims under Article 19* except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only (see *PCT Applicant's Guide*, Volume I/A, Annexes B1 and B2).

The attention of the applicant is drawn to the fact that amendments to the claims under Article 19 are not allowed where the International Searching Authority has declared, under Article 17(2), that no international search report would be established (see *PCT Applicant's Guide*, Volume I/A, paragraph 296).

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When? Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How? Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
LH/PB62046		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP2006/007869	08/08/2006	10/08/2005
Applicant		
SMITHKLINE BEECHAM CORPORATION		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 6 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language,** the international search was carried out on the basis of:
      [X] the international application in the language in which it was filed
      [ ] a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))
   b. [ ] With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. [X] **Certain claims were found unsearchable** (See Box No. II)

3. [ ] **Unity of invention is lacking** (see Box No III)

4. With regard to the **title,**
   [ ] the text is approved as submitted by the applicant
   [X] the text has been established by this Authority to read as follows:
   XANTHINE DERIVATIVES AS SELECTIVE HM74A AGONISTS

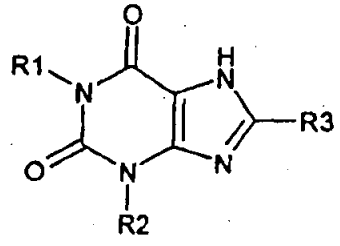
5. With regard to the **abstract,**
   [ ] the text is approved as submitted by the applicant
   [X] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings,**
   a. the figure of the **drawings** to be published with the abstract is Figure No. _____
      [ ] as suggested by the applicant
      [ ] as selected by this Authority, because the applicant failed to suggest a figure
      [ ] as selected by this Authority, because this figure better characterizes the invention
   b. [ ] none of the figures is to be published with the abstract

Box No. IV Text of the abstract (Continuation of item 5 of the first sheet)

The present invention relates to compounds of formula (I)

which are xanthine derivatives, processes for the manufacture of said derivatives, pharmaceutical formulations containing the active compounds and the use of the compounds in therapy, for example, in the treatment of diseases where under-activation of the HM74A receptor contributes to the disease or where activation of the receptor will be beneficial.



(I)

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D473/06 C07D473/04 A61K31/495 A61P3/00 A61P9/00

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)
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, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 03/004496 A (NOVO NORDISK AS [DK]) 16 January 2003 (2003-01-16) the whole document	1-19
A	WO 2005/016870 A (SMITHKLINE BEECHAM CORP [US]; CAMPBELL MATHEW [GB]; HATLEY RICHARD JON) 24 February 2005 (2005-02-24) the whole document	1-19
A	ARCH J R S ET AL: "INHIBITION OF TYPE 4 CYCLIC NUCLEOTIDE PHOSPHODIESTERASE BY 8-CHLOROXANTHINES" ARCHIV DER PHARMAZIE, VCH VERLAGSGESELLSCHAFT MBH, WEINHEIM, DE, vol. 329, no. 4, 1996, pages 205-208, XP008046719 ISSN: 0365-6233 the whole document	1-19

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 November 2006	12/12/2006

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	Fritz, Martin

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 1 338 595 A (EISAI CO LTD [JP]) 27 August 2003 (2003-08-27) the whole document -----	1-19

INTERNATIONAL SEARCH REPORT

PCT/EP2006/007869

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

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons: 693

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 14-15 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. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 03004496 A	16-01-2003	EP 1404675 A1	07-04-2004
		JP 2005502624 T	27-01-2005
WO 2005016870 A	24-02-2005	EP 1670749 A1	21-06-2006
EP 1338595 A	27-08-2003	US 2004082570 A1	29-04-2004

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2006/007869	08.08.2006	10.08.2005

International Patent Classification (IPC) or both national classification and IPC
INV. C07D473/06 C07D473/04 A61K31/495 A61P3/00 A61P9/00

Applicant
SMITHKLINE BEECHAM CORPORATION

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:
European Patent Office - P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk - Pays Bas
Tel. +31 70 340 - 2040 Tx: 31 651 epo nl
Fax: +31 70 340 - 3016

Date of completion of this opinion
See form PCT/ISA/210

Authorized Officer
Fritz, Martin
Telephone No. +31 70 340-3024

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

      ☐ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material:

      ☐ on paper

      ☐ in electronic form

   c. time of filing/furnishing:

      ☐ contained in the international application as filed.

      ☐ filed together with the international application in electronic form.

      ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

☐ the entire international application

☑ claims Nos. 14-15 with respect to industrial applicability

because:

☒ the said international application, or the said claims Nos. 14-15 with respect to industrial applicability relate to the following subject matter which does not require an international search *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☐ no international search report has been established for the whole application or for said claims Nos.

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b).

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-19
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-19
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-13,16-19
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 14-15 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Art. 34(4)(a) (i) PCT).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

D1: WO 03/004496 A (NOVO NORDISK AS [DK]) 16 January 2003 (2003-01-16)
D2: WO 2005/016870 A (SMITHKLINE BEECHAM CORP [US]; CAMPBELL MATHEW [GB]; HATLEY RICHARD JON) 24 February 2005 (2005-02-24)

The present application relates to compounds of the general formula (I) (claims 1-9), the compounds (I) for use in therapy (claims 10-13), methods of treatment by administering the compounds (I) (claims 14-15), pharmaceutical formulations thereof (claims 16-18) and a method for their preparation (claim 19).

For the assessment of the present claims 14-15 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

The compounds (I) are structurally comparable to the xanthine derivatives according to e.g. ex. 22, 23 of D1 (structural difference, cf. positions 7, 8 of the heterobicyclic system) which have a pharmacologically similar profile. D1 is, however, silent with regard to an eventual activity of the compounds disclosed therein towards the HM74A receptor.

Compounds which are agonists of the nicotinic acid receptor HM74A are described in D2; these known compounds are, however, structurally remote from the compounds (I) of the present case.

The subject-matter of claims 1-19 according to the present case is therefore novel in the sense of Article 33(2) PCT.

Closest prior art is D2.

The problem underlying the present application was to provide further compounds that are agonists of the nicotinic acid receptor HM74A.

This problem has been solved, as can be seen in the description.

The compounds (I) are not obvious for the man skilled in the art, as xanthine derivatives are a class of compounds whcih has not yet been suggested as displaying HM74A agonistic activities.

An inventive step in the sense of Article 33(3) PCT can therefore be acknowledged for the subject-matter of claims 1-19.

Further objections:

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1-D2 are not mentioned in the description, nor are these documents identified therein.

The term "pharmaceutically acceptable derivatives thereof" used in claim 1 is a functional definition and does not provide the skilled person with the necessary teaching for assessing what subject-matter is actually comprised therein.
By using the above term it is also attempted to define the invention by a result to be achieved which is not allowable (cf. also PCT International Preliminary Examination Guidelines III-4.7).
The subject-matter of claim 1 therefore does not fulfil the requirements of Article 6 PCT.

The same objection applies for "appropriate starting material" employed in claim 19 (the term "for example makes it claer that compounds (II) are not the only suitable starting

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materials) the subject-matter of which does, by consequence, also not fulfil the requirements of Article 6 PCT.

Bitte beachten Sie, dass angeführte Nichtpatentliteratur (wie z. B. wissenschaftliche oder technische Dokumente) je nach geltendem Recht dem Urheberrechtsschutz und/oder anderen Schutzarten für schriftliche Werke unterliegen könnte. Die Vervielfältigung urheberrechtlich geschützter Texte, ihre Verwendung in anderen elektronischen oder gedruckten Publikationen und ihre Weitergabe an Dritte ist ohne ausdrückliche Zustimmung des Rechtsinhabers nicht gestattet.

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 08-013173- -00000-0000

Fecha: 2008-02-11 12:31:27 Dep: 2020 NUECREACIONI
Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 703

Industria y Comercio
SUPERINTENDENCIA

REQUISITOS MINIMOS PARA ADMISION A TRAMITE
PCT

PATENTE DE INVENCION [X] MODELO DE UTILIDAD [ ]

- Indicación de que se solicita la concesión de una patente [X]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [X]
- Descripción de la invención [X]
- Dibujos de ser estos pertinentes [X]
- Comprobante de pago de las tasas establecidas [X]

COMPLETA [ ] INCOMPLETA [ ]

DISEÑO INDUSTRIAL [ ]

- Indicación de que se solicita el registro de Diseño Industrial [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica y fotográfica del Diseño Industrial o muestra del material que incorpora el diseño [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

ESQUEMA DE TRAZADO [ ]

- Indicación de que se solicita el registro de un Esquema de Trazado [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica del esquema trazado [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

JEAR

Firma Responsable

Fecha 11 FEB. 2008

Carrera 13 No. 27-00 Piso 5, 7 y 10
Conmutador: 3 82 08 40
Fax: 350 62 20
E-mail: info@sic.gov.co
www.sic.gov.co
Bogotá, D.C., Colombia

REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Folio 705

2020
Bogotá D.C.,

Doctor(a)
OLARTE GARCIA CARLOS REINALDO
Apoderado(a) y/o Representante de
SMITHKLINE BEECHAM COPORATION

REFERENCIA	Radicación No.	8 13173
	Solicitud internacional	PCT/EP2006/007869
	Fecha inicio fase nacional	10/03/2008
	Trámite	11
	Evento	378
	Actuación	416
	Oficio No.	5826
	Folios	1

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 Única 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, 10 ABR 2008

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

adpa11